From this investigation, two typical patterns of characteristic absorption bands are obtained as shown in Fig. 2. These patterns will be available for use in the qualitative analysis of such compounds.

The origin of these characteristic absorption bands in the region of 1650~2000 cm^{-1} is not known, but it is presumed that they perhaps arise from the summation tones of the out-of-plane CH bending vibrations. If it is true, the out-of-plane CH bending vibrations of substituted naphthalenes are generally more complex than those of substituted benzenes, and it is natural that their summation bands should also be more complex. As theoretical studies on the naphthalene ring is insufficient to date, these problems will become more clear in future.

The author expresses his gratitude to Prof. S. Takagi of the University of Kyoto for his helpful guidance throughout the work, and to Messrs. K. Ōya, Y. Yamaguchi, H. Yamura, S. Yoshida, and H. Yoshida of this Company for their kind encouragements.

Experimental

Method—The spectra were obtained with a Perkin-Elmer Model 21 recording infrared spectrophotometer, using a sodium chloride prism. The spectra of all standard substances were determined in 0.1 mol./L. solution with sodium chloride sealed cells of 1.0 mm. thickness. CS_2 was used as a solvent.

Materials—All of the compounds studied were commercially available. These compounds were used without further purification unless doubt existed as to their purity. If purification was necessary, standard methods of recrystallization were used.

Summary

In monosubstituted naphthalene compounds, the charateristic absorption bands in the region of 1650~2000 cm^{-1} could be correlated with their structure.

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26. Kazuo Miyatake, Atsuji Okano, Kazuhiko Hoji, and Tōsaku Miki : Studies on the Constituents of *Digitalis purpurea* L. II.[1] Paper Partition Chromatography of Cardioglycosides from Digitalis Seeds.

(*Yanagishima Research Laboratory, Daiichi Seiyaku Co., Ltd.**)

Studies on the cardioglycosides of digitalis have made a tremendous advance in recent years and the majority of glycosides contained in the plants have been isolated and their structure clarified. Naturally, these advances owe much to the progress of isolation technique but the establishment of paper partition chromatography had much to do with that.

Studies on cardioglycosides contained in the seeds of *Digitalis purpurea* are being made but they are insufficient compared to those in the leaves, reports published to date being on the isolation of digitalinum verum,[2,3] gitoxin,[4] strospeside,[4] and struc-

* Hirakawabashi, Sumida-ku, Tokyo (宮武一夫，岡野淳二，傍士和彦，三木藤作).

1) Part I : J. Pharm. Soc. Japan, **75**, 25(1955).
2) T. Reichstein, K. Mohr : Pharm. Acta Helv., **25**, 246(1949).
3) Y. Sasakawa : J. Pharm. Soc. Japan, **74**, 474(1954).
4) D. Satoh, H. Ishii, Y. Ogawa : Ann. Rept. Shionogi Research Lab., **5**, 113(1955).

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turally unknown substance[2,5] of $C_{23}H_{48}O_{19}$.

In order to isolate the glycosides from digitalis seeds, some improvements were made on the known method of isolation. Instead of the general method of extracting the cardioglycoside from the filtrate, after removal of cholesterol digitonide and treatment with lead hydroxide, as reported in the preceding paper,[1] the filtrate was concentrated and the syrupy extract was submitted to adsorption chromatography on alumina, using water-saturated butanol as the developing solvent. The sparingly soluble glycoside that eluted out first and subsequent fractions of water-soluble glycosides were examined by paper partition chromatography using numerous solvent systems reported to date. As a consequence, it was found that a fairly large amount of unknown glycosides, more soluble in water than digitalinum verum, were present in the seeds. Isolation and determination of these unknown glycosides are impossible when the numerous solvent systems[6~9] described in literature in connection with paper chromatography of digitalis glycosides are used. Satisfactory results could not be obtained either by the use of the solvent system employed by Reichstein and others[10] for the paper chromatography of a series of strongly polar glycosides, such as ouabain, uzarin, and odoroside-G.

In order to isolate such unknown glycosides from digitalis seeds and also to find paper chromatographic technique best suited for efficient separation, the present writers devised an ascending paper chromatography, using water-saturated methyl ethyl ketone as the moving phase and water-saturated filter paper as the stationary phase, and a good separation and identification were effected.

Each fraction from the foregoing alumina chromatography was submitted to paper chromatography by the present method and by the use of various coloring agents, numerous spots were made clearly visible. The numerous spots, some of which have been confirmed as not being a glycoside, which showed coloration similar to cardioglycosides by these coloring agents may be classified into the three following groups, as indicated in Fig. 1.

A Group : 20% $SbCl_3$-$CHCl_3$ solution sprayed and heated for 3 mins. at 70~80°. Shows the same bluish white fluorescence under ultraviolet rays as gitoxigenin.

B Group : 1% HCl-MeOH solution[11] sprayed and heated for 5~7 mins. at 100°. Shows the same dark blue coloration as that from 2,6-desoxysugar.

C Group : 25% *m*-Dinitrobenzene-benzene solution sprayed, dried, and 10% NaOH solution sprayed. Shows up as bluish violet spot in positions other than those in the A and B groups.

Some of the spots in the A and B groups in Fig. 1 show the same Rf values as those of the known glycosides, such as gitoxin, strospeside, purpurea glycoside-A and -B, and digitalinum verum, as indicated in Fig. 2. Since these spots show the same Rf values by the known chromatographic methods,[7~9] those corresponding to purpurea glycoside-A and -B were considered to be actually those, although they were not isolated. Other spots not corresponding to any of the known digitalis glycosides were considered to be those of unknown glycosides, although they were not confirmed as a glycoside in the strict sense. These were numbered consecutively in the descending order of Rf values within each group. As a result, the unknown glycosides found by

5) M. Okada, A. Yamada : J. Pharm. Soc. Japan, **73**, 525(1953).
6) R. Tschesche, G. Grimmer, F. Sechofer : Chem. Ber., **86**, 1235(1953).
7) T. Reichstein, O. Schindler : Helv. Chim. Acta, **34**, 108(1952).
8) Y. Sasakawa : J. Pharm. Soc. Japan, **75**, 946(1955).
9) F. Kaiser : Chem. Ber., 88, 556(1955).
10) E. Schenker, A. Hunger, T. Reichstein : Helv. Chim. Acta, **37**, 680(1954).
11) D.H. Gregg, O. Gisvold : J. Am. Pharm. Assoc., Sci. Ed., **43**, 106(1954); Limit of detection by coloration : 0.63 γ of acetyldigoxin.

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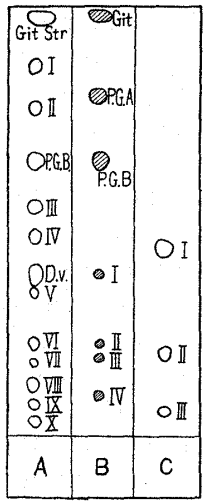

Fig. 1.
Paper Partition Chromatography of Cardioglycosides and Allied Substances in the Seed of *Digitalis Purpurea* L.

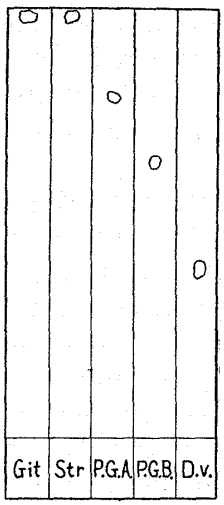

Fig. 2.
Paper Partition Chromatography of Known Cardioglycosides in *Digitalis Purpurea* L.

* Toyo Roshi No. 50, ascending method, at 18~25°.
Moving phase : Water-saturated methyl ethyl ketone. Stationary phase : Water.
Coloring agent : A-20% $SbCl_3$-$CHCl_3$ solution. B-1% HCl-MeOH solution
C-Raymond reaction.
Git : Gitoxin. Str : Strospeside. P.G.A. : Purpurea glycoside-A.
P.G.B. : Purpurea glycoside-B. D.v. : Digitalinum verum.

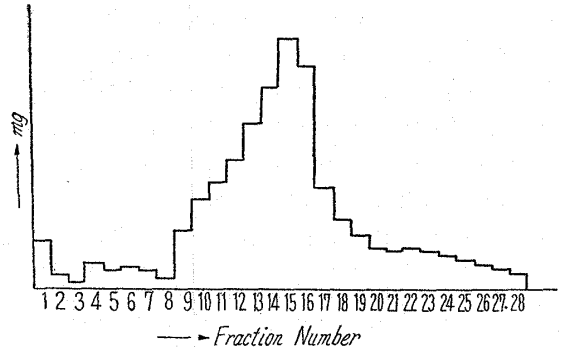

Fig. 3. Partition Chromatography of Digitalinum verum Fraction

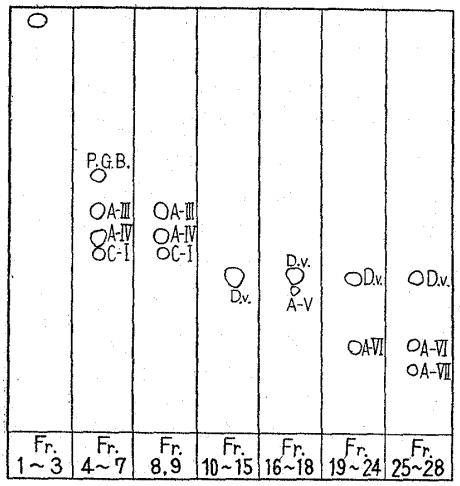

Fig. 4. Paper Partition Chromatography of Each Fraction from Partition Chromatography of Digitalinum verum Fraction

this paper partition chromatography totalled 17 in all, 10 in A group (A-I to A-X), four in B group (B-I to B-IV), and three in C group (C-I to C-III).

The solvent system of methyl ethyl ketone-water used in this experiment shows good separation efficiency in paper chromatography as well as in column partition chromatography. The fraction containing digitalinum verum, obtained by alumina chromatography, was submitted to partition by a column with Celite 535 (Johns-Manville product) as a carrier and the use of this solvent afforded crystals of pure digitalinum verum in a good yield of 0.15% (Fig. 3). It has been said that it is difficult to obtain digitalinum verum in crystalline state by the existing method of separation and Sasakawa[3] recently obtained crystalline digitalinum verum by the use of counter-current distribution.

Each fraction from the foregoing column partition chromatography was submitted to paper partition chromatography and the results obtained are presented in Fig. 4.

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Fraction Nos. 10~15, showing a single spot of digitalinum verum alone, was recrystallized from hydrated methanol and crystals were easily obtained. This substance was proved to be digitalinum verum from its melting point, admixture,* optical rotation, coloration reaction, hydrolysis, formation of a monoacetate, hexaacetate, and Rf value in paper chromatography.

Fraction Nos. 16~18 that followed gave a spot of digitalinum verum and a spot for a small amount of unknown glycoside, substance A-V. Recrystallization only resulted in colloidal precipitation and only a small amount of crystals separated out on seeding the crystals of digitalinum verum obtained from fractions 10~15.

The recrystallization mother liquor obtained after separation of digitalinum verum from fractions Nos. 10~15 was found to contain a trace of substance A-V by giving a spot by this paper partition chromatography and therefore difficult to obtain crystals of digitalinum verum further from the mother liquor. Further purification of digitalinum verum containing substance A-V by column partition chromatography finally gave crystals of digitalinum verum.[12]

It is considered from the foregoing results that the reason why digitalinum verum has not been obtained in crystalline state, in spite of its studies for a long time, is because it had been handled without knowing the presence of a similar glycoside, the foregoing substance A-V.

Further isolation of substance A-V is being continued but its content in the seeds seems to be far smaller than that of digitalinum verum.[13] Tschesche and others[14] had isolated a benzene-soluble acetate from crude digitalinum verum hexaacetate, obtained from the leaves of *Digitalis lanata*, and a repeated fractional crystallization of this acetate had afforded a minute amount of glucogitofucoside acetate. They reported that the glucogitofucoside obtained by its saponification gave the same Rf value as that of digitalinum verum. The crude substance A-V obtained in the present series of experiments was hydrolyzed with an acid and the hydrolyzate was submitted to paper chromatography. The paper chromatogram revealed spots assumed as that of dianhydrogitoxigenin as the aglycone and those as glucose and fucose as the sugars, so that the foregoing spot of substance A-V must be that of glucogitofucoside.

The writers are indebted to Dr. Junzo Shinoda, President of this Company, and to Mr. I. Nakano, Director of the Yanagishima Factory, for kind and unfailing guidance throughout the course of this work. They are also indebted to Messrs. Negishi and Abe for elemental analyses and to Messrs. Uemura and Kunikata of the Narita Farm of this Company for collecting the seeds used in this work.

Experimental

Paper Partition Chromatography

1) **Apparatus**—A large, thick-walled glass cylinder (internal diam., 14 cm., height, 45 cm.) with a ground-glass lid, same as that used by Sasakawa[3] and in general paper partition chromatography, was used. Cylindrically folded filter paper was stood along the wall of the vessel and the vessel was completely saturated with the vapor of MeCOEt.

* Grateful acknowledgement is made to Mr. Sasakawa of Takeda Research Laboratories for kind donation of a valuable sample of digitalinum verum.

12) Acetylation of digitalinum verum containing substance A-V easily gives a crystalline acetate whose melting point and optical rotation are almost identical with those of digitalinum verum acetate.

13) The fraction Nos. 16~18 of digitalinum verum containing substance A-V was hydrolyzed and submitted to paper partition chromatography for examination of the sugars. Only the spots for glucose and digitalose were identified but when an extremely large amount was submitted to paper partition chromatography, a spot appeared between those of the foregoing two sugars. The leaves of *D. purpurea* also contain this substance A-V and the amount seems to be much larger in proportion to digitalinum verum, than the ratio of two substances in the seed.

14) R. Tschesche, G. Grimmer : Chem. Ber., 88, 1569(1955).

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2) **Method**—Toyo Roshi No. 50 was cut into strips of 5~10 cm. in width and a line was drawn 6 cm. from one end for spotting the samples. The filter paper was then soaked in a mixture of water and Me_2CO (1:4 by vol.) for 5 mins., taken out, and pressed between two sheets of large filter paper. Three to seven samples were spotted at the original line drawn earlier, allowed to stand until no odor of Me_2CO was perceptible, and then developed in the cylinder by the ascending method, for 3~4 hrs. The coloration followed the method given in the text. Since the Rf value varies with the amount of water soaked in the paper, a standard substance was always developed with the samples to make comparative examination.

Adsorption Chromatography of Crude Cardioglycosides—Two kg. of seeds were pulverized, defatted, extracted, and cholesterol digitonide removed. The filtrate was treated with $Pb(OH)_2$ and the extract therefrom was dried with 50~100 mesh silica gel. A suspension of 1.2 kg. of alumina (Merck product) in water-saturated BuOH was flown into a chromatographic column (6×42 cm.) and when the solvent on top of the column became small, a suspension of the extract mixed with silica gel in water-saturated BuOH was added gently. The column was then developed with the same solvent and fractions of 200 cc. each were collected. The elution was made until the coloration of H_2SO_4 layer in the Keller-Kiliani reaction and Legal reaction became negative. Each fraction was examined by paper partition chromatography and results obtained are given in Table I.

Table I.

Fraction No.	Keller-Kiliani Reaction		Legal reaction	Paper Partition Chromatography
	AcOH layer	H_2SO_4 layer		
1~2	Dark	Red	+	Str., Git., A-I
3	〃	〃	+	PGA, PGB, A-I, A-II, D. v.
4~7	Colorless	〃	+	D. v., A-III, -IV, -V, B-I
8~9	〃	〃	+	D. v., A-V, -VI, C-I
10~13	〃	Orange red	+	A-VI, VII, VIII, B-II, -III, C-I, -II
14~16	〃	Red	+	A-VIII, -IX, B-III, -IV, C-II
17~20	〃	Orange red	+	A-IX, -X, B-IV, C-III
21~23	〃	Red	+	A-X, C-III

Partition Chromatography

First Partition Chromatography—The method of Reichstein, *et al.*[15] was followed. Water-saturated MeCOEt was added to a well-stirred mixture of 600 g. of Celite 535 in 600 cc. of water saturated with MeCOEt, allowed to stand for a few hrs. with occasional agitation, and filled in a glass tube (internal diam., 5 cm.) provided with a cock at one end, while pressing the Celite with a glass rod. When the amount of liquid on top of the column became small, the cock was closed. A total of about 6 g. of crude digitalinum verum from fraction Nos. 3~9 (Table I) was dissolved in MeOH, added to 20 g. of Celite 535, stirred thoroughly to make a homogeneous mixture, and dried. Further 20 g. of Celite 535 and 30 cc. of water were added to this mixture, stirred thoroughly, and placed on top of the column. This was developed with water-saturated MeCOEt and fractions of 500 cc. each were collected. Partitions shown in Fig. 3 were obtained and composition of each fraction is indicated in Fig. 4.

Fraction Nos. 10~15 (2.63 g.) was recrystallized from hydrated MeOH to 1.495 g. of needles, m.p. 230~240°.[16] Paper partition chromatography of the recrystallization mother liquor indicated the presence of a minute amount of substance A-V.

Fraction Nos. 16~18 (1.035 g.) was combined with the foregoing mother liquor (2.17 g.) and recrystallized from hydrated MeOH, seeded with crystals of digitalinum verum. A small amount of needles, m.p. 231~234°(0.385 g.), was obtained. The mother liquor failed to yield any more crystals.

Second Partition Chromatography—Fraction Nos. 19~24 (0.72 g.) (Fig. 3) and the foregoing recrystallization mother liquor were combined (total, 2.17 g.) and submitted to chromatography under the same conditions as in the first chromatography. Needle crystals of m.p. 231~234° (530 mg.) were also obtained from the digitalinum verum fraction. The crystallization mother liquor here obtained revealed spots of substances A-V and B-I, besides digitalinum verum, in paper chromatogram. Since this fraction failed to undergo crystallization, it was repeatedly submitted to adsorptions and partition chromatography and a total of 3 g. (0.15% from the seeds) of digitalinum verum was obtained as crystals.

Digitalinum verum—One g. of crystalline digitalinum verum, m.p. 231~234°, was recrystallized 3 times from hydrated MeOH and 0.6 g. of colorless needles, m.p. 241~244°, was obtained. The mother liquor in this case showed no spot of the substance A-V in paper partition chromatography. $[\alpha]_D^{28}$ +0.9°±2°(c=2.65, MeOH). *Anal.* Calcd. for $C_{36}H_{56}O_{14}$: C, 60.66; H, 7.92. Calcd. for $C_{36}H_{56}O_{14}$·

15) H. Hegedus, Ch. Tamm, T. Reichstein: Helv. Chim. Acta, **36**, 364(1953).
16) All m.p.s were determined on a Kofler block. Values are uncorrected.

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$2H_2O$: C, 57.67; H, 8.01. Found : C, 57.92; H, 8.27.

Hydrolysis of Digitalinum verum—A mixture of 50 mg. of digitalinum verum (m.p. 241~244°) in 10 cc. of 50% MeOH containing 3.5% of HCl was refluxed on a water bath for 6 hrs. while bubbling CO_2. MeOH was distilled off under a reduced pressure and the residual colorless needle crystals were recrystallized from dil. MeOH to needles, m.p. 212~214°. Extraction of the reaction mother liquor with $CHCl_3$ also afforded the same crystals. Total yield, 20 mg. No depression of m.p. occurred on admixture with dianhydrogitoxigenin obtained from strospeside* and from gitoxin. Ultraviolet absorption spectrum and paper partition chromatography† of this substance were identical with those of dianhydrogitoxigenin.

The aqueous solution was deacidified through Amberlite IR-4B, the solution was evaporated, and the syrupy residue was submitted to paper partition chromatography using Toyo Roshi No. 50, developed with BuOH : AcOH : H_2O (4 : 1 : 5 by vol.) by the ascending method at 24°. Coloration with aniline hydrogen phthalate revealed two brown spots at Rf 0.11 and 0.40, corresponding to the Rf 0.11 of glucose and 0.39 of digitalose, the sugar obtained by the hydrolysis of strospeside.

Digitalinum verum Hexaacetate—Acetylation by the usual method with Ac_2O and pyridine and recrystallization from Me_2CO-Et_2O mixture afforded the hexaacetate as colorless needles, m.p. 182~186°/228~231°; $[\alpha]_D^{28}$ −16.9°±2°(c=2.70, $CHCl_3$). *Anal.* Calcd. for $C_{48}H_{68}O_{20}$ (Hexaacetate): C, 59.73; H, 7.12. Found : C, 59.51; H, 7.17.

Digitalinum verum Monoacetate—In accordance with the method of Reichstein, *et al.*,[2] 510 mg. of the foregoing hexaacetate was dissolved in 51 cc. of MeOH, a solution of 510 mg. of $KHCO_3$ dissolved in 10 cc. of water was added, stoppered closely, and allowed to stand for 16 days at room temperature. To this mixture, 8 cc. of water was added, evaporated to about 15 cc. under a reduced pressure, at 20°, and the residual solution was extracted 5 times with 15 cc. each of a mixture (2 : 1 by vol.) of $CHCl_3$ and EtOH. The combined extract was washed with a small amount of water, dried over anhyd. Na_2SO_4, and concentrated under a reduced pressure. The residue was recrystallized from Me_2CO-Et_2O and MeOH-H_2O to needles, m.p. 238~246°, $[\alpha]_D^{21}$ −2.7°±2°(c=1.28, MeOH). Its paper partition chromatography with water-saturated MeCOEt gave Rf values about 1.7~1.8 times that of digitalinum verum and analytical values agreed with those calculated for digitalinum verum monoacetate. *Anal.* Calcd. for $C_{38}H_{58}O_{15}$ (Monoacetate) : C, 60.46; H, 7.73. Found : C, 60.18; H, 7.80.

Hydrolysis of Substance A-V—The fraction of digitalinum verum containing the substance A-V was submitted to partition chromatography under the same conditions as for the purification of digitalinum verum and by examination with paper partition chromatography, substance A-V containing a small amount of digitalinum verum was obtained. This was hydrolyzed under the same conditions as for digitalinum verum. MeOH residue was extracted with $CHCl_3$ and $CHCl_3$-soluble portion, *per se*, was submitted to paper partition chromatography, giving a spot with the same Rf as that of dianhydrogitoxigenin. The aqueous solution was treated with Amberlite IR-4B, concentrated, and submitted to the same paper partition chromatography as for the sugars of digitalinum verum. Two brown spots at Rf 0.11 and 0.26, and a weak-colored spot at Rf 0.40 were obtained. Of these, those at Rf 0.11 and 0.40 correspond respectively to those of glucose and digitalose. The spot at Rf 0.26 was extracted and again developed with upper layer of 4 : 1 : 2-mixture of BuOH : AcOH : H_2O, by which a spot of Rf 0.40 was obtained. This was found to agree with the Rf value of fucose.

Summary

It was found that various glycosides are present in the seeds of *Digitalis purpurea* and these were found to be separatory identifiable by paper partition chromatography using filter paper soaked in water and methyl ethyl ketone saturated with water as the developing solution. By the use of three kinds of coloring agents, a total of 17 spots were found, assumed to be those of unknown glycosides. This confirmed that a fairly large amount of water-soluble glycosides was present. The use of the foregoing solvent system for column partition chromatography resulted in extremely easy purification of digitalinum verum which was obtained finally as crystals. A presence of a small amount of cardioglycoside, extremely similar to digitalinum verum and very

* For the donation of valuable strospeside crystals, deep gratitude is expressed to Mr. Daisuke Satoh of Shionogi Research Laboratory.

† Toyo Roshi No. 50; developed with upper layer of cyclohexane : AcOH : $CHCl_3$: H_2O (100 : 30 : 20 : 1) by the ascending method at 22°. Rf 0.56.

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difficult to be separated from it, was detected and it was assumed to be glucogitofucoside, separated as the acetate from the leaves of *Digitalis lanata*, by paper partition chromatography of the sugar portion of the acid hydrolyzate.

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27. Kazuo Miyatake, Atsuji Okano, Kazuhiko Hoji, and Tōsaku Miki : Studies on the Constituents of *Digitalis purpurea* L. III. Gitostin, a New Cardiotonic Glycoside from Digitalis Seeds.

(*Yanagishima Research Laboratory, Daiichi Seiyaku Co., Ltd.**)

It was shown in the preceding paper[1] that a large number of unknown cardioglycoside-like substances were present, besides the known glycosides such as digitalinum verum, in the seeds of *Digitalis purpurea*. First, the fraction of a strongly polar glycoside, thought to be contained in a comparatively large amount, was taken up. The presence of a similar glycoside in the leaves was detected by paper partition chromatography and Sasakawa[2] also detected an unknown glycoside of gitoxigenin series by paper partition chromatography.

Reichstein and others employed the technique of hydrolysis with various enzymes for strongly polar glycosides and used the so-called secondary glycosides so formed for the isolation. Since the method of isolation described in the preceding paper had beed established, the primary glycoside was used, *per se*, for the separation.

The fraction containing a substance which gives a spot with smaller Rf value than that of digitalinum verum and which is more soluble in water, the fraction Nos. 10～16 (see Part II, Table I on p. 161 of this issue) obtained on alumina chromatography, was treated by the method of purification used for digitalinum verum.[1] A new cardiotonic glycoside was successfully separated.

This fraction Nos. 10～16 contains a small amount of various substances, besides several kinds of cardioglycosides. It was therefore submitted to alumina chromatography using water-saturated butanol to remove the occluded substances. The cardioglycosides were developed rapidly and each fraction was submitted to paper partition chromatography as described in the preceding paper. It was thereby assumed that the substance A-VIII would be present in the largest amount. Therefore, fraction No. 11, which contained the largest amount of A-VIII, was recrystallized but only a small amount crystallized out, the majority remaining in the solution. This fraction was then submitted to partition chromatography with Celite 535 (Johns-Manville product) as a carrier and water-saturated methyl ethyl ketone as the developing solvent, by which the substance A-VIII was isolated in a pure state and easily crystallized.

Repeated recrystallization of this substance from water-saturated butanol and hydrated ethanol-ether or methanol-ether afforded colorless needle crystals (Fig. 1), m.p. 252～254°; $[\alpha]_D^{22}$ −3.4°±2°(c=2.14, MeOH). It is extremely bitter to the taste, easily soluble in methanol and hydrated ethanol, soluble in dehydrated ethanol and water, and insoluble in chloroform, ether, and benzene. It gives positive Legal and Raymond reactions and its ultraviolet spectrum exhibits maximum absorption at 218 mμ (EtOH),

* Hirakawabashi, Sumida-ku, Tokyo (宮武一夫, 岡野淳二, 傍士和彦, 三木藤作).

1) Part II : This Bulletin, **5**, 157(1957).

2) Y. Sasakawa : J. Pharm. Soc. Japan, **75**, 947(1955).

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