Ethyl 2,4-Bis(2,4-dichlorophenoxy)acetoacetate—To a solution of 2 g. of 3,5-dimethylpyrazole and 0.4 g. of sodium in 20 ml. of tetrahydrofuran was added 5.6 g. of ethyl (2,4-dichlorophenoxy)acetate. After being stirred for 30 min. at room temperature, 300 ml. of H₂O was added to the mixture and the separated solid was collected (sodium compound, m.p. 217°) and then suspended in warm acetone. Acidification with 10% aq. HCl and recrystallization from n-hexane gave colorless crystals, m.p. 97°~98°; yield, 3.8 g.

(2-Hydroxymethyl-4-chlorophenoxy)acetic Acid Hydrazide—A mixture of 4.9 g. of ethyl 2-hydroxymethyl-4-chlorophenoxy)acetate and 1.5 g. of hydrazine hydrate (80%) was refluxed in 20 ml. of EtOH for 2 hr. After cooling, the separated solid was collected and recrystallized from DMF-H₂O to give colorless needles, m.p. 151.5°; yield, 4 g. (87%). Anal. Calcld. for C₉H₆O₂N₂Cl : C, 46.86; H, 4.81; N, 12.15. Found : C, 46.87; H, 4.79; N, 11.95.

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Summary

In view of recently reported chemical reactivities of the azolides, a number of 1-aryloxyacylpyrazoles were synthesized for their evaluation as plant growth regulator.

The structure of 1-aryloxyacylpyrazoles derived from unsymmetrical pyrazoles was discussed on the basis of nuclear magnetic resonance data.

Some reactions of 1-aryloxyacylpyrazoles were also described.

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91. Kōtarō Takahashi and Toshie Nakagawa : Studies on Constituents of Medicinal Plants. VIII. The Stereochemistry of Paulownin and Isopaulownin.

(Faculty of Pharmaceutical Sciences, Kanazawa University)

Paulownin, C₉H₁₄O₅, m.p. 105~106°, [α]₀ = 29.0, a new lignan, isolated together with d-sesamin, from the wood of Paulownia tomentosa (kiri) has been established as 1,4-bis(3,4-methylenedioxyphenyl)-tetrahydro-1H,3H-furo[3,4-c]furan-3a-ol. The present paper deals with certain nuclear magnetic resonance (NMR) evidence for the assignment of the stereochemistry of d-sesamin (Iα) and d-asarinin (IIβ), and with the stereochemistry of paulownin (IIα) and isopaulownin (IIβ), m.p. 132°, [α]₀ = 127.0°, the latter of which was derived from paulownin. Paulownin was refluxed with 20% formic acid or 5% ethanol-hydrochloric acid to give isopaulownin, C₉H₁₄O₅, which gave a monoacetate C₁₂H₂₀O₈, m.p. 105°, [α]₀ = 83.1°. The ultraviolet spectrum of IIβ is superimposable with that of IIα.

The NMR spectra of d-sesamin and d-asarinin has been reported by Jones, et al.⁴⁻⁵

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⁴ A part of this study was presented at the XXVth International Congress of the Pharmaceutical Sciences (F.I.P.), Prague, August 25, 1965. Part VII : Yakugaku Zasshi, 86, 441 (1966).
⁵ Takara-machi, Kanazawa (高橋幸太郎, 中川俊江).
and by us\(^1\) and recently Birch, \textit{et al.}\(^2\) presented the stereochemistry of \textit{d}-sesamin and \textit{d}-asarmin as \textit{Ia} and \textit{Ib}, respectively, from the study on their optical rotation, however, whether \textit{d}-sesamin should be formulated as \textit{Ia} has not been determined conclusively. So it seems to be necessary for us to begin our study with reexamination of their spectra in connection with the NMR spectral analysis of paulownin and isopaulownin. The NMR spectra of \textit{Ia}, \textit{Ib}, \textit{IIa}, and \textit{IIb}\(^3\) are shown in Fig. 1.\(^3\)

Fig. 1. The NMR spectra of \textit{d}-sesamin (\textit{Ia}), \textit{d}-asarmin (\textit{Ib}), paulownin (\textit{IIa}) and isopaulownin (\textit{IIb}).

\[^{\text{a3}}\text{ The NMR spectra were measured by the Varian Associates NMR spectrometer at 60 Mc. in CDCl}_{3}\text{ using tetramethylsilane as internal reference. The position of resonances were given as } \tau\text{-values.}\

**d-Sesamin and d-Asarinin**

The NMR spectrum of *d*-sesamin (Fig. 2) shows a doublet at 5.31 p.p.m. (J = 4.8 c.p.s., 2 protons), which would be assigned to equivalent protons C₄-H₁ and C₄-H₂ of Ia, of which the former proton is split by coupling with C₃-H and the latter, by coupling with C₅-H, respectively. The coupling constant J = 4.8 c.p.s. of the doublet indicates that C₃-H and C₅-H and also C₆-H and C₇-H are in a *trans* configuration, respectively.

The NMR spectrum of *d*-asarinin (Fig. 3) shows two doublets at 5.19 p.p.m. (J = 4.8 c.p.s., one proton) and at 5.61 p.p.m. (J = 7.2 c.p.s., one proton), which would be assigned to non-equivalent protons, C₄-H₁ and C₄-H₂ of Ib, of which the former is split by coupling with C₃-H and the latter, by coupling with C₅-H. The coupling constant J = 4.8 c.p.s. of the doublet of the lower field (5.19 p.p.m.) suggests that C₄-H₁ and C₄-H remain in a *trans* configuration and the coupling constant J = 7.2 c.p.s. of the doublet of the higher field (5.61 p.p.m.) suggests that C₄-H₁ and C₄-H are in a *cis* configuration.

These data indicate that the configurational change of 3,4-methylenedioxyphenyl and the proton at C₄ results in the upfield shift of the signal by the changed proton at C₄ and the downfield shift of the signal by the unchanged proton at C₅, which might be due to the anisotropy of the phenyl ring.

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**Fig. 2.**

**Fig. 3.**

The NMR spectrum of *d*-sesamin (Fig. 4) also exhibits two quartets at 5.64~5.91 p.p.m. (center 5.78 p.p.m., 2 protons) and at 6.07~6.27 p.p.m. (center 6.17 p.p.m., 2 protons), which would be assigned to two pairs of equivalent protons C₄-H₁ and C₄-H₂, and C₄-H₁ and C₄-H₂ of Ia, respectively. A possible explanation is as follows (Fig. 4):

C₄-H₁ and C₄-H₂ and also C₄-H₁ and C₄-H₂ are equivalent, respectively, however, C₄-H₁ and C₄-H₂ are non-equivalent and have different chemical shifts. C₃-H is coupled with C₅-H to give a doublet (J = 9.2 c.p.s.) and each peak of the doublet in the lower field (due to C₃-H) is split by coupling with C₅-H to give doublets (J = 7.0 c.p.s.), finally C₅-H exhibits a quartet at 5.64~5.91 p.p.m. The observed coupling constant J = 7.0 c.p.s. suggests that C₅-H₁ and C₅-H are in a *cis* configuration. C₅-H₂, which is equivalent
to \( C_7-H_e \) also exhibits a similar quartet. On the other hand, \( C_7-H_i \) is coupled with \( C_7-H_e \) to give a doublet \((J = 9.2 \text{ c.p.s.})\) and then each peak of the doublet in the higher field (due to \( C_7-H_i \)) is again split by coupling with \( C_5-H \) to give doublets \((J = 3.5 \text{ c.p.s.})\), finally \( C_7-H_i \) shows a quartet at \( 6.07 \sim 6.27 \text{ p.p.m.} \). The observed coupling constant \( J = 3.5 \text{ c.p.s.} \) suggests that \( C_7-H_i \) and \( C_8-H \) are in a \textit{trans} configuration. \( C_7-H_i \), which is equivalent to \( C_7-H_i \), also exhibits a similar quartet. These data are almost in agreement with those of pinoresinol, reported by Ludwig\(^4\) as follows:

\[
\begin{align*}
H_e &= 5.76 \text{ p.p.m.}, \quad H_i = 6.17 \text{ p.p.m.}, \quad J(H_e-H_i) = 9.23 \text{ c.p.s.}, \\
J(C_7-H_i \cdots C_8-H) &= J(C_7-H_i \cdots C_1-H) = 7.0 \text{ c.p.s.}, \\
J(C_7-H_i \cdots C_8-H) &= J(C_8-H_i \cdots C_1-H) = 3.8 \text{ c.p.s.}
\end{align*}
\]

**Paulownin and Isopaulownin**

The assignment of the stereochemistry of paulownin and isopaulownin as \( \text{IIa} \) and \( \text{IIb} \) can be made by their NMR analysis as follows:

\[
\text{IIa : } R_3 = R_4 = 3,4\text{-methyleneedioxyphenyl,} \\
R_5 = H_e, \quad R_6 = H_i
\]

\[
\text{IIb : } R_3 = R_4 = 3,4\text{-methyleneedioxyphenyl,} \\
R_5 = H_e, \quad R_6 = H_i
\]

The spectrum of paulownin (Fig. 5) exhibits two signals at 5.15 p.p.m. and 5.23 p.p.m., which are assigned to the protons at \( C_7 \) and \( C_8 \) and these two signals are equivalent to two protons, it is considered that the signal at 5.15 p.p.m. comes from a doublet with a hidden signal in the signal at 5.23 p.p.m.. The fact that the \( J \) of this doublet is about 4.8 c.p.s. and not larger than 5.5 c.p.s. suggests that the proton at \( C_8 \) and the proton at \( C_1 \) are in a \textit{trans} configuration, and the signal at 5.23 p.p.m. is assigned to the proton at \( C_8 \), as shown in \( \text{IIa} \).

The spectrum of isopaulownin (Fig. 6) shows a doublet at 4.87 p.p.m. (one proton), which could be assigned to \( C_7-H_i \) and a singlet at 5.51 p.p.m. (one proton), which could be assigned to \( C_7-H_i \). As is observed in the case of \( \text{d}-\text{sesamin} \) and \( \text{d}-\text{asarinin} \), \( C_7-H_i \) signal of isoform shifts to the lower field and \( C_8-H_e \) of isoform to the higher

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field. The observed coupling constant $J=5.0$ c.p.s. of $C_7$-H$_8$ suggests that the stereochemistry of $C_7$-H$_9$ and $C_7$-H is unchanged in a *trans* configuration, however, that of $C_8$-H$_e$ and $C_8$-OH is in a *cis* configuration as shown in IIb.

![Fig. 5.](image)

![Fig. 6.](image)

The spectrum of paulownin exhibits a complicated, but symmetrical sextet at 6.87 p.p.m., 6.95 p.p.m., 7.00 p.p.m., 7.04 p.p.m., 7.08 p.p.m., and 7.18 p.p.m. (center 7.03 p.p.m., one proton) (Fig. 7), which would be assigned to the proton at $C_7$. This would be analyzed as follows:

The proton at $C_7$ is first split by coupling with $C_8$-H$_e$ to give a doublet ($J=8.0$ c.p.s.) and then each of peaks is split by coupling with $C_7$-H$_9$ to give a quartet ($J=5.0$ c.p.s.) and finally by coupling with $C_7$-H$_9$ to give an octet ($J=5.5$ c.p.s.). The signal appears as a sextet, which actually is shown in Fig. 7.

The methylene protons of paulownin give a complicated and asymmetrical multiplet between 5.39 p.p.m. and 6.34 p.p.m. (4 protons), of which the sum of intensities of signals at 5.39 p.p.m., 5.53 p.p.m., and 5.67 p.p.m. are equivalent to one proton and the sum of intensities of signals at 5.89 p.p.m., 6.05 p.p.m., 6.09 p.p.m., 6.18 p.p.m., 6.24 p.p.m., and 6.34 p.p.m. are equivalent to three protons. This multiplet might be tentatively analyzed as follows (Fig. 8).

The methylene protons at $C_8$, $C_7$-H$_e$ and $C_7$-H$_9$ are non-equivalent, as are those of $d$-sesamin, and have different chemical shifts, showing characteristic signals at 5.53 p.p.m. and 6.21 p.p.m., respectively. These protons are coupled with each other to give two doublets ($J=9.0$ c.p.s.). The lower field doublet (due to $C_8$-H$_e$) is further coupled with $C_7$-H to give a quartet ($J=8.0$ c.p.s.) and higher field doublet (due to $C_7$-H$_9$) is also coupled with $C_7$-H to give a quartet ($J=5.5$ c.p.s.). $C_7$-H$_e$ and $C_7$-H$_9$, which are also non-equivalent and have different chemical shifts, are coupled with each other to give a quartet ($J=9.3$ c.p.s.) between 5.89 p.p.m. and 6.24 p.p.m. These signals are synthesized to give a multiplet which is almost equal to that of paulownin. The assumption that
the methylene protons at C₄C₅-H₄ and C₅-H₅ are of AB type and show signals at 5.89 p.p.m. (signal 1), 6.05 p.p.m. (signal 2), 6.09 p.p.m. (signal 3), and 6.24 p.p.m. (signal 4) (O point is at 6.07 p.p.m.), might be supported by the following calculation.

\[ 4-3=2-1=J_{AB} \]  \hspace{1cm} (1)

The observed value of (2-1) is 0.16 p.p.m. and that of (4-3) is 0.15 p.p.m.

\[ 3-1=4-2=\sqrt{(\delta_b-\delta_A)^2-J_{AB}^2} \]  \hspace{1cm} (2)

The observed value of (3-1) is 0.20 p.p.m. and (4-2) is 0.19 p.p.m. Using the value of $J_{AB}$ as 0.16 p.p.m. and that of (3-1) as 0.20 p.p.m., the following equation is derived from the equation 2,

\[ 0.04=(\delta_b-\delta_A)^2-0.16^2 \]

and so \[ \delta_b-\delta_A=0.12 \text{ p.p.m.} \]

Consequently,

\[ \delta_A=6.07-\frac{1}{2}\times0.12=6.01 \text{ p.p.m.} \]

\[ \delta_b=6.07+\frac{1}{2}\times0.12=6.13 \text{ p.p.m.} \]

The relative intensities are given by (3) and (4), where $J_{AB}$ is 0.16 p.p.m. and $(\delta_b-\delta_A)$ is 0.12 p.p.m.,

\[ 1=4=1-J_{AB}[(\delta_b-\delta_A)^2-J_{AB}^2]^{-1/2}=0.2 \]  \hspace{1cm} (3)

\[ 2=3=1+J_{AB}[(\delta_b-\delta_A)^2-J_{AB}^2]^{-1/2}=1.8 \]  \hspace{1cm} (4)

Thus, the relative intensities of both signals 1 and 4 are 0.2 and those of both signals 2 and 3 are 1.8, indicating that the ratio of the relative intensity of signal 1 to that of the signal 2 is 1/9. This value is well in accord with the observed value about 1/9 of the spectrum.

Difference in chemical shifts of C₄-methylene and C₅-methylene protons may be derived from a sum of effects, shielding and deshielding of two phenyl rings and one hydroxyl group in the compound. The exact factor which may govern the NMR information of these protons is under way.

The methylene signals of isopaulownin is observed in a rather high field at 5.78 ~6.86 p.p.m. (4 protons) than that of paulownin, which might be due to the anisotropy of the phenyl ring. Its analysis is not completed yet. The signals of the phenyl protons, methylenedioxy protons and hydroxy proton are observed\(^1\) as shown in Fig. 1. All these NMR data support the configurational assignment of paulownin and isopaulownin as IIa and IIb, respectively. In this case, the configurational change is considered to have taken at C₅ which is neighbored to C₅-OH. This conclusion is supported by the observed change in the optical rotation,\(^3\) that is, the observed values of optical rotation for paulownin and isopaulownin are +29.0°, and +127.0°, respectively. This change with difference +98.0° corresponds with the change in the optical rotation between d-sesaminin and d-asarinin with the difference of +49.0°.
Consequently, the stereochemistry of \( d \)-sesamin, \( d \)-asarinin, paulownin and isopaulownin could be elucidated as \( \text{Ia, Ib, Ila and IIb, respectively, and epi-asarinin as Ic.} \)

**Experimental**

**Isomerization of Paulownin to Isopaulownin**——a) Paulownin (2.5 g.), dissolved in 120 g. of 50% EtOH-HCl (w/w) solution, was refluxed for 7 hr. After cooling, the solvent was distilled off to give brown substance, which was, after recrystallization from CH\(_2\)OH, separated into paulownin and isopaulownin by the thin-layer chromatography (the dry method) as follows. The substance (50 mg.), after drying completely, dissolved in a minimum volume of CHCl\(_3\) was spotted on a glass plate (20 x 5 cm.), which was covered with alumina (thickness 0.5 mm.) and the plate was twice developed with ethylacetate-benzene solution (1:3, v/v). After drying, the plate showed two bands under UV illumination, of which the lower band was removed off and extracted with CHCl\(_3\) and CHCl\(_3\) solution was evaporated to give white crystals, which was mainly consisted of isopaulownin. Thus obtained isopaulownin was again chromatographed as mentioned above to give pure isopaulownin as white rhombic crystals, C\(_{20}\)H\(_{12}\)O\(_7\), m.p. 132\( ^\circ \), \([\alpha]\) = 127.0\( ^\circ \)(c=0.795, CHCl\(_3\)). from methanol. Yield, 15%. Isopaulownin gave a superimposible UV** curve with that of paulownin. UV \( \lambda_{	ext{max}} \) mp \( \mu \) (\( \varepsilon \)):

- 237.5 (9180), 287 (8160). IR \( \nu_{	ext{max}} \) cm\(^{-1} \): 3400, 2860, 1610, 1510, 1500, 1450, 1400, 1375, 1380, 1300, 1270, 1250, 1210, 1190, 1105, 1060, 1040, 1030, 1000, 970, 940, 866, 830, 815, 795, 785, 746, 720. **Anal. Calcd. for C\(_{20}\)H\(_{12}\)O\(_7\): C, 64.86; H, 4.90. Found: C, 64.98; H, 4.72.

b) Paulownin (0.3 g.), suspended in 50 ml of 20% formic acid, was refluxed for 10 hr. and then formic acid solution was evaporated in vacuo to give brown substance, which was purified by the thin-layer chromatography as mentioned above, to give isopaulownin, m.p. 132\( ^\circ \). This was proved to be identical with isopaulownin, mentioned above, by the mixed melting determination, UV and IR spectra.

**Acetylation of Isopaulownin**——A mixture of 0.2 g of isopaulownin, 3 ml of Ac\(_2\)O and 0.2 g of CH\(_3\)COONa was gently refluxed on an oil bath for 2 hr. and after cooling, the mixture was poured into ice water. After standing overnight in an ice-box, the precipitates were filtered, dried and then recrystallized from methanol to give white crystalline substances, m.p. 105\( ^\circ \), \([\alpha]\) = 83.1\( ^\circ \)(c=0.830, CHCl\(_3\)). UV \( \lambda_{	ext{max}} \) mp \( \mu \) (\( \varepsilon \)):

- 238.5 (9120), 288 (8020). IR \( \nu_{	ext{max}} \) cm\(^{-1} \): 2880, 1730, 1620 (w, broad), 1510, 1500, 1450, 1380, 1350, 1250, 1240, 1190, 1110, 1065, 1040, 945, 870, 830, 815, 795, 745, 720. **Anal. Calcd. for C\(_{20}\)H\(_{12}\)O\(_6\): C, 64.07; H, 4.89. Found: C, 64.10; H, 4.86.

**Isomerisation of \( d \)-Sesamin to \( d \)-Asararin**——According to the method by Beroza,\(^5\) 1 g. of \( d \)-sesamin was refluxed for 16 hr. with 50 g. of EtOH-HCl solution (10% w/w) to give \( d \)-asararin, which was purified by the thin-layer chromatography as in the case of isopaulownin, m.p. 121.5\( ^\circ \), \([\alpha]\) = 121\( ^\circ \)(c=0.9, CHCl\(_3\)). UV \( \lambda_{	ext{max}} \) mp \( \mu \) (\( \varepsilon \)):


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**Summary**

The stereochemistry of paulownin, isopaulownin, m.p. 132\( ^\circ \), which was derived from paulownin with 20% EtOH-HCl or 5% HCOOH, \( d \)-sesamin and \( d \)-asararin were elucidated as \( \text{IIa, IIb, Ia and Ib by the analysis of their NMR spectra, respectively and consequently, epi-asarinin as Ic.} \)

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\(^{44}\) Ultraviolet absorption spectra were taken in ethanol solution using Hitachi EPU-2A spectrophotometer.

Infrared absorption spectra were taken in KBr pellet, if not otherwise stated, by Nippon Bunko Model IRS infra code.