2,3,4,5-Tetramethylpyridine (XIV)—3.5 g. of the chloromethyl compound (XIII) in 150 cc. of methanol was reduced in hydrogen stream with 1 g. of Pd-$CaCO_3$ (Pd: 5%) as a catalyst. The absorption of hydrogen, 480 cc. (theoretical volume: 497 cc.). The product was a colorless liquid, b.p. 218°. Yield, 2.5 g. (83%). Picrate, yellow needles, m.p. 166°. *Anal.* Calcd. for $C_9H_{13}N \cdot C_6H_3O_7N_3$ (2,3,4,5-Tetramethylpyridine picrate): C, 49.45; H, 4.39; N, 15.38. Found: C, 49.75; H, 4.74; N, 15.72. Mercuric chloride salt, colorless needles, m.p. 141°. *Anal.* Calcd. for $C_9H_{13}N \cdot HCl \cdot HgCl_2$: N, 3.16. Found: N, 3.01. Chloroplatinate, yellow needles, m.p. 153~154°.

Summary

2,3,4,5-, 2,3,4,6-, and 2,3,5,6-Tetramethylpyridines were synthesised for the purpose of comparing these compounds with polymethylpyridines found in coal tar bases.

(Received March 27, 1953)

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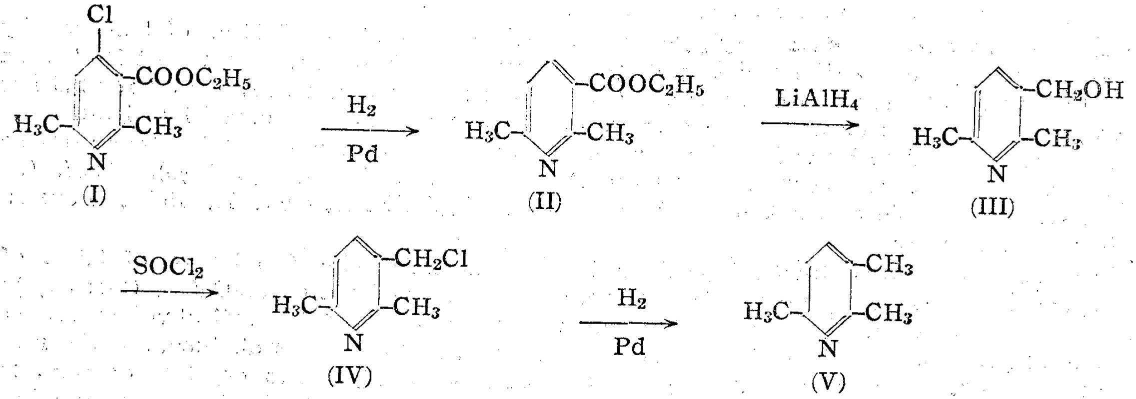
30. Kyousuke Tsuda, Nobuo Ikekawa, Akira Iino, Minoru Furukawa, and Tetsuyasu Hattori: Studies on Coal Tar Bases. II[1]. Synthesis of Trimethylpyridines (1).

(*Pharmaceutical Institute, Medical Faculty, University of Kyushu**)

Having the same object as for the previous report[2], four trimethylpyridines were prepared with the exception of 2,4,6- and 3,4,5-trimethylpyridine. There are some references to the synthesis of 2,4,6-[3], 2,3,4-[4~6], and 2,3,6-trimethylpyridine[4], but the others have not been synthesized as yet.

2,3,6-Trimethylpyridine—3-Carbethoxy-2,6-dimethylpyridine (II), prepared by catalytic reduction of 3-carbethoxy-4-chloro-2,6-dimethylpyridine (I)[7], was reduced by lithium aluminum hydride to 3-hydroxymethyl compound (III), and derived to 2,3,6-trimethylpyridine (V) by chlorination and catalytic reduction, as a liquid of b.p. 173°. Picrate, yellow needles, m.p. 144.5~145.5°; mercuric chloride salt, m.p. 105~106°; chloroplatinate, m.p. 136~137°.



2,3,5-Trimethylpyridine—Errera[8] synthesized 2,5-dimethylpyridine via 3-carbethoxy-2,5-dimethyl-6-hydroxypyridine (VI)**. By the chlorination and catalytic reduction of (VI),

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* Hakata, Fukuoka (津田恭介, 池川信夫, 飯野 彰, 古川 稔, 服部哲靖).

[1,2] This Bulletin, **1**, 122 (1953).

[3] A. Hantzsch: Ann., **215**, 1 (1882); Ber., **18**, 1744 (1885).

[4] M. P. Oparina: Ber., **64**, 569 (1931).

[5] I. Guareschi: Chem. Zentr., **70**, I, 289 (1899).

[6] R. L. Frank, R. P. Seven: J. Am. Chem. Soc., **71**, 2629 (1949).

[7] A. Michaelis: Ann., **366**, 324 (1909).

[8] G. Errera: Ber., **34**, 111, 3691 (1901).

** This compound was obtained by cyclization of cyanopropionic amide and ethoxymethyleneacetoacetic ester, with conc. hydrochloric acid, in 22% yield.

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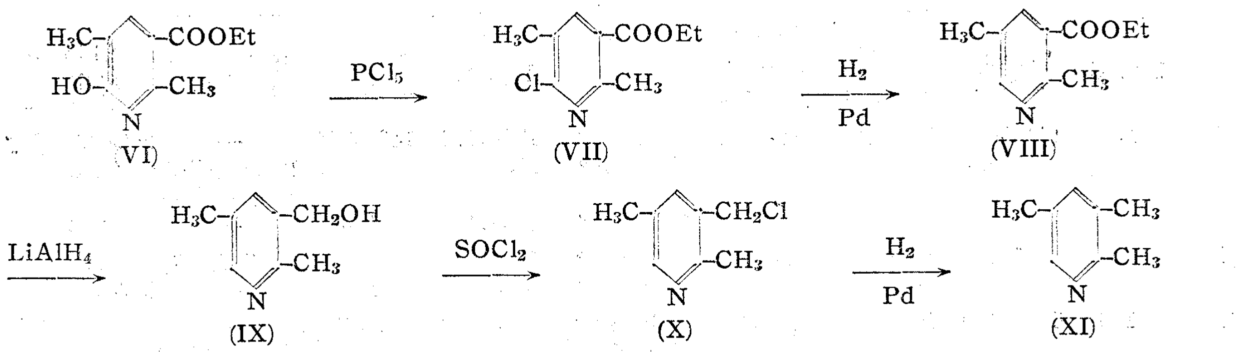
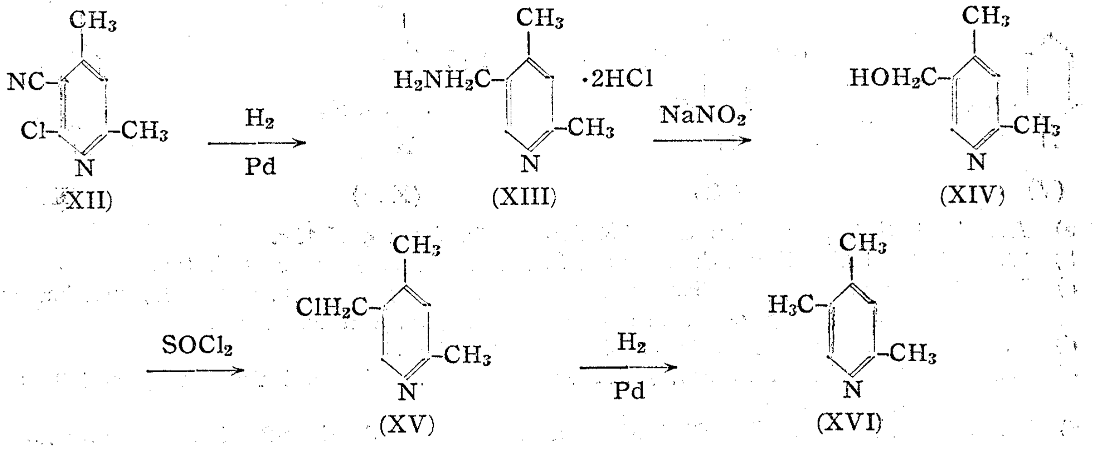
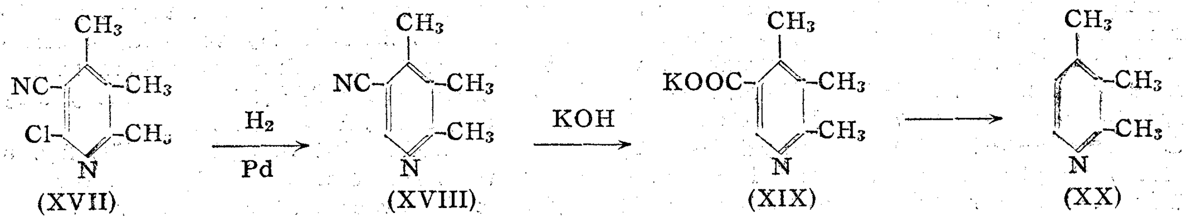
we derived it to 3-carbethoxy-2,5-dimethylpyridine (VIII), and further to 2,3,5-trimethylpyridine (XI) by reduction using lithium aluminum hydride, chlorination, and catalytic reduction. Product was obtained as colorless liquid, b.p. 184°. Picrate, yellow needles, m.p. 181°; mercuric chloride salt, m.p. 110~111°; chloroplatinate, m.p. 146~147°.



2,4,5-Trimethylpyridine—2,4-Dimethyl-5-hydroxymethylpyridine, prepared from 6-chloro-5-cyano-2,4-dimethylpyridine (XII)[9] by Mariella and Leech[9], was derived to the 5-chloromethyl compound (XV), which was reduced catalytically to 2,4,5-trimethylpyridine (XVI), b.p. 188°, giving a picrate of needles, m.p. 159~160°; mercuric chloride double salt, m.p. 101°; chloroplatinate, m.p. 189~190°.



2,3,4-Trimethylpyridine—2,3,4-Trimethyl-5-cyanopyridine (XVIII), obtained from 6-chloro-5-cyano-2,3,4-trimethylpyridine (XVII), described in our previous report[1], by catalytic reduction, was derived to 2,3,4-trimethylpyridine (XX) by saponification and decarboxylation, as a liquid of b.p. 187°. Picrate, needles, m.p. 164°; mercuric chloride double salt, m.p. 119~120°; chloroplatinate, m.p. 177~179°. Oparina[4] synthesized 2,3,4-trimethylpyridine from 6-chloro-2,3,4-trimethylpyridine and reported the picrate of this base as melting at 164.5°. Frank and Seven[6] obtained this base (b.p$_{25}$ 78~81°; picrate, m.p. 163~164°) from vinyl methyl ketone and ammonium acetate. Our product was identical with the constants given in these literatures.



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[9] Mariella (R. P. Mariella, J. L. Leech: J. Am. Chem. Soc., 71, 331 (1949)) reported m.p. of this compound as 94.5~95° but the present one gave m.p. 99~100°.

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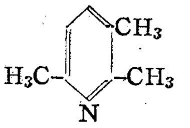
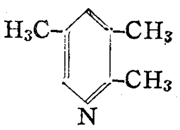
Infrared absorption spectrograms of trimethylpyridines will be described in the following report, the physical constants of these bases and hitherto reported are as follows:

TABLE I Properties of Trimethylpyridines

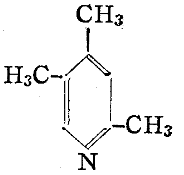
	Present Authors'				Literature				
	b.p.°C	Picrate m.p.°C	$HgCl_2$ salt m.p.°C	Chloroplatinate m.p. °C		b.p. °C	Picrate m.p. °C	$HgCl_2$ salt m.p. °C	Chloroplatinate m.p. °C
V	173	144.5~145.5	105~106	136~137	Eckert[a]	173~174	143~144	—	250~252 (H_2O)
					Eguchi[b]	172.8	148	104($2HgCl_2$) 165($6HgCl_2$)	220
					Oparina[c]	173~174	146	—	228
XI	184	181	110~111	146~147	Eguchi[b]	186.8	184	110($3HgCl_2$)	212
					Oparina[c]	183~185	183	—	227~228
XVI	188	159~160	100~101	189~190	Ahrens[d]	165~168	128~131	—	205(H_2O)
					Eguchi[b]	189.8	161	112($3HgCl_2$)	192
					Oparina[c]	188~190	159~160	—	191~192($2H_2O$)
XX	187	164	119~120	177~179	Guareschi[e]	185~188	—	—	211~212
					Eckert[a]	182~183	179	—	211~212
					Oparina[f]	—	164.5	—	—
					Frank[g]	—	163~164	—	—



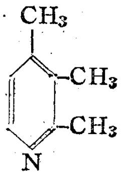
(V)



(XI)



(XVI)



(XX)

a) A. Eckert, S. Loria: Monatsh., 38, 225 (1917), from coal tar.
b) T. Eguchi: Bull. Chem. Soc. Japan, 3, 227, 235 (1928), from shale tar.
c) M. P. Oparina: Ber., 64, 562 (1931), from coal tar; *ibid.*, 64, 569 (1931), synthesized from acetone, methyl ethyl ketone, formaldehyde, and ammonia.
d) F. B. Ahrens: Ber., 29, 2996 (1896), from coal tar.
e) I. Guareschi: Chem. Zentr., 71, I, 1161 (1900), synthesized from 5-cyano-2,3,4-trimethyl-6-pyridone.
f) M. P. Oparina: Ber., 64, 569 (1931), synthesized from 6-chloro-2,3,4-trimethylpyridine.
g) R. L. Frank, R. P. Seven: J. Am. Chem. Soc., 71, 2629 (1949), synthesized from methyl vinyl ketone and ammonia.

This work was supported by the Grant from the Ministry of Welfare.

Experimental

3-Carbethoxy-2,6-dimethylpyridine (II)—When 17 g. of 3-carbethoxy-4-chloro-2,6-dimethylpyridine dissolved in 60 cc. of methanol containing 2 g. of $Pd-CaCO_3$ (Pd: 15%) was shaken in hydrogen stream, 1780 cc. of H_2 was absorbed during ca. 7 hrs. (theoretical amount: 1780 cc.). Filtration of palladium and evaporation of methanol gave the hydrochloride of (II). The colorless liquid of this free base showed b.p$_{11}$ 122~124°. Yield, 13.5 g. (92.5%).

2,6-Dimethyl-3-hydroxymethylpyridine (III)—To 2.5 g. of $LiAlH_4$ suspended in 40 cc. of dry ether, solution of 10 g. of (II) was added slowly under stirring by which greyish precipitate appeared instantly. After refluxing on a water bath for an hour, water was added to the reaction mixture until the grey color disappeared and the precipitate was filtered. By the evaporation of ether after drying, white crystals remained, which were recrystalized from petroleum benzine to white needles, m.p. 72.5~73°. Yield, 5.5 g. (72%). *Anal.* Calcd. for $C_8H_{11}ON$(2,6-Dimethyl-3-hydroxymethylpyridine): C, 70.00; H, 8.03; N, 10.21. Found: C, 69.28; H, 7.81; N, 9.90.

3-Chloromethyl-2,6-dimethylpyridine (IV)—To 5 g. of well-chilled thionyl chloride, 2 g. of 3-hydroxymethyl compound was added under stirring and the mixture was heated on a water bath for 1 hour. After evaporation of the excess of thionyl chloride in vacuum, the residue was treated in the usual manner. Yield of white crystals, m.p. 45~46°, 1.9 g. (84%). *Anal.* Calcd. for $C_8H_{10}NCl$ (3-Chloromethyl-2,6-dimethylpyridine): C, 61.8; H, 6.4; N, 9.01. Found: C, 61.65; H, 6.51; N, 8.50.

2,3,6-Trimethylpyridine (V)—One g. of 3-chloromethyl compound dissolved in 30 cc. of methanol was reduced in the presence Pd-$CaCO_3$ (Pd: 5%) as a catalyst. Product of colorless liquid, b.p. 173°. Yield, 0.7 g. (90%). Picrate, yellow plates, m.p. 144.5~145.5°. *Anal.* Calcd. for $C_8H_{11}N\cdot C_6H_3O_7N_3$ (2,3,6-Trimethylpyridine picrate): C, 48.00; H, 4.00; N, 16.00. Found: C, 48.12; H, 3.96; N, 15.87. Mercuric chloride salt, colorless needles, m.p. 105~106°. *Anal.* Calcd. for $C_8H_{11}N\cdot HCl\cdot HgCl_2$: N, 3.26. Found: N, 3.12. Chloroplatinate, yellow needles, m.p. 136~137°.

3-Carbethoxy-6-chloro-2,5-dimethylpyridine (VII)—A mixture of 10 g. of 2,5-dimethyl-3-carbethoxy-6-pyridone and 15.1 g. of phosphorus pentachloride was refluxed at 160~170° in an oil bath for 8 hours. The residue after evaporation of phosphoryl chloride in vacuum, was poured into ice water, the solution was neutralized by sodium carbonate, and extracted with ether. Ether extract gave a brown crude product, which was recrystallized from petroleum ether to white plates, m.p. 45°. Yield, 10 g. (92%). *Anal.* Calcd. for $C_{10}H_{12}O_2NCl$ (3-carbethoxy-6-chloro-2,5-dimethylpyridine): C, 56.3; H, 5.6. Found: C, 55.83; H, 5.61.

3-Carbethoxy-2,5-dimethylpyridine (VIII)—Ten g. of (VII) dissolved in methanol was reduced catalytically with 1 g. of Pd-C (Pd 20%). Absorption of hydrogen, 1238 cc. at 20° (theoretical amount: 1170 cc.). Residue obtained by the evaporation of methanol was dissolved in water, made alkaline with sodium carbonate, and extracted with ether. From this ether extract, yellow liquid of b.p$_{15}$ 125° was obtained. Needles of this base melted at 27~28°. Yield, 6.5 g. (75%). Picrate of yellow needles, m.p. 143°. *Anal.* Calcd. for $C_{10}H_{15}O_2N\cdot C_6H_3O_7N_3$ (3-Carbethoxy-2,5-dimethylpyridine picrate): N, 15.29. Found: N, 14.80.

2,5-Dimethyl-3-hydroxymethylpyridine (IX)—To 1.8 g. of lithium aluminum hydride suspended in 100 cc. of dry ether, 5 g. of the above ester was added under stirring, by which white precipitate appeared. The mixture was refluxed on a water bath for 3 hours, and treated in the usual manner, from ether layer white needles, which melts at 73.5°, are obtained. Yield is 2.6 g. (70%). *Anal.* Calcd. for $C_8H_{11}ON$ (2,5-dimethyl-3-hydroxymethylpyridine): N, 11.7. Found: N, 11.11.

2,5-Dimethyl-3-chloromethylpyridine (X)—2.5 g. of 2,5-dimethyl-3-hydroxymethylpyridine was chlorinated by 4.5 g. of thionyl chloride by the same method as above. White needles, m.p. ca. 30°, was obtained from ether. Yield, 2 g. (90%). Picrate, yellow needles, m.p. 140.5° *Anal.* Calcd for $C_8H_{10}NCl\cdot C_6H_3O_7N_3$ (2,5-Dimethyl-3-chloromethylpyridine picrate): C, 43.68; H, 3.64; N, 14.56. Found: C, 43.35; H, 3.23; N, 14.68.

2,3,5-Trimethylpyridine (XI)—Two g. of chloromethyl compound was reduced catalytically with Pd-C (Pd: 15%) in methanol. Absorption of hydrogen, 540 cc. (theoretical amount: 578 cc.). Treatment by the usual manner yielded 1.5 g. (85%) of 2,3,5-trimethypyridine, b.p. 184°, picrate yellow needles, m.p. 181°. *Anal.* Calcd. for $C_8H_{11}N\cdot C_6H_3O_7N_3$ (2,3,5-Trimethylpyridine picrate); C, 48.00; H, 4.00; N, 16.00. Found: C, 48.64; H, 3.98; N, 16.28. Mercuric chloride salt, colorless needles, m.p. 110°~111°. *Anal.* Calcd. for $C_8H_{11}N\cdot HCl\cdot 2HgCl_2$: N, 1.99. Found: N, 1.75. Chloroplatinate, yellow needles, m.p. 146~147°.

5-Chloromethyl-2,4-dimethylpyridine (XV)—0.9 g. of 2,4-dimethyl-5-hydroxymethylpyridine was chlorinated with 3 g. of thionyl chloride according to the manner described. The chloromethyl compound melted at 52~54°. Yield, 0.9 g. (78%). Picrate, yellow prism, m.p. 151~152°. *Anal.* Calcd. for $C_8H_{10}NCl\cdot C_6H_3O_7N_3$ (5-Chloromethyl-2,4-dimethylpyridine picrate): C, 43.69; H, 3.64; N, 14.56. Found: C, 43.68; H, 3.32; N, 14.37.

2,4,5-Trimethylpyridine (XVI)—0.5 g. of the chloromethyl compound was catalytically reduced with 0.1 g. of Pd-$CaCO_3$ (Pd: 5%) in methanol. Absorption of hydrogen, 75 cc. (theoretical amount: 71 cc.). Yield, 0.4 g. (XVI), b.p. 188°. Picrate, yellow prism, m.p. 159~160°. *Anal.* Calcd. for $C_8H_{11}N\cdot C_6H_3O_7N_3$ (2,4,5-Trimethylpyridine picrate): C, 48.00; H, 4.00; N, 16.00. Found: C, 48.40; H, 4.11; N, 15.96. Mercuric chloride salt, colorless needles, m.p. 100~101°. *Anal.* Calcd. for $C_8H_{11}N\cdot HCl\cdot HgCl_2$: N, 3.26. Found: N, 3.17. Chloroplatinate, orange needles, m.p. 189~190°.

5-Cyano-2,3,4-trimethylpyridine (XVIII)—2.7 g. of 6-chloro-5-cyano-2,3,4-trimethylpyridine was reduced catalytically with Pd-$CaCO_3$ (Pd: 5%) in methanol. Absorption of hydrogen, 350 cc. at 20° (theoretical amount: 336 cc.). White needles, from ether, melted at 90~91°. Yield, 1.7 g. (79%) *Anal.* Calcd. for $C_9H_{10}N_2$ (5-Cyano-2,3,4-trimethylpyridine): C, 73.97; H, 6.84; N, 19.17. Found: C, 73.65; H, 6.51; N, 18.98.

2,3,4-Trimethylpyridine (XX)—After the mixture of (XVIII) and 10% KOH was boiled on a water bath, the water was evaporated, and the residue was mixed with CaO and destilled. The distillate was extracted with ether. Evaporation of ether gave a product which boiled at 187°. Picrate, yellow needles, m.p. 164°. *Anal.* Calcd. for $C_8H_{11}N\cdot C_6H_3O_7N_3$ (2,3,4-Trimethylpyridine picrate): C, 48.00; H, 4.00; N, 16.00. Found: C, 48.56; H, 3.92; N, 16.41. Picrolonate, m.p. 24~242°. Mercuric chloride salt, colorless prisms, m.p. 119~120°. *Anal.* Calcd. for $C_8H_{11}N\cdot HCl\cdot HgCl_2$; N, 3.26. Found: N, 3.18. Chloroplatinate, yellow needles, m.p. 177~179°.

Summary

2,3,6-, 2,3,5-, 2,4,5- and 2,3,4-trimethylpyridines were synthesized and were compared

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with data reported. There were some that did not coincide but according to the mode of the synthesis, these products were considered to be correct. These compounds were synthesized in order to compare with polymethylpyridines obtained from coal tar bases.

(Received March 27, 1953)

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31. **Kôzô Hayashi, Yukihide Abe, Tatsuo Noguchi, und Kyôko Suzushino:**

Studien über Anthocyane. XXII[1]. Beiträge zur papier-chromatographischen Analyse der natürlichen Anthocyane und Anwendung derselben zur Untersuchung von Farbstoffen in den roten *Impatiens*-Blüten und den blutroten Pfirsich-Früchten**.

(*Research Institute for Natural Resources, Tokyo**)

Zwecks Eingehens in die Erforschung der Anthocyane, die im Pflanzenreich weit verbreitet sind, haben wir uns seit kurzem mit der Aufstellung von papier-chromatographischem Arbeitsgang beschäftigt, um damit die Farbstoffanalyse an den farbärmeren, sogar an schwer zugänglichen Gegenständen zu ermöglichen. Bereits fanden wir einige wertvolle Arbeiten von Bate-Smith *et al.*[2], wobei aber ihr Hauptziel darin liegt, die Zusammenhänge zwischen den papier-chromatographischen Beschaffenheiten und der chemischen Konfiguration genannter Farbstoffgruppe ausfindig zu machen.

Leider scheint aber das geeignete Schema des Arbeitsganges, welches im allgemeinen für die Bestimmung von pflanzlichen Anthocyanen brauchbar ist, bis heute noch nicht aufgestellt worden zu sein. Somit wollen wir einige Ergebnisse unserer bisherigen Arbeiten, die mit dieser Absicht ausgeführt wurden, unten im (I) Abschnitt zusammenfassend berichten. Sie müssen natürlich auch für unsere chemischen Weiterarbeiten gute Dienste darbieten.

Zunächst haben wir unserer papier-chromotographischen Technik zur Farbstoffanalyse gegenüber zwei pflanzliche Materialien verwendet, deren Farbstoffbestandteile noch nicht bekannt sind; d.h. die orangeroten Blüten von *Impatiens Balsamina* L. und die blutroten Früchte von *Prunus persica* Batsch. Dabei hat es sich gezeigt, dass der Hauptfarbstoff in den ersten aus Pelargonin, und derselben in den zweiten aus Chrysanthemin bestand. Dieselben Sachlagen konnten wir schliesslich auf rein chemischem Wege beweisen, worüber unten im Abschnitt II und III näher beschrieben werden.

Unter stetiger Anregung und gütiger Leitung von Ehrenprof. Y. Asahina und Prof. Sh. Hattori wurde diese Arbeit durchgeführt, wofür wir ihnen unseren besten Dank aussprechen. Dem Unterrichtsministerium danken wir für die finanzielle Unterstützung bei der Ausführung dieser Untersuchung.

Beschreibung der Versuche

I. Gang der papier-chromatographischen Analyse der Anthocyane in den Pflanzenorganen[3]

—(a). **Vorversuche mit den krystallinischen Anthocyanpräparaten:** Unsere papier-chromatographische Aufarbeitung verlief ganz nach dem aufsteigenden Prinzip unter Benutzung von Tôyô Filtrierpapier, Nr. 50 (oder Nr. 2), welches sich ohne besondere Vorbehandlung gut als anwendbar erwies. Der ursprüngliche Farbstoff-flecken wurde dadurch dargelegt, dass man einen

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** Mitteilung aus der Forschungsanstalt für Naturerzeugnisse, Nr. 559.

1) XXI. Mitteil.: Proc. Japan Acad., 28, 429 (1952).

2) E. C. Bate-Smith: Nature, 161, 835 (1948); E. C. Bate-Smith, R. G. Westall: Biochim. et Biophys. Acta, 4, 427 (1950).

3) Vgl. auch K. Hayashi, Y. Abe: Misc. Repts. Research Inst. Nat. Resources (Japan), 28, 1 (1952) (Japanisch).