Among the indole derivatives (**20**—**42**) several compounds were found active as platelet aggregation inhibitors. Compounds (**22, 23, 25, 26, 32, 33**) were as effective as adenosine against collagen-induced platelet aggregation. Compounds (**27, 29, 34**) were active against both adenosine 5′-diphosphate- and collagen-indiuced platelet aggregation. Of these indole derivatives, N(1-pyrrolidinyl)ethyl-2-phenyl-5-methoxy-indole (**34**) was found most effective, and it showed rather stronger inhibition than adenosine at 10^{-4}M against adenosine 5′-diphosphate- and collagen-induced platelet aggregation. This series of compounds are structural analogs of a nonsteroidal antiinflammatory drug such as indomethacin which have been reported to inhibit collagen-induced platelet aggregation.[20]

Benzo[*b*]thiophene derivatives (**43**—**47**) had rather strong inhibitory activity except compound (**44**) against both adenosine 5′-diphosphate- and collagen-induced platelet aggregation. 3-Cyano-2-methylthio-4-oxo-6,7-dihydrobenzo[*a*]quinolizine (**48**) was also effective as an inhibitor of platelet aggregation mediated by both inducers. These compounds (**43, 45, 46, 47, 48**) could be appreciated to be of new classes of platelet aggregation inhibitors and these are valuable compounds for further pharmacological studies.

In summary, several heterocyclic compounds were found effective *in vitro* as inhibitors of platelet aggregation. It is of interest that some of them inhibited both adenosine 5′-diphosphate- and collagen-induced platelet aggregation and others inhibited only the aggregation mediated by collagen. The utility of these active compounds as antithrombotic agents depends on further pharmacological investigations.

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20) J.R. O'Brien, *Lancet*, **1968**, 894.

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Isolation of 5-Hydroxymethylfurfural from *Trachelospermum asiaticum* var. *intermedium*

Sansei Nishibe, Sueo Hisada, and Isao Inagaki

Faculty of Pharmaceutical Sciences, Nagoya City University[1]

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As one of carbohydrate components of several *Trachelospermum* species (Apocynaceae), we have reported the isolation of dambonitol (1,3-di-O-methyl-*myo*-inositol).[2]

This report is concerned with the isolation and identification of sucrose and 5-hydroxymethylfurfural from the stems of *Trachelospermum asiaticum* Nakai var. *intermedium* Nakai.

The procedure of extraction was as described in the experimental section. The extract with chloroform–methanol (2:1) was subjected to a column chromatography of activated charcoal and eluted successively with water, methanol–water (1:99), methanol–water (1:1) and methanol alone. The colorless grains (I), $C_{12}H_{22}O_{11}$, mp 176—179°, $[\alpha]_D^{21}$ +66.0° (water)

1) Location: *Tanabe-dori, Mizuho-ku, Nagoya, 467, Japan.*
2) S. Nishibe, S. Hisada, and I. Inagaki, *Yakugaku Zasshi*, **93**, 539 (1973).

were obtained from the eluate with methanol–water (1:99). I was identified as sucrose by the infrared (IR) spectrum and a mixed melting point.

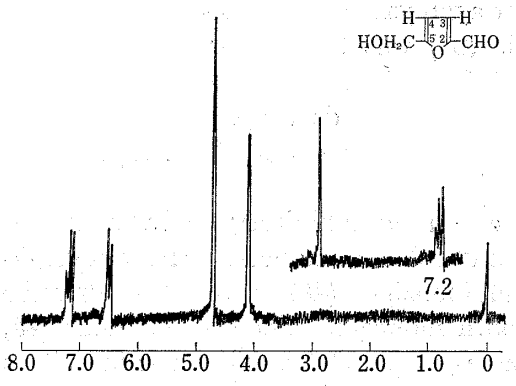

Fig. 1. Nuclear Magnetic Resonance Spectrum of II

Then the brown oily residue was obtained after the evaporation of the eluate with methanol–water (1:1), which showed a spot at *Rf* 0.35 on thin-layer chromatography (TLC) using ethyl acetate–chloroform (1:1) as the developer. The oily residue was subjected to a silica gel column chromatography for the purification to give a light yellow, mobile oil (II), $C_6H_6O_3$, mass spectrum (MS) *m/e* 126 (M^+). II shows the positive reaction to Fehling's reagent. The IR spectrum of II shows absorption at 1678 cm^{-1} due to aldehyde group and the ultraviolet (UV) spectrum has the absorption maximum at 227 and 282 nm.

The nuclear magnetic resonance (NMR) spectrum are as shown in Fig. 1.

II was identical with an authentic 5-hydroxymethylfurfural in all respects.

The isolation of II from the natural source, the separation procedure from which was carried out in a short time without the storage of the extract, is an interesting example.[3]

Experimental

All the melting points are not corrected. The following equipment was used: IR spectra, Infrared Spectrophotometer IR-S and IRA-2 (JASCO); UV spectra, Hitachi Recording Spectrophotometer Model EPS-3T; NMR spectra, JNM-MH-60 (JEOL) with tetramethylsilane ($\delta=0$) as internal standard; Mass spectra, Hitachi Mass Spectrometer Model RMU-6C; Optical rotation values, Direct Reading Polarimeter Model OR-10 (Yanagimoto).

TheTLC values were obtained with Kieselgur G nach Stahl (Merck) as adsorbent; the spots were detected by spraying with 10% sulfuric acid and heating. For column chromatography activated charcoal for chromatography (Wako) and silica gel (100 mesh, Mallinckrodt) were used.

The abbreviation used are as follows: s, singlet; d, doublet.

Isolation——The air-dried and cut stems (25 kg) collected in May 1969 at Kushimoto were extracted with hot MeOH (36 liter each, 4 times). The MeOH solution was evaporated to a small volume under reduced pressure, diluted with H_2O and filtered. The filtrate was extracted successively with petr. ether, ether, and $CHCl_3$. The aqueous layer was concentrated to a syrup, which was extracted with hot AcOEt. The residue after hot AcOEt extraction was extracted with hot $CHCl_3$–MeOH (2:1). The extract with $CHCl_3$–MeOH (82 g) was chromatographed on a column of activated charcoal (400 g). Fractions (1 liter each) were eluted successively with MeOH–H_2O (1:99) (No. 1—2), MeOH–H_2O (1:1) (No. 3—7) and MeOH alone (No. 8—13). The eluate of fraction No. 1—2 was evaporated and the residue was treated with hot AcOEt–MeOH (10:1). Then residue was recrystallized from EtOH to give crystals (I), 129 mg. The brown oily residue (500 mg) obtained from the eluate of fraction No. 5 was chromatographed on a silica gel column (12 g) with AcOEt–$CHCl_3$ (1:1) as the eluting solvent. Fractions (20 ml each) were monitered by TLC using AcOEt–$CHCl_3$ (1:1) as developer. The fractions showing a spot at *Rf* 0.35 were evaporated to dryness and the residue was rechromatographed to give oil (II), 60 mg.

Sucrose (I)——Colorless grains, mp 176—179°. $[\alpha]_D^{21}$ +66.0° ($c=1.5$ in H_2O). IR ν_{max}^{KBr} cm^{-1}: 3600—3200 (OH). *Anal.* Calcd. for $C_{12}H_{22}O_{11}$: C, 42.10; H, 6.48. Found: C, 42.06; H, 6.19.

I was identified with an authentic sample by IR and a mixed melting point.

5-Hydroxymethylfurfural (II)——A light yellow, mobile oil. Fehling's reagent (+). TLC *Rf*: 0.35 (AcOEt:$CHCl_3$=1:1). UV λ_{max}^{EtOH} nm(log ε): 227 (3.39), 282 (4.18). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (OH), 1678 (CO), 1585, 1515 (C=C). *Anal.* Calcd. for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 56.94; H, 5.03. Mass Spectrum *m/e*: 126 (M^+). NMR (in $CDCl_3$) δ: 4.10 (1H, s, –O<u>H</u>, quenched by addition of D_2O), 4.70 (2H, s, –C<u>H</u>$_2$–),

3) As the other similar examples, a few isolations, for examples, from tabacco leaves (I. Ōnishi and K. Yamamoto, *Bull. Agr. Chem. Soc. Japan*, **21**, 181 (1957).), wheat germs (P. Linko, *Suomen Kemistilehti*, **34**, 104 (1961)) and so on, are reported so far as the authors know.

6.47 (1H, d, $\underline{H}_{(4)}$>=<, J=3 cps), 7.15 (1H, d, $\underline{H}_{(3)}$>=<, J=3 cps), 9.25 (1H, s, -C$\underline{H}$O).

II was identified with an authentic sample by IR, NMR, TLC and MS.

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Cardiovascular Effects of Some Peptide Analogues consisting of Cystine and/or Tyrosine

Yoshikazu Yamatake, Hitoshi Kato, and Keijiro Takagi

Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, University of Tokyo[1)]

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Compounds that competitively block the pharmacological effects of posterior pituitary hormones have been sought for a long time. Some peptides containing tyrosine and/or cystine were synthesized for this purpose, and examined to have a competitive inhibitory effect on the contraction induced by oxytocin in the rat uterus by Ishida, *et al.*[2–4)]

In the present study, we studied the effect of such synthetic peptides on the cardiovascular system as well as on the pressor action of vasopressin.

Experimental

Method——1. Blood Pressure and Heart Rate in Anesthetized Rats: Male rats (Donryu strain, 240—460 g) were anesthetized with a mixture of urethane (600 mg/kg) and α-chloralose (60 mg/kg) intraperitoneally. Arterial blood pressure was taken from the cannulated carotid artery on a polygraph (Nihon Kohden, RM-150) using a pressure transducer (Nihon Kohden, MP U-0.5). Heart rate was measured by an instantaneous ratemeter (Nihon Kohden, RT-2) triggered from the pulse pressure. Drug solutions were injected into the cannulated femoral vein in volumes of 0.2 ml.

2. Peripheral Blood Flow in Anesthetized Dogs: The effects of the peptides on peripheral vascular resistance were studied in the autoperfused dog hindquarter and coronary beds. Male mongrel dogs weighing about 10 kg were anesthetized with sodium pentobarbital, 35 mg/kg, intravenously, the left femoral artery was cannulated, and blood flow into the left hindquarter was recorded with an electromagnetic flowmeter (Nihon Kohden, MF-2). Similarly, coronary blood flow was measured from the left anterior descending coronary artery which was perfused with the blood derived from the left carotid artery in an anesthetized open-chest dog under artificial respiration. Peripheral vascular resistance was calculated as the ratio of pressure to flow. Drugs were injected intraarterially in volumes of 0.4 ml for ten seconds.

Materials——The synthetic peptides examined are as follows:

I: L-cystine diethylester (CyS–OEt)$_2$·2HCl
II: L-cystinyl-di-L-tyrosine ethylester (CyS–Tyr–OEt)$_2$·2HBr
III: L-cystinyl-di-L-tyrosyl-L-tyrosine ethylester (CyS–Tyr–Tyr–OEt)$_2$·2HBr
IV: di-carbobenzoxy-L-cystinyl-di-L-tyrosyl-L-tyrosine ethylester (Cbz–CyS–Tyr–Tyr–OEt)$_2$
V: L-tyrosyl-L-tyrosine ethylester Tyr–Tyr–OEt·HBr

1) Location: *Hongo 7-3-1, Bunkyo-ku, Tokyo.*
2) Y. Ishida, *Yakugaku Zasshi*, **81**, 1722 (1961).
3) Y. Ishida and K. Hara, *Chem. Pharm. Bull.* (Tokyo), **12**, 872 (1964).
4) Y. Ishida and M. Onishi, *Chem. Pharm. Bull.* (Tokyo), **14**, 748 (1966).