should be substituted with α-aminoacyl groups to obtain antileukemic activity. The amino hydrogen may form a hydrogen bond with certain cell components. The configuration and bulk of substituents on the α-carbon atom are also critical factors.

On the other hand, bactobolin and actinobolin have the same skeleton, hexahydroisocoumarin. As cited above, the former was found to possess antitumor activity at 2.5 mg/kg/day or less, while the latter has been reported to have antitumor activity at high doses such as 1 g/kg/day.[7-9] Since the structural difference is the presence or absence of the 3-dichloromethyl group, it is apparent that the high antitumor potency of bactobolin is due to the presence of this group. Ueda *et al.*[5] reported that the L-alanylamino moiety at the 4 position of bactobolin is linked to the isocoumarin ring by a hydrogen bond, and that a hydrophilic hole is formed by this moiety and the dichloromethyl group. This hydrophilic hole may play some role in the antitumor action. It is also likely that the L-alanine moiety at the N position of these two antibiotics is essential for their antitumor actions.

Although no improvement in antileukemic effectiveness over bactobolin was observed among compounds in the series of bactobolin analogs used in this study, additional structural modifications of this antibiotic to obtain analogs with improved therapeutic effectiveness are being attempted on the basis of the present findings.

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Photochemistry of Flavonoids. III.[1] Photorearrangement of Flavonols

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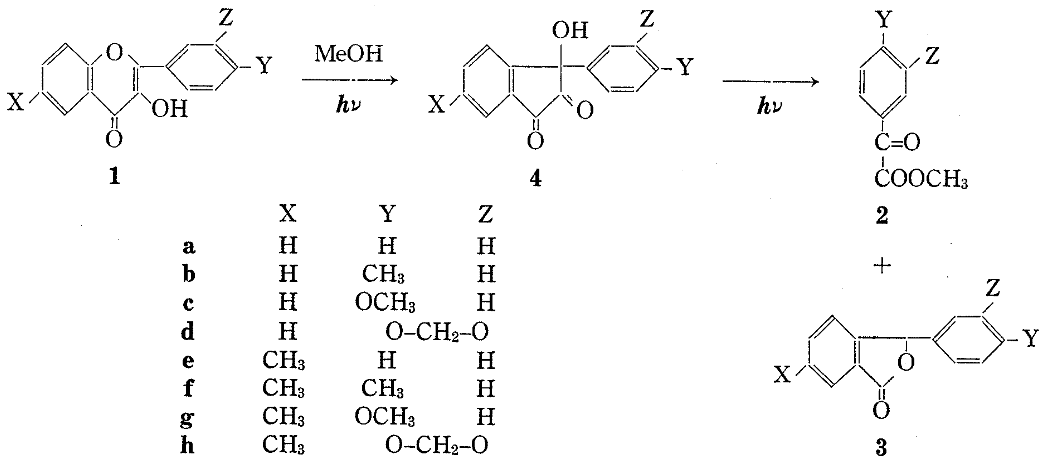
Irradiation of flavonols (**1**) in methanol gave 3-arylphthalides (**3**) which were formed *via* the diketones (**4**). Metal ions (Cu^{2+}, Ni^{2+}, Fe^{3+}, Co^{2+} and Be^{2+}) inhibited this rearrangement.

Keywords——flavonols; photochemical rearrangement; 3-arylphthalides; methyl phenylglyoxylates; metal ions; 3-aryl-3-hydroxy-1,2-indandiones

Studies on the photo-oxidation and rearrangements of flavonols were reported by Matsuura.[2a,b] During the course of our work on the photochemistry of flavonoids, however, we found that some metal ions, such as Cu^{2+}, Ni^{2+}, Fe^{3+}, Co^{2+} and Be^{2+}, prevented the photochemical rearrangement of flavonols. In contrast to these ions, Ca^{2+}, Mg^{2+}, and Hg^{2+} had no effects on the photochemical reactivities of flavonols, and the same photoproducts as in methanol alone were obtained.



	X	Y	Z
a	H	H	H
b	H	CH_3	H
c	H	OCH_3	H
d	H	O-CH_2-O	
e	CH_3	H	H
f	CH_3	CH_3	H
g	CH_3	OCH_3	H
h	CH_3	O-CH_2-O	

Fig. 1

In addition, we isolated some new photorearranged products. In this paper we report the structural determination of these products. A methanol solution of flavonol (**1a**) was irradiated for 4 hr under nitrogen with stirring. **3a** (mp 117°) and **4a** (oil) were obtained from the reaction mixture by chromatography on silica gel. The mass spectrum (MS) of **3a** showed a molecular ion (M^+) at *m/e* 210 ($C_{14}H_{10}O_2$) and fragment peaks at *m/e* 165 (M^+-$H^\cdot$-CO_2) and 105. A lactone carbonyl absorption band was observed at 1740 cm^{-1} in the infrared (IR) spectrum of **3a**. The proton nuclear magnetic resonance (PMR) spectrum ($CDCl_3$) of **3a** showed a signal at δ 6.41 (1H, s) due to the C_3-proton. From these spectral data, **3a** was assumed to be 3-phenylphthalide, and this was finally confirmed by direct comparison with an authentic sample prepared as follows.[3] The structure of **4a** was confirmed by comparison of its IR and PMR spectral data with those reported by Matsuura.[2b]

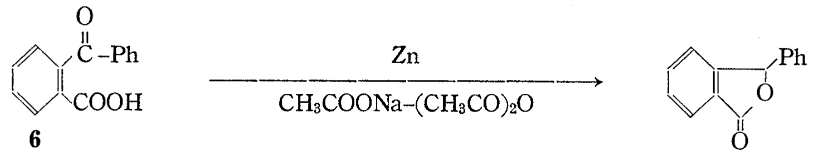


Fig. 2

In the presence of Ca^{2+}, the same products were obtained but Fe^{3+} retarded the photoreaction and the starting material was recovered quantitatively after irradiation for 10 hr.

Photolysis of **1c** under the same conditions afforded **2c**, mp 50°[4] and **3c**, mp 115—117°.[5] The structure of **2c** was determined from its spectral data [IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1730, 1670. PMR δ 3.90 (3H, s, $-OCH_3$), 3.96 (3H, s, $-\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}-\mathrm{OCH_3}$). MS *m/e* 194 ($M^+=C_{10}H_{10}O_4$)]. The MS of **3c** showed a molecular ion peak at *m/e* 240 ($C_{15}H_{12}O_3$) and the fragments resembled those of **3a**. The IR spectrum of **3c** showed an absorption band at 1750 cm^{-1} (C=O) and the PMR spectrum indicated the presence of a methoxy group (δ 3.81, 3H, s), a methine group (δ 6.37, 1H, s) and showed A_2B_2 type aromatic proton signals centered at δ 6.98 (2H, d, $J=9$ Hz) and 7.86 (2H, d, $J=9$ Hz). From these data, **3c** was identified as 3-(4′-methoxyphenyl)phthalide.

Compound **1b** gave the corresponding phthalide (**3b**), mp 130—131°, and diketone (**4b**), mp 139°. These structures were deduced from the spectral data.

Table I. Products obtained by the Irradiation of Flavonol in Methanol

Starting material (**1**)	Products; mp (yield in %) **2**	**3**	**4**
a		117—119° (0.7)	Oil (8)
b		130—131°d) (2)	139° (44)
c	50°b) (6)	115—117°e) (12)	
d	62—64°c) (14)	175—177° (6)	
e		135—137°f) (2)	209° (15)
f		111°g) (3)	
g	50° (1)	Oil (0.2)	
h	62—64° (4)	GC–MSa)	

a) **3h** was identified by GC-MS.
b) Lit.,4) 46—48°.
c) Lit.,7) 66°.
d) Lit.,5) 127—128°.
e) Lit.,5) 113—114°.
f) Lit.,8) 137—139°.
g) Lit.,9) 109—110°.

Table I summarizes the results of photolyses of flavonols. Table I suggests that the formation of phthalides is a general reaction of flavonols. No substitution effect was observed.

Although the yields of the phthalides were unsatisfactory, this photorearrangement is the first in the photochemistry of flavonoids.

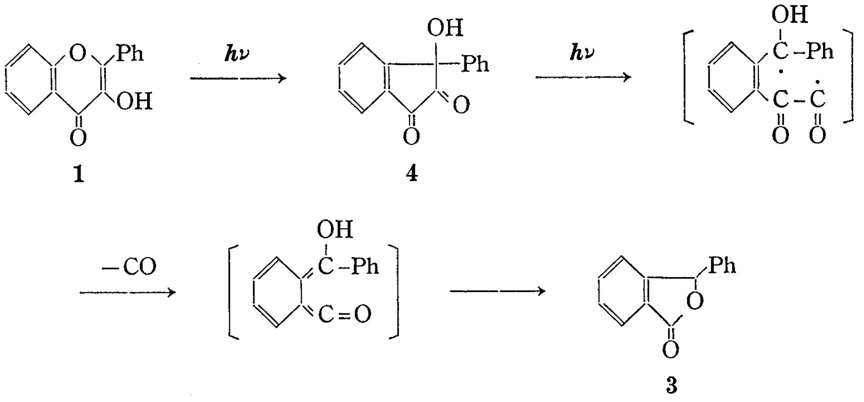


Fig. 3

Table II. The Properties of 3-Aryl-phthalides (**3**)

Compounds	IR (cm^{-1})	MS (M$^+$)	PMR δ (CDCl$_3$) C_3–H	CH_3	OCH_3	O–CH_2–O
3a	1740	210	6.41			
3b	1760	224	6.38	2.35		
3c	1750	240	6.37		3.81	
3d	1750	254	6.32			5.97
3e	1760	224	6.37	2.48		
3f	1755	238	6.33	2.58, 2.71		
3g	1750	254				

Though the mechanism of this reaction is now under detailed investigation, we tentatively propose the following mechanism for the formation of phthalide **3**.

The flavonol rearranged to compound **4** *via* the n-π^* triplet6) followed by a loss of CO to afford compound **3** upon further irradiation.10)

In the case of **1c**, colorless crystals of mp 117—119°, (**5c**), were obtained in addition to **2c** and **3c**. This compound showed two carbonyl bands at 1760 and 1700 cm^{-1} in its IR spectrum. The PMR spectrum revealed two methoxy signals [δ($CDCl_3$): 3.70, 3.89]. The structure of this compound is now under investigation.

Experimental

Melting points were recorded on a Yanagimoto MP-S3 micromelting point apparatus and are uncorrected. UV and IR measurements were made on Nihonbunko UVIDEC-1 and IRA-1 spectrometers, MS were taken on a Shimadzu LKB-9000 spectrometer, high resolution MS on a JEOL D-300 machine, and ^{1}H NMR spectra on a JEOL PS-100 machine. Chemical shifts are given on δ (ppm) scale with TMS as an internal standard (s, singlet; d, doublet; m, multiplet). Column chromatography was carried out with Wakogel C-200.

Photolyses were carried out in a quartz immersion apparatus equipped with a high pressure mercury lamp (Toshiba 400 P) which was cooled internally with running water. Irradiation was conducted through a Pyrex filter under nitrogen with stirring.

Irradiation of Flavonol (1a)——A solution of 1.0 g of flavonol (**1a**) in 400 ml of methanol was irradiated for 4 hr, when the starting material had disappeared. The residue obtained after removal of the solvent was chromatographed on silica gel. Elution with hexane–benzene (3:1 v/v) afforded the 3-phenylphthalide (**3a**) (6 mg), mp 117°. Elution with benzene afforded the diketone (**4a**) (75 mg). **3a**, mp 117—118° (hexane–ether). MS *m/e* 210 ($M^+ = C_{14}H_{10}O_2$), 165 ($M^+ - H^{\cdot} - CO_2$), 105 (M^+−PhCO). IR ν_{max}^{KBr} cm^{-1}: 1740. UV λ_{max}^{MeOH} nm: 210, 275. PMR δ ($CDCl_3$): 6.41 (1H, s, C_3–H), 7.36—8.02 (9H, m, arom.-H). **3a** was identical with an authentic sample prepared as described below. **4a**, reddish amorphous material, MS *m/e*: 238 ($M^+ = C_{15}H_{10}O_3$), 210 (M^+−CO), 181, 165. IR ν_{max}^{Liq} cm^{-1}: 3100 (OH), 1740 (C=O). PMR δ ($CDCl_3$): 6.60—8.03 (9H, m).

Irradiation of 1b——A methanol solution of **1b** (1.0 g) was irradiated for 5 hr. After removal of the solvent, the reaction mixture was purified as above to give 3-*p*-tolylphthalide **3b** (17 mg), mp 130—131° [MS *m/e*: 224 ($M^+ = C_{15}H_{12}O_2$), 223 ($M^+ - H^{\cdot}$). IR ν_{max}^{KBr} cm^{-1}: 1760. PMR δ ($CDCl_3$): 2.34 (3H, s, CH_3), 6.38 (1H, s, C_3–H)] and **4b** (439 mg), mp 139° [MS *m/e*: 252 ($M^+ = C_{16}H_{12}O_3$). IR ν_{max}^{KBr} cm^{-1}: 3320 (OH), 1725 (C=O). PMR δ ($CDCl_3$): 2.32 (3H, s, CH_3), 6.6—7.7 (8H, m, arom.-H.)].

Irradiation of 1c——**1c** (1.0 g) in methanol was irradiated for 13 hr under the same conditions as above. The residue obtained after removal of the solvent was chromatographed on silica gel. Elution with benzene–hexane (1:1 v/v) yielded 39 mg of **2c**, mp 50—51°4) and 104 mg of **3c**, mp 115—117°. Further elution with benzene afforded 273 mg of a crystalline product **5c**, mp 117—119° [UV λ_{max}^{MeOH} nm (log ε): 224 (4.12), 294 (4.13). MS *m/e*: 298 ($M^+ = C_{17}H_{14}O_5$), 239 ($M^+ - COOCH_3$), 168, 135. IR ν_{max}^{KBr} cm^{-1}: 1760, 1700. PMR δ ($CDCl_3$): 3.70 (3H, s), 3.89 (3H, s), 6.98 (2H, d, $J=9$ Hz), 7.86 (2H, d, $J=9$ Hz), 7.6—7.9 (4H, m).] whose structure is now under investigation.

General Procedure for Irradiation of 1d Through 1h——A solution of **1d**—**1h** (1.0 g) in 400 ml of methanol was irradiated until the starting material had disappeared completely (4—8 hr). After irradiation the solvent was evaporated off under reduced pressure. The residue was chromatographed on silica gel. Elution with benzene–hexane (1:3 v/v) afforded methyl phenylglyoxylates (**2g** and **2h**; identical with **2c** and **2d**, respectively.). Elution with benzene–hexane (1:1 v/v) afforded 3-aryl-phthalides (**3d** to **3h**). Elution with benzene gave **5** (**5d**, **5f**, **5g** and **5h**). IR, MS and PMR data of **3** are summarized in Table II. In the case of **1e**, the diketone **4e**, mp 209°, (149 mg) was obtained. MS *m/e*: 252 ($M^+ = C_{16}H_{12}O_3$), 224, 195, 181 and 165. IR ν_{max}^{KBr} cm^{-1}: 3000 (OH), 1725 (C=O). PMR δ ($CDCl_3$): 2.52 (3H, s, CH_3), 7.11—7.79 (8H, m).

Irradiation of Flavonol in the Presence of Metal Ions——A solution of 1.0 g of **1a** and 4.8 g of $CaCl_2$ (10 eq.) in methanol (400 ml) was irradiated for 4 hr, and treated as above to provide **3a** and **4a** (5 mg and 77 mg, respectively). Almost the same results were obtained in the presence of $MgCl_2$ and $HgCl_2$. $CuSO_4$, $NiCl_2$, $FeCl_3$, $CoCl_2$ and $Be(NO_3)_2$ inhibited these reactions and the starting material was recovered quantitatively after irradiation for 10 hr.

Irradiation of 4——A solution of **4a** (5 mg) in methanol (3 ml) was irradiated for 5 hr; **3a** was detected in the reaction mixture by GC–MS and TLC. In the case of **4b**, the corresponding **3b** was detected.

Synthesis of 3-Phenylphthalide (3a)——o-Benzoylbenzoic acid (1.0 g) was dissolved in acetic anhydride (20 ml) and to this solution powdered Zn (6.0 g) and CH_3CO_2Na (8.0 g) were added. The reaction mixture was heated at 160° for 3 hr, poured into ice-water mixture, and extracted with ether. The extract was dried over Na_2SO_4, and concentrated, and the residue was recrystallized to afford 0.6 g of 3-phenylphthalide mp 117° (ether–hexane). IR ν_{max}^{KBr} cm^{-1}: 1740. UV λ_{max}^{MeOH} nm: 210, 275. PMR δ ($CDCl_3$): 6.41 (1H, s), 7.36—8.02 (9H, m).

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