the Rf of the photodecomposition products of V. $B_2$ is almost the same whether developed with an acidic solvent or with a neutral solvent. In the present study the spots of Lum. F. and Lum. C. were identified from their Rf values and fluorescence colors described in the report of Shimizu because the samples were not at hand. And the yellow spot at Rf 0.57 was regarded as the remaining V. $B_2$, the yellow spot at Rf 0.70 as Lum. F. and the blue spot at Rf 0.83 as Lum. C. Among the spots that of Lum. C. was appeared in the photodecomposition product at any pH but that of Lum. F. was observed only in the products at a pH higher than 6.52. This result also is in good agreement with that of Shimizu.

The authors are grateful to Professor Kihachiro Uehara of the School of Pharmacy, Osaka University for his kindness in giving a suggestion to the present study.

Thanks are also due to all the members of the Research Laboratories and Technical Division of Takeda Chemical Industries who helped the present work.

## Summary

To determine whether the V Comp. detected in the extract of *Er. ashbyii* was present originally in it or produced supplementally by photooxidation of G Comp., the mycelium was extracted in an atmosphere of nitrogen and the extract was investigated by TLC. The result proved the original existence of all of V. $B_2$, G and V Comps. But taking into consideration Uehara's report on hypoxanthine. G Comp. was examined if it is photooxidized to V Comp. Namely, the extract of the mycelium was exposed to sunlight and investigated by TLC, when GH and Lum. C were detected apparently but V Comp. did not increased. On the other hand, G Comp. was photodecomposed in phosphate buffer at various pHs, when GH was produced at any pH, while V Comp. was formed only at pH>6.52 besides GH. The same experiment was conducted in the presence of V. $B_2$, when Lum. C was produced at any pH, but Lum. F. at pH>6.52 in addition to the above products.

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*UDC 615.415[615.778.475+615.777.93]-011*

## 43. Ken Ikeda and Hajime Takeda : Reaction between Salicylic Acid and Zinc Oxide in the Presence of Water.

(*Pharmaceutical Institute, Tohoku University School of Medicine*[*1])

Zinc oxide is compounded with salicylic acid in various dermatological preparations such as lotion, ointment, and paste. It has been known that various unexpected phenomena occur in such preparations. Kitchin[1] and Anon[2] observed the appearance and solidification of a lotion containing zinc oxide and salicylic acid. Kitchin reported that the change did not occur for two or three days after preparation of the lotion that when it did occur on the fourth day, the change was very rapid. They concluded that such change was due to the formation of basic zinc salicylate, but did not ascertain its formation of chemically. Meanwhile, Strakosch[3] observed that keratolytic action of salicylic acid was inhibited when it was compounded with zinc paste. In recent years,

*1 Kita-4-bancho, Sendai (池田 憲, 武田 元).

1) G. S. Kitchin : Pharm. J., **104**, (1920).
2) *Idem* : *Ibid.*, **132**, 565 (1934) (C. A., **29**, 6363 (1935)).
3) E. A. Strakosch : Arch. Dermatol. Syphilol., **43**, 384 (1943).

Young, *et al.*[4] observed by patch test that dermatological action of salicylic acid on the skin of those who are known to be hypersensitive to salicylic acid was prevented when it was compounded in a paste containing zinc oxide. They also observed that percutaneous absorption of salicylic acid was markedly prevented in the presence of zinc oxide. They attributed by brief chemical study these results to the formation of a salt between the two components.

The reaction in this system seems to be very complex because salicylic acid is dibasic and zinc is an amphoteric bivalent metal which has a tendency to form a complex with either acid or base. A well-known zinc salicylate is 2:1 salt, $Zn(C_6H_4OHCOO)_2 \cdot 3H_2O$, which is described in the U. S. Dispensatory.[5] However, very little is known of basic zinc salicylate, which has been said to cause the above phenomenon. The system composed of salicylic acid, zinc oxide, and water is creamy or a magma-like mass according to the ratio of the two components. In preliminary investigations it was found that the change of appearance with time was considerably affected by shaking conditions and the reaction rate in such a heterogenous system seems to be complicated. The change of appearance may be related to the transition of crystal form as was found by Feitknecht[6] on the salt formed in an alkaline solution. Analysis of the solid phase was also tried in the preliminary investigations, but it was found that the salt formed and unreacted salicylic acid both dissolved in various solvents and their separation was not effected. In the present study chemical changes occurring in such a system was investigated by determination of zinc and salicylic acid in the aqueous phase after an equilibrium state was attained. For the study of heterogenous systems, T. Higuchi, *et al.*[7] recently proved that such a phase solubility method is very effective. In the systems in his study, the solid phase changed or lost their components on washing or recrystallization.

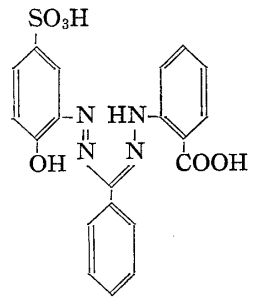
## Experimental

**Determination of Zinc**——Colorimetric method with O-{2-[α-(2-hydroxy-5-sulfophenylazo)-benzylidene]-hydrazino}benzoic acid*2 used Hitachi spectrophotometer EPU-2A type at a wave length of 620 mμ, which is essentially the same as that of Rush, *et al.*[8]

**Determination of Salicylic Acid**——Colorimetry with ferric ion was used according to the method of Keller.[9]

**Procedure**——Predetermined amount of salicylic acid, varying amount of freshly ignited ZnO in 0.1～1.3 g., and distilled $H_2O$ were taken in a well-stoppered glass bottle. The amount of $H_2O$ was always 40 ml. The bottles were shaken up and down in a thermostat of 40±0.1° at the rate of 80 times per minute for 24 hr. This period was proved to be sufficient for the equilibration of the systems. For the determination of Zn and salicylic acid in the aqueous phase, 1 ml. of the aqueous phase was

*2




4) E. Young, N. Weiffenbach : Dermatologica, **118**, 74 (1959).
5) United States Despensatory 25th. Ed., p. 1933, J. B. Lippincott Co., (1955).
6) W. Feitknecht, H. Burki : Helv. Chim. Acta, **39**, 589 (1956).
7) T. Higuchi, F. S. Hom : J. Pharm. Sci., **52**, 426 (1963).
8) R. M. Rush, J. H. Yoe : Anal. Chem., **26**, 1314 (1956).
9) W. J. Keller : Am. J. Clin. Pathol., **17**, 415 (1954).

pipetted out. The orifice of the pipette was covered with cotton and gauze to prevent solid phase being sucked in.

**Preparation of $Zn(C_6H_4OHCOO)_2 \cdot 3H_2O$**——The Method described in Hagers Handbuch der Pharmazeutischen Praxis[10] was used.

## Results and Discussions

Fig. 1 shows the amount of salicylic acid in the aqueous phase after the equilibrium state was attained versus the amount of zinc oxide added in the system. Solid lines I, II, III, and IV represent results in systems containing 1.0, 1.5, 2 0, and 2.5 g. of salicylic acid, respectively. Fig. 2 shows the amount of zinc ion in aqueous phase at equilibrium state. Fig. 3 shows pH of the system at equilibrium state.

As is shown in Fig. 1 when the amount of zinc oxide added is not so much, salicylic acid in the aqueous phase increases linearly as the amount of zinc oxide increases in every series. The slopes of increasing lines in molar ratio are always 1:2. The dotted lines on every curve show that the molar ratio of salicylic acid to zinc oxide is 2:1 on these lines. These results show that when the molar ratio is below about 2:1, a 2:1 salt which has a comparatively large solubility is formed in the aqueous phase. In these regions, the solid phase was found to be the unreacted salicylic acid and its amount decreased as the amount of zinc oxide added was increased. In the neighborhood of the dotted lines, the solid phase in the system was not seen or was in a trace if any.

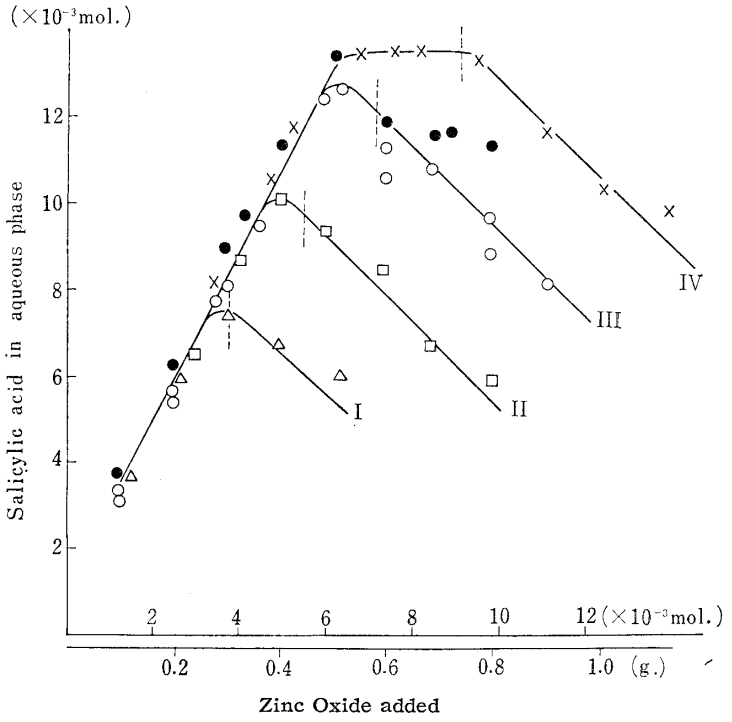



Fig. 1. Salicylic Acid in Aqueous Phase *versus* Zinc Oxide added

× amount of salicylic acid 2.5 g.
○ 〃 2.0
□ 〃 1.5
△ 〃 1.0
● 2.0 g. of salicylic acid was given as $(C_7H_5O_3)_2 \cdot Zn \cdot 3H_2O$

In the regions where the amount of zinc oxide added is more than 2:1, salicylic acid in the aqueous phase decreases as the amount of zinc oxide added increases. The slope of the decreasing lines was −1 in every series. In these regions, the solid phase was found to be composed of gelatinous (fibrous through a microscope) mass and a solid which seemed to be the excess zinc oxide. Amount of the solid increases as the zinc oxide added increases. In the neighborhood of the right end of the curves magma-like mass occupied a whole volume of the systems and it became a plastic mass in a further right region. In these conditions, it was difficult to take the aqueous phase for analysis and the results obtained were not reproducible. From above results it is evident that, in the decreasing region, 1:1 salt which has a comparatively low solubility is formed and deposited. The

10) Hagers Handbuch der Pharmazeutischen Praxis, Band 2, p. 989, Julius Springer, Berlin (1893).

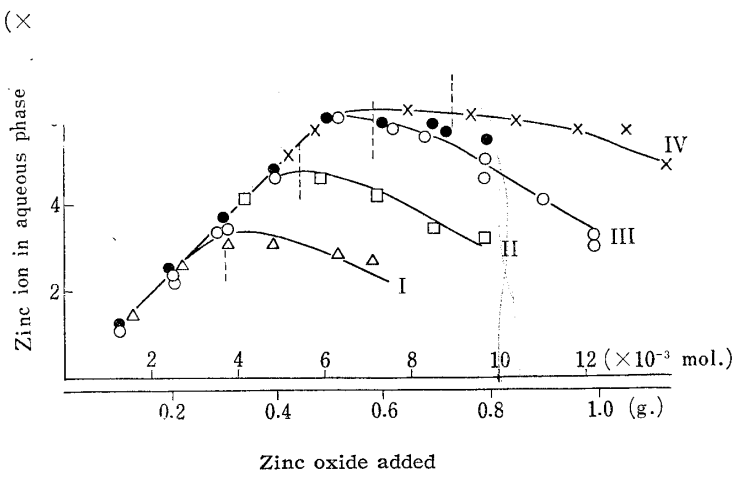



Fig. 2. Zinc Ion in Aqueous Phase *versus* Zinc Oxide added

| | | |
|---|---|---|
| × | amount of salicylic acid | 2.5 g. |
| ○ | 〃 | 2.0 |
| □ | 〃 | 1.5 |
| △ | 〃 | 1.0 |
| ● | 2.0 g. of salicylic acid was given as $(C_7H_5O_3)_2 \cdot Zn \cdot 3H_2O$ | |

plateau of the curve (Ⅳ) may be explained as the limit of solubility of 2:1 salt.

As a proof of above discussions, 2.0 g. of salicylic acid, which corresponds to curve (Ⅲ), was taken in the form of 2:1 salt and a balanced amount of zinc oxide and water were added to it. In these systems as shown by ● mark in Figs. almost the same result was obtained.

As is shown in Fig. 2, zinc ion in the aqueous phase in an equilibrium state increases as the amount of zinc oxide added increases. The slope of the increasing lines is 1 in every series. This agrees with the formation of 2:1 salt stated above. The decreasing lines where more zinc oxide was added were not stoichiometrically so simple as those of salicylic acid in Fig. 1. This was not exactly clarified in the present study, but there may be a complexed zinc ion which has no relation to the concentration of salicylic acid in the aqueous phase. The abrupt change of pH of the system nearly at the molar ratio of 2:1 which is shown in Fig. 3 may endorse this assumption.

In various dermatological preparations for practical use, the amount of zinc oxide is usually much more than 1:1 to salicylic acid. In these preparations, the solid phase may contain 1:1 salt and excess zinc oxide. Even in the preparations which has no water in the prescription, such as Lassar's zinc paste, the above reactions will occur because there is a small amount of water in the components. It is known that the complete removal of moisture from zinc oxide is difficult by ordinary mean. When these preparations are applied on the skin, sweat will take a part in promoting the above reaction, as pointed out by Young, *et al*[4]

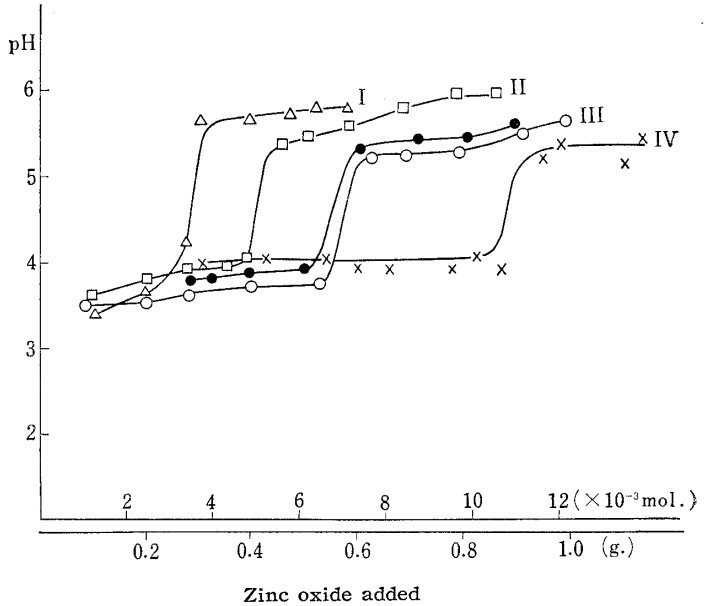



Fig. 3. pH of Aqueous Phase

| | | |
|---|---|---|
| × | amount of salicylic acid | 2.5 g. |
| ○ | 〃 | 2.0 |
| □ | 〃 | 1.5 |
| △ | 〃 | 1.0 |
| ● | 2.0 g. of salicylic acid was given as $(C_7H_5O_3)_2 \cdot Zn \cdot 3H_2O$ | |

The authors express their gratitude to Professor Kanzo Okazaki for his advice and criticism.

**Summary**

For the explanation of chemical changes and loss of dermatological activity of salicylic acid in external preparations containing salicylic acid and zinc oxide, systems composed of salicylic acid, zinc oxide, and water were investigated. By the determination of salicylic acid and zinc ion in the aqueous phase after an equilibrium state was attained, the formation of 1:1 and 2:1 salts of salicylic acid and zinc was ascertained quantitatively.

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*UDC 547.816.07*

## 44. Seigo Fukushima, Akira Ueno, and Yukio Akahori: Studies on Benzochromones. V.*1 Synthesis and Ring Isomerization of 2-Methyl-5,8-dimethoxy-6,7-benzochromone.*2

(*Shizuoka College of Pharmacy**3)

The synthesis of 2-methyl-5,8-dimethoxy-6,7-benzochromone (V), in which the furan ring of khellin (Ⅵ) was replaced by a benzenoid ring, has attracted considerable interest concerning its physiological activity, and several attempts[1,2] have been made unsuccessfully. We wish to report herein the successful synthesis and the ring isomerization of this compound.

Methyl 3,4-dimethoxy-2-naphthoate which was prepared from 3-hydroxy-2-naphthoic acid, was condensed with acetone by means of sodium hydride to form 3-acetoacetyl-1,2-dimethoxynaphthalene. Cyclization of the diketone in hydriodic acid gave 2-methyl-8-hydroxy-6,7-benzochromone (I). When hydroxylation of I was carried out by means of potassium persulfate, there was obtained 2-methyl-5,8-dihydroxy-6,7-benzochromone (Ⅳ) as red prisms, m.p. 250° (decomp.), in poor yield (ca. 10%). Coupling of I with diazotized sulfanilic acid gave a red violet, water soluble azo dye which on reduction with sodium hydrosulfite was converted into yellow needles of 2-methyl-5-amino-8-hydroxy-6,7-benzochromone (Ⅱ), m.p. 252° (decomp.). Oxidation of Ⅱ with sodium nitrite in acidic medium afforded 2-methyl-4*H*-naphtho[2,3-*b*]pyrane-4,5,10(5*H*,10*H*)-trione (Ⅲ), m.p. 165° (decomp.), and Ⅲ was reduced to Ⅳ with sodium hydrosulfite. If the reduction was carried out without isolation of Ⅲ, the overall yield of Ⅳ from I was more than 30%. The compound (Ⅳ) was then converted to 2-methyl-5,8-dimethoxy-6,7-benzochromone (V), m.p. 146°, by prolonged action of ethereal diazomethane solution, in the presence of methanol. Heating of Ⅳ with hydrochloric acid on a boiling water bath gave yellow needles, m.p. 224°, which was proved to be 2-methyl-5,6-dihydroxy-7,8-bezochromone (Ⅷ) reported previously.[2] Drastic demethylation of V using hydriodic acid and acetic anhydride also produced Ⅷ. Such a ring isomerization might proceed through cleavage of γ-pyrone ring to an intermediate, 2-acetoacetyl-1,3,4-naphthalenetriol (Ⅳ'),

*1 Part Ⅳ: This Bulletin, **9**, 127 (1961).
*2 A preliminary communication on this subject appeared in this Bulletin, **10**, 638 (1962).
*3 Oshika, Shizuoka (福島清吾, 上野 明, 赤堀幸男).
1) S. Wawzoneck, *et al.*: J. Org. Chem., **17**, 1419 (1952).
2) K. Yamaguchi, S. Fukushima, H. Yamada: This Bulletin, **8**, 1028 (1960).