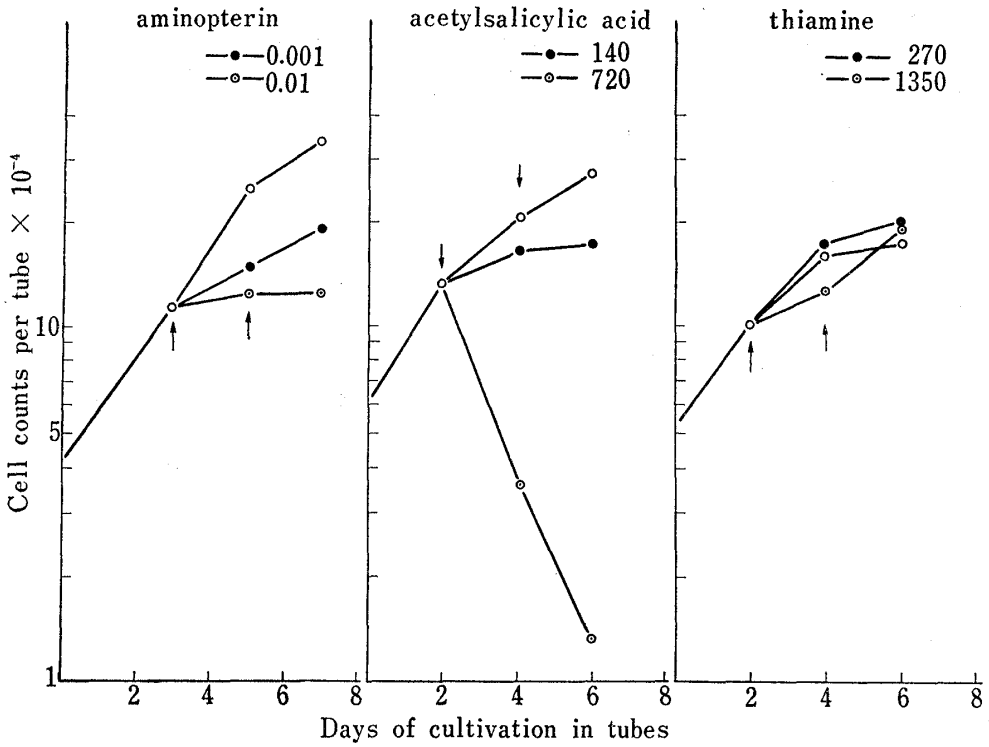

Fig. 4. Some References of Toxicity on HeLa Cell Growth

Concentrations are expressed in mg/liter. Control for every case is shown by —○—. Each compound was added to medium at renewals (arrows). Each point is the mean of cell numbers of three tubes.

Acknowledgement This work was supported in part by Science Research Grant from the Educational Ministry, and the authors express their appreciation to Dr. Y. Ito of the University of Tokyo for his kindness as representative of the Grant. The authors are also indebted to Mrs. S. Saotome, Miss T. Kobayashi and Miss S. Oshida for their technical assistance.

[Chem. Pharm. Bull. 16(11)2292—2296(1968)]

UDC 547.857.4.07

A Convenient Synthesis of 2-Methyl-4-pyrone from Kojic Acid

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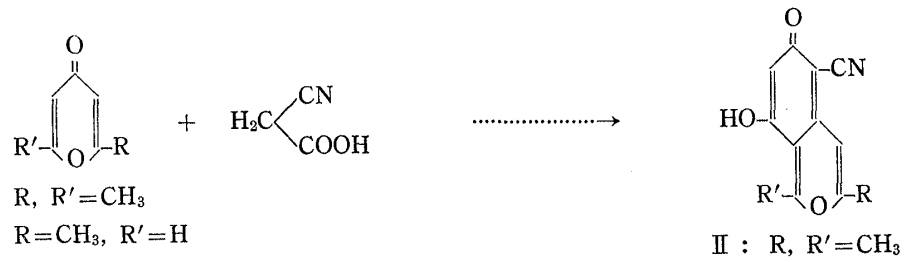
(Received July 26, 1968)

In a lot of fungal metabolites, there are many pigments which contain simple or further extended pyrono–quinonoid systems.[2] Recently, we found the simple method to prepare such a pyrono–quinonoid system as shown in Chart 1.[3]

In the pyrono–quinonoid systems of natural pigments, however, they have an alkyl group (or alkenyl group) only at C_2 position. Accordingly, it is necessary to use such a 2-alkyl-,

1) Location: *Yagotourayama, Tenpaku-cho, Showa-ku, Nagoya.*
2) W.B. Whalley, "Chemistry & Biochemistry of Fungi & Yeasts," Butterworths, London, 1963, p. 565.
3) S. Yamamura, K. Kato and Y. Hirata, *Tetrahedron Letters*, **17**, 1637 (1967).



I : R, R′=CH_3
III : R=CH_3, R′=H

II : R, R′=CH_3

Chart 1

or 2-alkenyl-4-pyrone instead of 2,6-dimethyl-4-pyrone (I) in the above synthesis. In the present paper, the synthesis of 2-methyl-4-pyrone (III) from kojic acid (IV), which is commercially available, was carried out with the intention of finding a simple route to 2-alkyl-, or 2-alkenyl-4-pyrones.

Generally, a phenolic hydroxyl group as well as alcoholic one is readily reacted with sulfonyl chlorides in pyridine at a low temperature to afford the corresponding sulfonates. When treated with two equivalents of methanesulfonyl chloride in pyridine at 0°, kojic acid (IV) has been known to afford a dimesylate (V).[4] However, the reaction of IV with two equivalents of *p*-toluenesulfonyl chloride under the same condition as described above did not give the desired ditosylate, but a monotosylate (VI), mp 126—127°, which contain a chlorine atom. In the nuclear magnetic resonance (NMR) spectrum (in $CDCl_3$), there appeared two singlets at 6.45 (1H) and 8.07 ppm (1H), which are assinged to two protons attached to the 4-pyrone nucleus at C_3 and C_6 respectively, in addition to a singlet at 4.32 ppm (2H), which is attributable to a chloromethyl group. Furthermore, the appearance of a methyl singlet at 2.46 and two doublets at 7.43 (2H, J=8 cps) and 7.89 ppm (2H, J=8 cps) indicates the presence of a *p*-tosyloxy group.

On the basis of the above spectral properties coupled with the reactivities of two hydroxyl groups, the monotosylate is regarded as 2-chloromethyl-5-tosyloxy-4-pyrone (VI). In fact, the structure (VI) was confirmed by the followings; when treated with thionyl chloride under reflux, kojic acid (IV) afforded 2-chloromethyl-5-hydroxy-4-pyrone (VII).[5] Tosylation of VII with *p*-toluenesulfonyl chloride in pyridine then gave 2-chloromethyl-5-tosyloxy-4-pyrone (VI). All of its physical properties are in complete agreement with that of the monotosylate (VI) which was directly obtained by the treatment of IV with two equivalents of *p*-toluenesulfonyl chloride as described above. On the other hand, the reverse sequence, tosylation followed by chlorination with thionyl chloride was also resulted in the formation of VI through an intermediate (VIII). Results thus obtained are shown in Chart 2.

The key stage in this synthesis is to remove the tosyloxy group at C_5, as shown in Chart 3. Dechlorination of 2-chloromethyl-5-tosyloxy-4-pyrone (VI) obtained by the above experiments was effected with zinc powder–acetic acid to afford in high yield 2-methyl-5-tosyloxy-4-pyrone (IX), mp 129—130°, which was subsequently reacted with one equivalent of sodium ethylmercaptide in ethanol under reflux to give a colorless oily product, bp 132—134° (6 mmHg), in 25% yield. The NMR spectrum (in $CDCl_3$) (1.23 (3H, d, J=7 cps), 2.28 (3H, s), 2.83 (2H, d, J=7 cps), 6.17 (1H, s) and 7.85 ppm (1H, s)) is consistent with the structure (X) of 5-ethylthio-2-methyl-4-pyrone. Treatment of X with Raney Ni in water then led to the formation of a desirable product, 2-methyl-4-pyrone (III), bp 85° (5 mmHg), in good yield. All of its spectral data and the elemental microanalysis shown in the experimental part are satisfactory.

Finally, an attempted synthesis 2-methyl-4-pyrone (III) from diethyl acetylenedicarboxylate (XI) and ethyl acetoacetate was carried out under various conditions without success.

4) J.H. Looker, T.T. Okamoto, E.R. Magnuson, D.L. Shaneyffet and R.J. Prokop, *J. Org. Chem.*, **27**, 4349 (1962).
5) T. Yabuta, *J. Chem. Soc.*, **125**, 575 (1924).

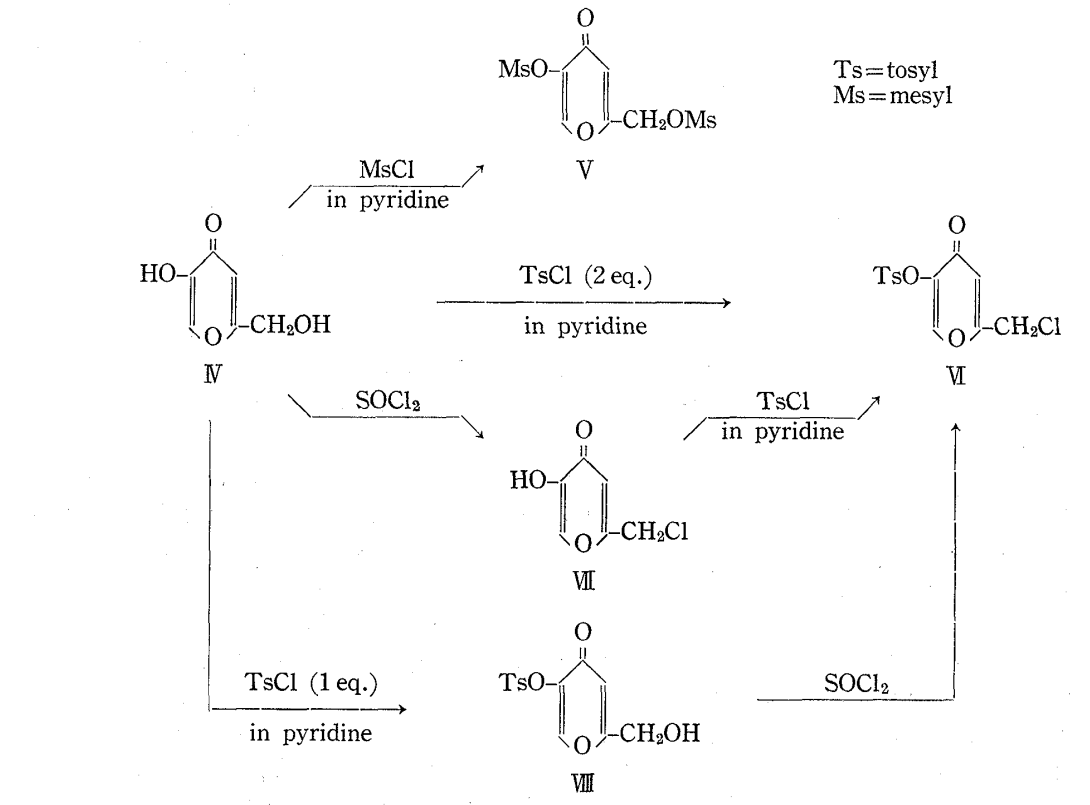


Chart 2[6]

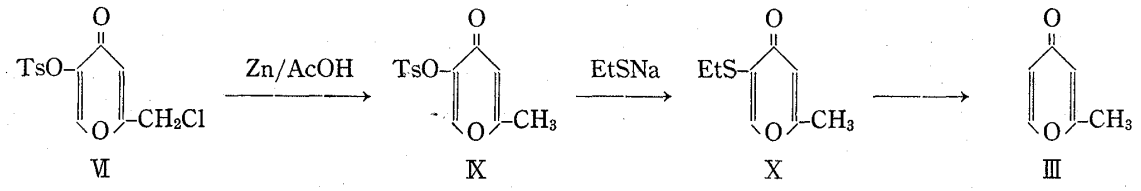


Chart 3

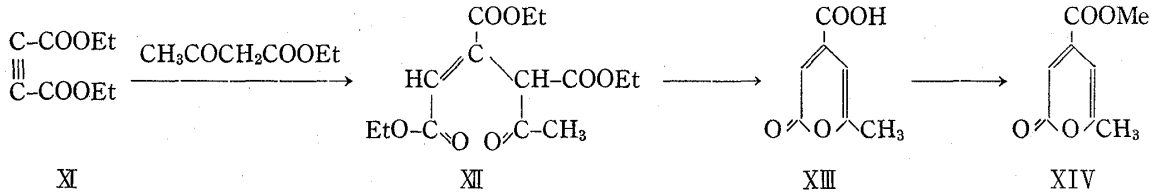


Chart 4

When treated with ethyl acetoacetate in the presence of sodium ethoxide, XI afforded a Michael condensation product (XII), bp 157—159° (6 mmHg). Treatment of XII with concentrated hydrochloric acid followed by esterification with methanol saturated with hydro-

6) Chlorination of a hydroxyl group with *p*-toluenesulfonyl chloride in pyridine at room temperature has been known as a side-reaction of tosylation (R.S. Tipson (ed.), "Advances in Carbohydrate Chemistry," Vol. 8, Academic Press, New York, N.Y., 1953, p. 107). If the hydroxyl group is located at an *α*-position of an unsaturated group (a carbonyl or a double bond), attempted tosylation is apt to result in chlorination even under mild conditions. In such a case, methanesulfonyl chloride in pyridine may be used for the sulfonation of such a hydroxyl group. Studies are now in progress to examine the different behavior between *p*-toluenesulfonyl chloride and methanesulfonyl chloride.

gen chloride then afforded, through an acid (XIII), the corresponding methyl 6-methyl-2-pyrone-4-carboxylate (XIV), mp 75—76°. After all, the above method is not used for the synthesis of 2-methyl-4-pyrone (III), but very convenient for the synthesis of a 2-pyrone nucleus.

Experimental[7]

2-Chloromethyl-5-tosyloxy-4-pyrone (VI)——To a solution of kojic acid (IV) (100 g) in pyridine (500 ml) was slowly added *p*-toluenesulfonyl chloride(267 g) at −5° with stirring. The reaction temperature was then elevated to about 10°. After stirred for additional 3 hr, the reaction mixture was poured into a large amount of ice–water to give white crystals which were washed with H_2O and dried under reduced pressure. Recrystallization from MeOH afforded 140 g of colorless plates, mp 126—127°. IR ν_{max}^{Nujol} cm^{-1}: 1680, 1650, 1600, 1205. *Anal.* Calcd. for $C_{13}H_{11}O_5SCl$: C, 49.47; H, 3.48. Found: C, 49.47; H, 3.20.

2-Chloromethyl-5-hydroxy-4-pyrone (VII)——This compound (VII) was prepared by essentially the same method of Yabuta[5] from IV (25 g) and $SOCl_3$ (40 ml). After the reaction was completed (we refluxed the reaction mixture for 30 min), excess $SOCl_2$ was distilled off under reduced pressure to give a crystalline mass, which was washed with ice–water. Recrystallization from benzene gave 29.5 g of colorless needles, mp 166—167°. IR ν_{max}^{Nujol} cm^{-1}: 3200, 1650, 1610, 1580. *Anal.* Calcd. for $C_6H_6O_3Cl$: C, 44.86; H, 3.11. Found: C, 45.11; H, 3.11.

Tosylation of 2-Chloromethyl-5-hydroxy-4-pyrone (VII)——To a solution of 10 g of VII in pyridine (50 ml) was added slowly *p*-toluenesulfonyl chloride (19.4 g) at −5° with stirring. The reaction mixture was treated similarly as described under the tosylation of IV. Recrystallization from MeOH afforded 7.2 g of 2-chloromethyl-5-tosyloxy-4-pyrone (VI) (mixed mp and IR psectrum).

2-Hydroxymethyl-5-tosyloxy-4-pyrone (VIII)——Prepared from IV (25 g) and *p*-toluenesulfonyl chloride (33.4 g) in the same way as in the case of VI. Recrystallization from MeOH gave 23.1 g of white plates, mp 147—148°. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1650, 1600, 1180. *Anal.* Calcd. for $C_{13}H_{12}O_6S$: C, 52.71; H, 4.08. Found: C, 52.76; H, 4.06.

Chlorination of 2-Hydroxy-5-tosyloxy-4-pyrone (VIII)——VIII (5 g) was chlorinated with 10 ml of $SOCl_2$ by the same way as described in VII. The product was identical with 2-chloromethyl-5-tosyloxy-4-pyrone (VI) by mixed mp and IR spectrum.

2-Methyl-5-tosyloxy-4-pyrone (IX)——To a solution of VI (70 g) in AcOH (350 ml) was added portionwise 70 g of Zn powder with stirring (the time required for the addition was about one hour). After refluxed gently for 30 min, the reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. A large amount of H_2O was added to the residue with vigorous shaking to give yellow crystals which were collected and dried. Recrystallization from MeOH afforded colorless needles (58 g), mp 129—130°. IR ν_{max}^{Nujol} cm^{-1}: 1650, 1625, 1590, 1200, 1180. *Anal.* Calcd. for $C_{13}H_{12}O_5S$: C, 55.71; H, 4.28. Found: C, 55.79; H, 4.20.

5-Ethylthio-2-methyl-4-pyrone (X)——To a solution of IX (18 g) in hot abs. EtOH (120 ml) was added a solution of EtSNa (prepared from Na (1.48 g) and EtSH (4 g) in 40 ml of abs. EtOH) with stirring and the mixture was refluxed for one hour. After cooling a deep red reaction mixture was filtered and the filtrate was concentrated under reduced pressure until a deep red oily product began to separate. A small amount of H_2O was added to the residual mixture which was extracted with ether. The ether extract was dried over Na_2SO_4. Removal of the solvent left an oily product which was chromatographed on silica gel (Izutu No. II-B), employing *n*-hexane–chloroform (3:7) as the eluent. A pale yellow oil thus obtained was distilled under reduced pressure to give 2.7 g of colorless liquid, bp 133—134° (6 mmHg). Mass *m/e*: 170 (M^+). IR ν_{max}^{neat} cm^{-1}: 1645, 1620, 1570. UV λ_{max}^{MeOH} mμ (log ε): 239 (3.56). *Anal.* Calcd. for $C_8H_{10}O_2S$: C, 56.47; H, 5.89. Found: C, 56.62; H, 6.07.

2-Methyl-4-pyrone (III)——To a solution of X (1.9 g) in H_2O (80 ml) was added 8 g of wet Raney Ni. The reaction mixture was stirred under reflux for 5 hr, and then filtered. The filtrate was concentrated under reduced pressure to give an oily residue which extracted with a lot of ether quite well. After the ether extract was dried over Na_2SO_4, the solvent was removed to give a crude oily product which was distilled under reduced pressure to afford 0.9 g of a pale yellow liquid, bp 85° (5 mmHg). Mass *m/e*: 110 (M^+). IR ν_{max}^{neat} cm^{-1}: 1660, 1615, 1585. UV λ_{max}^{MeOH} mμ (log ε): 248 (3.76). NMR (in $CDCl_3$): 2.27 (3H, s), 6.17 (1H, broad s), 6.25 (1H, q, J=2.3, 5.6 cps) and 7.93 ppm (1H, d, J=5.6 cps). *Anal.* Calcd. for $C_6H_6O_2$: C, 65.48; H, 5.45. Found: C, 65.67; H, 5.51.

Condensation of Diethyl Acetylenedicarboxylate (XI) with Ethyl Acetoacetate——To a suspension of EtONa (8 g) in dry ether (200 ml) was added dropwise a mixture of XI (20g) and ethyl acetoacetate (15.2 g)

7) All melting points are uncorrected. The spectra were recorded on the following instruments: IR, Nihon–Bunko IR-E; UV, Shimazu MPS-50L; NMR, Varian A-60 using TMS as an internal standard (TMS=0 ppm), abbreviations: s=singlet, d=doublet, q=quartet; Mass, Hitachi RMU-6E.

in dry ether (30 ml) at −15° with stirring. The reaction temperature was gradually rised to room temperature. After standing overnight, H_2O was added to the reaction mixture and the separated ether layer was removed. The aq. layer was shaken with ether and then acidified with 10% HCl to isolate an oily product which was taken up in ether. The ethereal solution was dried over Na_2SO_4. Evaporation of the solvent gave an oily product which was chromatographed on silica gel (Wako gel C-100), eluted with $CHCl_3$ and distilled under reduced pressure to afford 14 g of a pale yellow liquid, bp 157—159° (6 mmHg). Mass *m/e*: 300 (M^+). IR ν_{max}^{neat} cm^{-1}: 1730, 1640, 1615, 1245. *Anal.* Calcd. for $C_{14}H_{20}O_7$ (triethyl 4-oxo-1-pentene-1,2,3-tricarboxylate (XII)): C, 56.00; H, 6.67. Found: C, 56.27; H, 6.82.

6-Methyl-2-pyrone-4-carboxylic Acid (XIII)——A solution of XII (2.8 g) in conc. HCl (15 ml) was heated under reflux for 8 hr, and then concentrated under reduced pressure to dryness. The residue was dissolved in aq. $NaHCO_3$ and shaken with ether to remove an insoluble portion. After separation of ether layer, the aq. layer was made acidic with 10% HCl and extracted with ether. The extract was dried over Na_2SO_4. The solvent was removed to give a solid which was recrystallized from benzene to colorless needles (1.35 g), mp 183—184° (decomp.). Mass *m/e*: 154 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1750, 1700, 1610, 1560. UV λ_{max}^{MeOH} $m\mu$ (log ε): 323(3.74). *Anal.* Calcd. for $C_7H_6O_4$: C, 54.55; H, 3.92. Found: C, 54.69; H, 3.92.

Methyl 6-Methyl-2-pyrone-4-carboxylate (XIV)——A solution of XIII (1.2 g) in MeOH (50 ml) was saturated with HCl at −5°, and the resulting reaction solution was allowed to stand at room temperature overnight. Excess MeOH was removed under reduced pressure to give a solid, which was dissolved in ether. The ether solution was washed with aq. $NaHCO_3$ and dried over Na_2SO_4. Removal of the solvent gave a crystalline product which was recrystallized from *n*-hexane to 0.35 g of colorless needles, mp 75—76°. Mass *m/e*: 168 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1745, 1635, 1570, 1260. UV λ_{max}^{MeOH} $m\mu$ (log ε): 323 (3.69). NMR (in $CDCl_3$): 2.30 (3H, near s), 3.91 (3H, s), 6.48 (1H, near s) and 6.62 ppn (1H, near s). *Anal.* Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.17. Found: C, 57.21; H, 4.24.