1.3 cps, H_X), 4.54 (1H, doublet, $J=10.0$ cps, H_B), 3.49 (1H, singlet, C_5–H). UV λ_{max}^{MeOH} mμ (log ε): 235 (4.19), 285 (3.87). Mass spectrum *m/e*: 341 (M^+), 340 (M^+–H), 324 (M^+–3H–CH_3), 313 (M^+–CO), 312 (M^+–H–CO), 298 (M^+–CH_2=N–CH_3). *Anal.* Calcd. for $C_{20}H_{23}O_4N \cdot H_2O$: C, 66.9; H, 7.16; N, 3.51. Found: C, 67.27; H, 7.40; N, 3.76.

Reduction of Dienone (IVa or IVb) with $NaBH_4$——To a mixture of 300 mg of the dienone (IVa or IVb), 50 ml of MeOH and a small amount of water was added portionwise 1.0 g of $NaBH_4$ within 1 min at room temperature, and the above mixture was heated under reflux for 1 hr. Evaporation of the solvent gave an orange oil, to which was added 10 ml of water and extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated to give 300 mg of a colourless caramel, which was chromatographed on 9 g of silicagel to give two compounds using $CHCl_3$–MeOH (99:1) and (98:2) as an eluant. The first compound was crystallised from $CHCl_3$–*n*-hexane to give 60 mg of XV as colourless needles, mp 186—187°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH), 1640 (C=C). NMR (in $CDCl_3$) τ: 7.57 (3H, singlet, N–C<u>H</u>$_3$), 6.68 (3H, singlet, aliphatic O–C<u>H</u>$_3$), 6.18 (3H, singlet, aromatic O–C<u>H</u>$_3$), 5.93 (1H, multiplet, H_X), 4.55 (1H, doublet, $J=10.5$ cps, H_A), 4.23 (1H, a pair of doublets, $J=10.5$, 5.0 cps, H_B), 3.5 (1H, singlet, C_5–H). *Anal.* Calcd. for $C_{20}H_{27}O_4N$: C, 69.54; H, 7.88. Found: C, 70.01; H, 7.37.

The second compound (XVI) was obtained as a green oil (54 mg). NMR (in $CDCl_3$) τ: 7.58 (3H, singlet, N–C<u>H</u>$_3$), 6.78 (3H, singlet, aliphatic O–C<u>H</u>$_3$), 6.16 (3H, singlet, aromatic O–C<u>H</u>$_3$), 5.87 (2H, broad, 2O<u>H</u>), 3.52 (1H, singlet, C_5–H). This compound (XVI) was converted into its hydrochloride, which was recrystallised from MeOH–ether to give 30 mg of pale yellowish prisms, mp 208—210°. *Anal.* Calcd. for $C_{20}H_{29}O_4N \cdot HCl$: C, 62.58; H, 7.82; N, 3.65. Found: C, 62.53; H, 7.94; N, 3.69.

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Quantitative Analysis of Pharmaceutical Preparations by X-Ray Diffractometry. IX.[1] Direct Quantitative X-Ray Diffraction Analysis of Salicylic Acid Plaster

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For the precise determination of active components in plasters, the chemical assay has long been used. The method of chemical assay used for salicylic acid plaster, for instance, is prescribed in the "United States Pharmacopoeia". An extraction with chloroform was made to liberate salicylic acid from plaster masses. After several steps of procedures, the determination was made finally by the bromine titration. It takes about a day for each measurement.

In the preceding paper,[1] the direct X-ray diffraction technique was reported to be very useful for the assay of the active components in oral suspensions. In this paper, this technique was attempted to utilize for the assay of salicylic acid plaster with acceptable accuracy and minimum investment of operation time.

The assay of salicylic acid contents in plaster by the direct X-ray diffraction method was developed as an alternative method for the chemical assay.

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1) Part VIII: K. Kuroda, G. Hashizume, and K. Fukuda, *J. Pharm. Sci.*, **57**, 250 (1968).
2) Location: *a*) *Kusunoki-cho, Ikuta-ku, Kobe*; *b*) *Kamitezaki-cho, Suma-ku, Kobe.*

Experimental

X-Ray Equipment——For the experimental work, a Rigakudenki Geigerflex diffractometer was used. X-ray source was a copper target X-ray tube with a Ni-foil filter. The slit system used in this work were divergence slit 1°, scatter slit 1°, and recieving slit 0.2 mm. The time constant of rate-meter was 2 seconds. A Geiger Müller tube was used as a detection device. The scanning speed of the goniometer was 1/4° 2θ per minute, and the chart speed was adjusted in 2 cm per minute throughout this work.

Preparation of Synthetic Salicylic Acid Plaster——The commonly used plasters are all made on a large scale by machinery, but it is unnecessary in this work to make plasters on a large scale. The synthetic plaster used in this work, therefore, was made by hand-spreading. The procedure was as follows: 10 g of natural rubber mass was dissolved in about 50 ml of benzene at room temperature and a clear and heavy syrupy solution was obtained. Salicylic acid[3] was triturated well in a mortar adding a small amount of rubber solution and the trituration was continued with an addition of the rubber solution, from time to time,

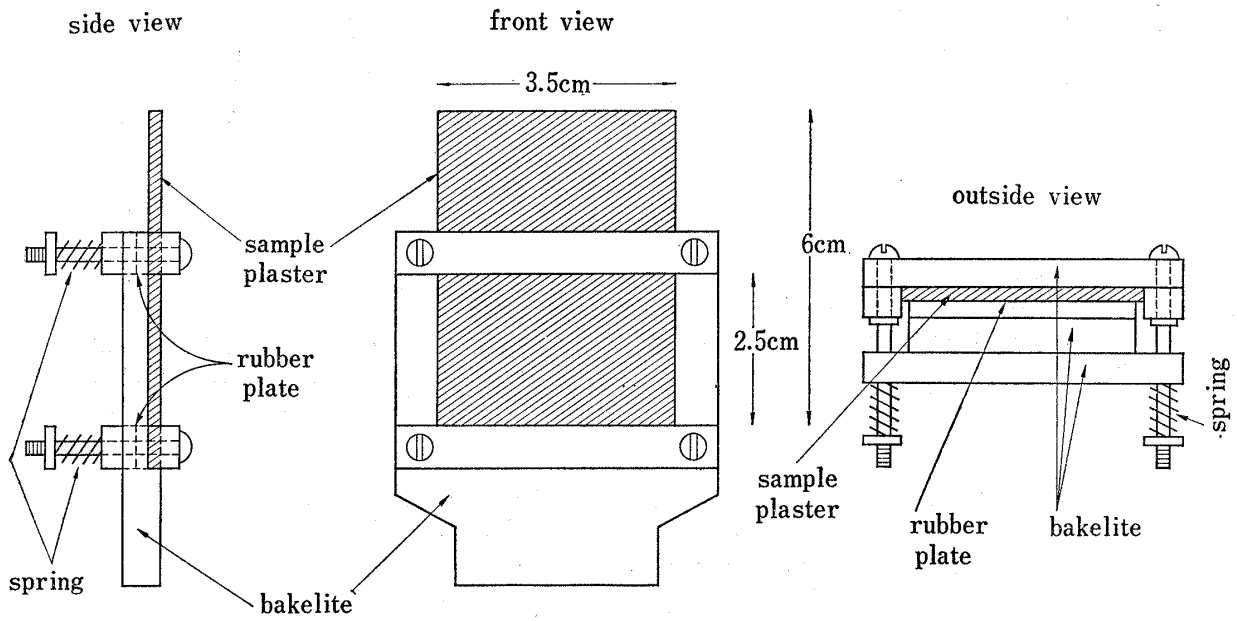

Fig. 1. Plaster Sample Cell

until all the solution was added and a smooth mixture was obtained. The mixture was then poured onto the center of a filter paper (a back cloth) and spreaded out as it stands. Moreover, it was allowed to keep standing in a room for about one week untill the odor of benzene had left completely, then a crude plaster was obtained. A surface of the crude plaster was covered with a sheet of cellophan paper (a face cloth) and pressed with a hydraulic press under 100 kg/cm at 80° for 5 minutes. In this way, the satisfactory products were obtained.

Quantitative Analysis of Salicylic Acid Plaster——The sample plaster was cut to a size of about 3.5×6.0 cm, and placed in the specially designed sample holder made of bakelite. The holder was fastened to the diffractometer and scanned. This sample holder is illustrated in Fig. 1. The diffraction

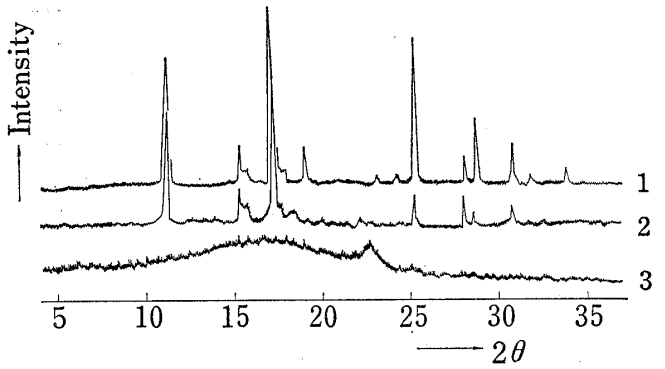

Fig. 2. X-Ray Diffraction Patterns of Powdered Salicylic Acid, Salicylic Acid Plaster, and Placebo Plaster

1. powdered salicylic acid 40 kV, 2.1 mA
2. salicylic acid plaster 40 kV, 0.6 mA
3. placebo plaster 40 kV, 0.6 mA

3) Salicylic acid used in this work was coated with Tween 80 to disperse easily and to sediment slowly. The procedure of coating was as follow: 150 g of powdered salicylic acid was placed in a glass stoppered container, adding about 300 ml of benzene contained 30 ml of Tween 80. The mixture was allowed to stand in a room for about two days with shaking sometimes. Crystals are filtered and dried in air.

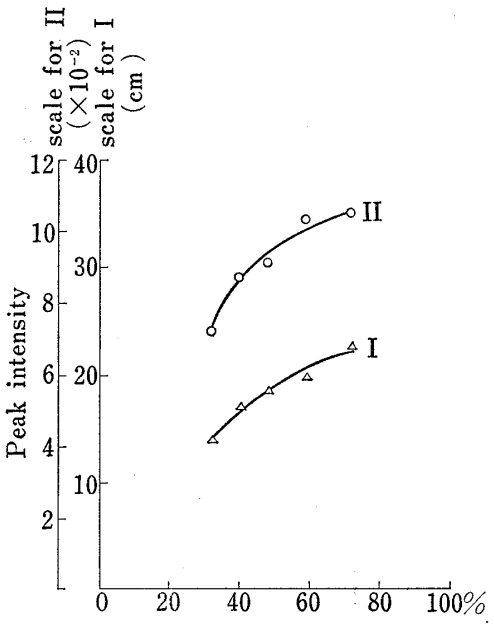

Fig. 3. Calibration Curves for Salicylic Acid in Salicylic Acid Plaster

Concn. of salicylic acid in plaster assayed by the chemical method.
I (△) by peak height
II (○) by peak area

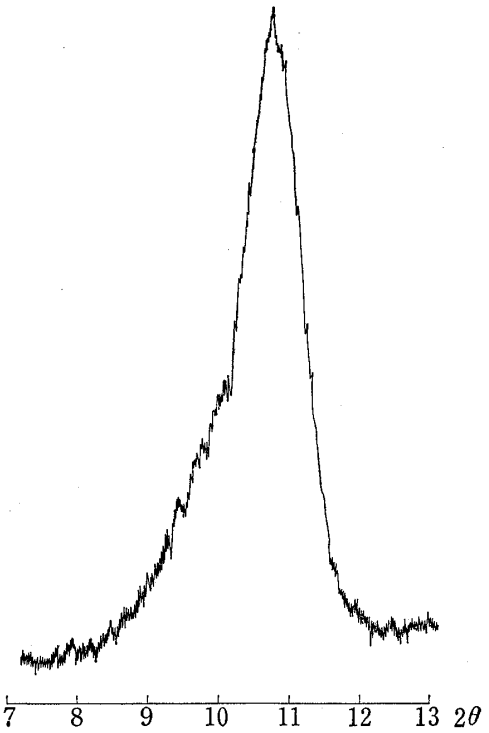

Fig. 4. X-Ray Differaction Pattern of Salicylic Acid in Salicylic Acid Plaster, obtained for the Reflection at 10.8° 2θ

Table I. Reproducibility of Diffraction Peak Intensity Values in Six Times Observations obtained from Six Synthetic Salicylic Acid Plasters

Plaster No.	Peak hight (cm)	Peak area[a)]
1	17.61	1114
2	22.41	1082
3	23.62	1087
4	19.29	976
5	20.10	1034
6	19.31	939
Mean value	20.39	1039
Standard dev. (%)	10.90	6.63

a) peak hight (cm) × scanning time (sec)/2

patterns of powdered salicylic acid, placebo plaster, and salicylic acid plaster on market are shown in Fig. 2, an examination of which showed that the diffraction peak at 10.8° 2θ is due to crystalline salicylic acid and the intensity of this peak is not influenced by the other peaks. The peak at 10.8° 2θ, therefore, was chosen as a basis for the determination. For each synthetic plaster the diffraction peak height and/or the peak area intensities were measured. After the diffraction peak intensity was measured, the plaster was dissolved and measured by the chemical method.[4)] The calibration curves were prepared by plotting the compositions against the peak height and/or peak area intensities. They are shown in Fig. 3.

The reproducibility of the values observed for six times are summarized in Table I. Table II shows the comparison of the chemical and diffraction analyses of 6 synthetic salicylic acid plasters. The results of the diffraction and chemical analyses of salicylic acid plaster on market are also shown in Table II.

4) "The United States Pharmacopoeia XVII" p. 575.

Table II. Comparison of Diffraction and Chemical Analyses of Individual Standard and Marketing Saliclyic Acid Plaster

Plaster No.	Diffraction analysis by peak hight (%)	Deviation from mean (%)	Diffraction analysis by peak area (%)	Deviation from mean (%)	Chemical analysis (%)	Deviation from mean (%)
	Standard salicylic acid plasters					
1	57.5	8.2	47.5	1.2	49.4	2.9
2	56.5	6.4	53.1	10.3	49.7	3.5
3	46.2	12.9	43.1	10·3	44.9	6.4
4	65.0	22.4	49.5	2.9	47.2	1.6
5	40.0	24.6	45.2	6.0	46.4	3.3
6	53.4	0.5	50.0	3.9	50.2	4.5
Av.	53.1	12.5	48.1	5.7	48.0	3.7

	Concn. indicated (%)	Diffraction[a] analysis by peak hight (%)	Diffraction[a] analysis by peak area (%)	Chemical[b] analysis (%)
	Salicylic acid plaster on the market			
	50.0	38.7	50.1	49.3

a) means of 6 times observations b) mean of 3 times observations

Results and Discussion

From the results of Tables I and II, it was found that there are remarkable differences between the reproducibility of the values obtained by the peak height and those obtained by the peak area. That is, the former is found to be worse than the latter. It was also noted that the diffraction technique based on the peak area intensity is as sensitive as chemical method. The cause of this remarkable discrepacy of reproducibility was discussed and was shown to be an asymmetry of diffraction line profile. The observed diffraction line profile of salicylic acid reflected at 10.8° 2θ of Bragg angle was shown in Fig. 4. This asymmetry of diffraction line profile might be due to the crystal size distribution, the dispersion of the crystallities, and the absorption and the thickness of matrix. Furthermore, the instrumental weight functions contribute to the breadth of the diffraction profile, as described by Klug and Alexander.[5] Thus, the better reproducibility was obtained by the use of the peak area intensity than the peak height intensity.

From the results of Table II, it can be concluded that the reproducibility measured by the peak area intensity may be adequate for practical purpose: furthermore, only 30 minutes is needed to assay six individual salicylic acid plasters, while the chemical method takes about one day.

5) H.P. Klug and L.E. Alexander, "X-Ray Diffraction Procedures," John Wiley & Sons Inc., New York, N.Y., 1954, pp. 253.