LIGNANS FROM *TAXUS WALLICHIANA*

ROGER W. MILLER, JERRY L. MCLAUGHLIN,[1] RICHARD G. POWELL, RONALD D. PLATTNER, DAVID WEISLEDER, and CECIL R. SMITH, JR.

Northern Regional Research Center, Agricultural Research Service, United States Department of Agriculture,[2] Peoria, Illinois 61604

ABSTRACT.—Three lignans have been isolated from the roots, stems, and needles of *Taxus wallichiana* Zucc. Two of these have been identified as epimers of conidendrin (**1a**+**1b**) and hydroxymatairesinol (**2a**). The structure of the third, a previously unknown lignan named isoliovil (**3a**), has been established by ^{1}H and ^{13}C nmr and mass spectrometry.

Lignans have been found in all parts of seed-bearing plants (1). Isolariciresinol, secoisolariciresinol, isotaxiresinol, and isotaxiresinol-6-methyl ether are found in several species of *Taxus* (2). *T. cuspidata* Sieb. and Zucc. also has lariciresinol (2), *T. baccata* L. contains taxiresinol (3), and *T. mairei* S. Y. Hu has α-conidendrin (4). Examination of *T. wallichiana* Zucc. for cytotoxic substances resulted in the isolation of three lignans associated with cytotoxic taxane derivatives whose characterization has been reported (5, 6). Spectral characteristics of these biologically inactive compounds revealed that they were lignans, one of which has not been reported previously in the literature. This paper describes the characterization of these lignans.[3]

As detailed in earlier papers (5, 6), silica chromatography of the chloroform solubles from roots, stems, and needles of *T. wallichiana* extract yielded numerous fractions; two of these (F207 and F212) were combined, purified by tlc, and then crystallized from ethanol. In the aromatic proton region of the ^{1}H nmr of these crystals the following could be detected: (a) two singlets, indicative of para protons coupled to no others; (b) a doublet with a coupling of 2 Hz, indicative of protons meta to each other; (c) a doublet with $J=8$ Hz, indicative of protons ortho to each other; and (d) a doublet of doublets ($J=2,8$ Hz), indicative of a proton with ortho and meta couplings. ^{1}H nmr also showed the presence of two methoxyl groups (at δ3.73 and 3.78). ^{1}H nmr of the acetylated product (**1c**+**1d**) indicated, in addition to two methoxyl groups (singlets at δ3.70 and 3.77), acetate singlets at δ2.18 and 2.26 (table 1). These strong signals were accompanied by satellites at δ2.24, 3.72 and 3.78 with intensities roughly half those of the larger peaks, suggesting that two closely related isomers were present. The stronger signals are in reasonable agreement with those recorded by Cambie *et al.* (8) for α-conidendrin diacetate (**1c**) and the lesser with those of β-conidendrin diacetate (**1d**). From these observations, we concluded that our crystals from F207 and F212 are a mixture of **1a** and **1b** in a ratio of about 2:1.

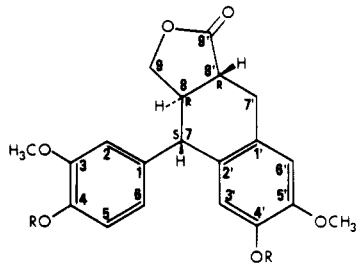
A similar conclusion regarding the structures was reached from ^{13}C nmr data (table 2), which also indicated the presence of a γ-lactone (δ177.1 for **1a** and 176.6 for **1c**). The major peaks were in good agreement with those recorded for **1c** by Cambie *et al.* (8); in addition, the less intense peaks (at δ38.5, 41.0, 46.5, 71.2, 112.9, 113.5, 121.5, 122.8 and 123.1) were characteristic of **1d** (8). Furthermore, eims results for the mixture of **1a**+**1b** agree with literature values for β-conidendrin (9); stereoisomeric lignans are not distinguished by ms (10). The largest peak by far was M^{+} and this fragmentation behavior is typical of lignans containing the 1,2,3,4-tetrahydronaphthalene ring system (11).

---

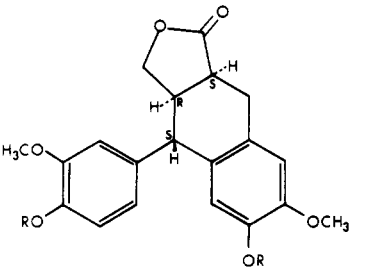
[1]On leave from Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, 1979–1980.

[2]The mention of firm names or trade products does not imply that they are endorsed by the United States Department of Agriculture over other firms or similar products not mentioned.

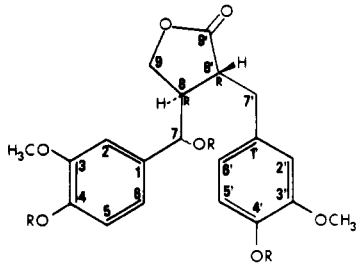
[3]We have used the numbering system advocated by Gottlieb (7), which emphasizes biogenetic relationships.



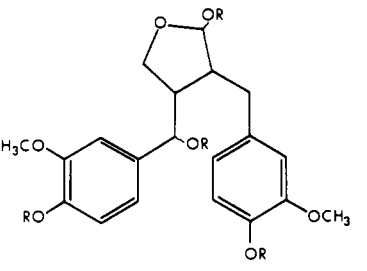
1a R = H
1c R = CH_3CO



1b R = H
1d R = CH_3CO



2a R = H
2b R = CH_3CO
2c R = $(CH_3)_3Si$



3a R = H
3b R = CH_3CO
3c R = $(CH_3)_3Si$

TABLE 1. ^1H nmr of *Taxus wallichiana* lignans.

Protons on	δ in $CDCl_3$ and J in Hz		Protons on[c]	δ in $CDCl_3$ and J in Hz		
	1a[a]	1c[b]		2a[d]	2b[e]	3b
C-2	6.53 d, J=2	6.62 s	C-2	6.49 or 6.57 d, J=2	6.69 or 6.73 d, J=2	
C-5	6.73 d, J=8	6.95 d, J=8	C-5	6.68 or 6.75 d, J=8	6.88 or 6.96 d, J=8	6.7–7.0 m
C-6	6.58 d, J=8	6.71 dd, J=2, 8	C-6	6.39 or 6.51 dd, J=2, 8	6.58 or 6.66 dd, J=2, 8	
C-7	3.9–4.2 m	3.8–4.2 m	C-7	4.52 d, J=6	5.77 d, J=6	5.78 d, J=10
C-8	2.5 m	2.56 br	C-8	2.6 br	2.6–3.1 m	2.7 m
C-9	3.9–4.2 m	3.8–4.2 m	C-9	3.88 d, J=7 4.0–4.4 m	3.88 d, J=7 4.01 dd, J=7, 18	3.7–3.9 m
C-2'	——	——	C-6'	6.39 or 6.51 dd, J=2, 8	6.58 or 6.66 dd, J=2, 8	
C-3'	6.26 s	6.47 s	C-5'	6.68 or 6.75 d, J=8	6.88 or 6.96 d, J=8	6.7–7.0 m
C-6'	6.62 s	6.74 s	C-2'	6.49 or 6.57 d, J=2	6.69 or 6.73 d, J=2	
C-7'	2.7–3.1 m	2.8–3.4 m	C-7'	2.83 br	2.6–3.1 m	2.7 m
C-8'	2.5 m	2.56 br	C-8'	2.6 br		
C-9'	——	——	C-9'	——	——	6.12 d, J=7
OMe	3.73 s 3.78 s	3.70 s 3.77 s	OMe	3.70 s 3.72 s	3.74 s (6H)	3.82 s 3.84 s
OAc	——	2.81 s 2.26 s	OAc	——[f]	2.07 s (3H) 2.25 s (6H)	1.99 s (3H) 2.05 s (3H) 2.30 s (6H)

[a] CD_3OD added to dissolve sample. Also present **1b** as indicated by ratio of the two OMe signals compared to those of a standard sample of **1a**.

[b] **1d** Indicated with weak singlets at 2.24 (OAc), 3.72 (OMe), and 3.78 (OMe).

[c] In accordance with Gottlieb's rules for numbering lignan skeletons (7), certain aromatic carbons in compounds **2a**, **2b** and **3b** are numbered differently than those in **1a** and **1b**. Chemical shifts here presented in the same horizontal row pertain to the same carbon, regardless of how it is numbered.

[d] Isomer indicated with weak singlets at 3.68 (OMe) and 3.69 (OMe).

[e] Isomer indicated with weak singlets at 2.04 (OAc) and 3.72 (OMe).

[f] Signals for OH's at 2.6 (br) and 5.72 (br s).

TABLE 2. ^{13}C nmr of *Taxus wallichiana* lignans.

Carbon number	δ in $CDCl_3$		Carbon number[c]	δ in $CDCl_3$		
	1a[a]	**1c**[b]		**2a**	**2b**	**3b**
1	134.8	140.9	1	133.6	136.1	137.7[d]
2	112.7	112.0	2	108.3	110.7	111.3[e]
3	148.6	151.8	3	146.9[f]	151.4[f]	151.2[f]
4	146.0	139.3	4	145.8[g]	139.9[g]	139.8
5	115.8	123.3	5	114.0[h]	122.8[h]	123.0
6	121.8	120.7	6	118.9	118.5	120.9
7	48.2	47.6	7	75.4	75.4	76.6
8	42.5	41.7	8	45.2	43.4	48.2
9	72.9	71.7	9	68.5	67.7	69.9
1'	126.6	133.8	1'	129.5	136.1	137.8[d]
2'	132.4	130.6	6'	122.6	121.7	119.4
3'	116.5	123.8	5'	114.5[h]	123.2[h]	123.0
4'	145.2	138.6	4'	144.6[g]	138.8[g]	139.8
5'	147.2	150.0	3'	146.8[f]	151.1[f]	151.3[f]
6'	111.9	113.1	2'	112.0	113.7	113.1[e]
7'	29.6	29.7	7'	35.2	34.9	33.7
8'	50.2	50.0	8'	43.8	43.5	50.0
9'	179.2	176.6	9'	178.9	178.0	102.9
OCH_3	56.2	56.0	OCH_3	55.9	55.8	56.0
CO_2CH_3	—	20.7	CO_2CH_3	—	20.5 (2) 20.9	20.7 (4)
CO_2CH_3	—	169.0	CO_2CH_3	—	168.7 168.9 169.7	169.2 (4)

[a]CD_3OD added to aid solubility.
[b]Has less intense peaks at 38.5, 41.0, 46.5, 71.2, 112.9, 113.5, 121.5, 122.8 and 123.1, all indicative of β-conidendrin diacetate (**1d**).
[c]See footnote "c" to Table 1.
[d–h]Signals may be interchanged.

Fraction P5 from countercurrent distribution (CCD) of F214 and F215 (5) yielded an amorphous solid (**2a**) which also appeared to be a lignan judged by its spectral characteristics. The presence of a γ-lactone was suggested by a ^{13}C nmr shift at δ178.9 for **2a** and 178.0 for **2b**. The ^1H nmr spectrum of **2a** showed strong singlets at δ3.70 and 3.72 associated with aromatic methoxyl groups; in addition, there was a satellite pair of singlets at δ3.68 and 3.69, about one-third as intense as the dominant pair, apparently due to a closely related isomer. ^1H nmr also indicated a doublet at δ4.52 for **2a** which moved downfield to δ5.77 when **2a** was acetylated. Three acetate singlets were revealed for **2b** indicative of two aromatic acetates (δ2.25) and one nonaromatic acetate (δ2.07). The latter had a satellite peak about one-third as intense—another indication of the presence of a closely related isomer. Mass spectrometry of lignans containing substituted 3,4-dibenzyl 2-tetrahydrofuranones exhibits easily identifiable molecular ions and prominent fragment peaks arising from benzylic cleavage of the molecular ion (11). Eims of **2a** showed a base peak of *m/z* 153 (indicating the presence of an α-hydroxyvanillyl ion); the second most intense peak was at *m/z* 137 (indicating a vanillyl ion), and a molecular ion at *m/z* 374. Eims of **2c** matched values reported by Ekman (10), and high resolution eims of the triacetate of **2a** gave mass values consistent with **2b**. The ^1H and ^{13}C nmr of **2a** and **2b** were consistent with literature values for derivatives of **2a** (12). All of these observations indicate that this mixture of epimers is hydroxymatairesinol [whose configuration at C–7 is *R*, according to Nishibe *et al.* (12)] and allohydroxymatairesinol [C–7 configuration is *S* (12)] in about a 3:1 ratio.

Column chromatography of F216 (6) gave a fraction that yielded crystals of a new lignan (**3a**) which we have named isoliovil. The ^1H nmr of the acetate (**3b**) (table 1) indicated two aromatic methoxyl groups (singlets at δ3.82 and 3.84),

two aromatic acetate groups (a six-proton singlet at δ2.30), two aliphatic acetate groups (singlets at δ1.99 and 2.05), a one-proton doublet at δ5.78 with a coupling of 10 Hz, a one-proton doublet at δ6.12 ($J=7$ Hz) and several multiplets: δ2.7 (four protons), 3.7–3.9 (two protons) and 6.7–7.0 (six aromatic protons). This spectrum suggests a lignan containing four hydroxyl and two methoxyl groups, isomeric with liovil (13). The only reported ^{1}H nmr of liovil (14) was done in DMSO-d_6 and is of limited value for comparisons. However, this spectrum does show that liovil contains no hydroxyl groups on the tetrahydrofuran ring; in contrast, the ^{1}H nmr of **3b** does indicate the presence of one hydroxyl group on this ring since there is a doublet at δ6.12 due to the methine proton attached to C–9'. Allowing for the downfield shift due to acetate, this doublet ($J=7$ Hz) can be compared to the doublet at δ5.22 ($J=4$ Hz) of R–CH(OH)–O–R' of cubebin (15), although the coupling constant would suggest a different configuration at C–9' and/or C–8' for the two compounds. The other doublet of **3b** (δ5.78, $J=10$ Hz) is quite similar to the doublet (δ5.79, $J=9.6$ Hz) occurring for R–CH(OAc)–R' in the tetraacetate of compound I reported by Andersson *et al.* (16).

The ^{13}C nmr of **3b** (table 2) is very similar to that of **2b** except that the γ-lactone carbonyl at δ178.0 was absent in **3b** and was replaced with a signal at δ102.9 suggesting the presence of the grouping R–CH(OAc)–O–R'. The grouping R–CH(OAc)–R' was indicated by δ76.6 in **3b** (75.4 in **2b**).

Eims of **3a** and its derivatives **3b** and **3c** support the proposed structure of isoliovil but cannot unequivocally distinguish it from its isomers (10, 14, 16).

^{1}H and ^{13}C nmr define the presence of 2-tetrahydrofuranol and confirm the rest of the proposed structure for isoliovil (**3a**). The stereochemistry of the four asymmetric centers (C–7, C–8, C–8' and C–9') is not known. The 3,4-dibenzyl-2-tetrahydrofuranols are relatively uncommon as only five others have been reported: cubebin (15), 3,4-dimethoxy-3,4-desmethylenedioxycubebin (17), kusunokinol (18), acanthotoxin (19) and podotoxin (20).

EXPERIMENTAL[4]

GENERAL PROCEDURES.—Fractionation of the ethanol extract of *Taxus wallichiana* Zucc. needles, roots and stems has been described in detail previously (5, 6).

ISOLATION AND IDENTIFICATION OF CONIDENDRIN (**1a**).—Because of similar tlc patterns, fractions F207 and F212 (fig. 1, ref. 5) were combined, and 209 mg of the mixture was separated by tlc (5% methanol in chloroform) on 2 mm preparative silica gel plates, yielding 115 mg of crude conidendrin. The last-named compound was separated preparatively on 0.25 mm silica gel plates (10% methanol in chloroform) to yield 59 mg which was recrystallized from 95% ethanol, mp 230–237°C, $[\alpha]^{23}$D −57.9° (*c*. 0.14, acetone). Literature: α-conidendrin, mp 255–256°, $[\alpha]$D −53.7 (acetone); β-conidendrin, mp 210–212°, $[\alpha]$D +28° (acetone) (21). ^{1}H nmr, table 1; ^{13}C nmr, table 2. Eims, *m/z* (relative intensity, %): 356 (M^+, 100), 271 (9), 259 (7), 255 (11), 241 (23), 137 (14) and 135 (17).

Acetylation of **1a**+**1b** (acetic anhydride/pyridine at room temperature) gave conidendrin diacetate (**1c**+**1d**) as an amorphous solid. ^{1}H nmr, table 1; ^{13}C nmr, table 2. Literature, see refs. 8 and 9.

ISOLATION AND IDENTIFICATION OF HYDROXYMATAIRESINOL (**2a**).—Upon evaporation, transfers 551–559 from countercurrent fraction P5 (fig. 3, ref. 5) yielded 560 mg of amorphous solid; 217 mg of this solid was applied to a preparative tlc plate and developed with chloroform-methanol (9:1). The major tlc band provided 202 mg of an amorphous solid, **2a**; $[\alpha]^{23}$D −0.95° (*c*. 1.27, ethanol), literature: hydroxymatairesinol, $[\alpha]^{25}$D −11.0° (*c*. 4.0, tetrahydrofuran) and −6.3° (*c*. 4, ethanol); allohydroxymatairesinol, $[\alpha]^{25}$D −9.8° (*c*. 4.0, tetrahydrofuran) and +4.9° (*c*. 4, ethanol) (13). ^{1}H nmr, table 1; literature values for the dimethyl ethers (12).

[4]Melting points were determined on a Fisher-Johns apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded in deuterochloroform (except as noted) on a Bruker WH-90 instrument with tetramethylsilane as the internal reference (90 MHz for ^{1}H and 22.63 MHz for ^{13}C). Eims were obtained with a Kratos MS-30 spectrometer at 70 eV. Nominal mass scans were done at a resolution of 1000 (low resolution ms), and accurate mass measurements (called high resolution in this paper) were made at a resolution of 3000 on the double beam instrument with PFK as a reference in beam 2. Optical rotations were determined on a Perkin-Elmer model 241 Polarimeter. Tlc was accomplished with silica gel 60 F254 plates, both 0.25 mm and 2 mm (E. Merck) with various mixtures of chloroform-methanol as developing solvent. For preparative use, the plates were viewed under uv light; for analytical purposes, the plates were charred after spraying with 1% $K_2Cr_2O_7$ in 40% H_2SO_4.

^{13}C nmr, table 2; literature values are similar (12). Eims, *m/z* (rel. intensity, %): 374 (M^+, 40), 356 (M^+-H_2O, 5), 153 (100), 137 (67) and 93 (28).

Acetylation of **2a** (acetic anyhydride/pyridine at room temperature) gave the triacetate, **2b**. ^1H nmr, table 1, ^{13}C nmr, table 2; literature values for the acetylated dimethyl ethers compare favorably (12). High resolution eims of **2b** *m/z* (rel. intensity, %): 500.1831 (M^+, 6), calcd. for $C_{26}H_{28}O_{10}$ 500.1661; 458.1613 ($M^+-H_2C=C=O$, 57), calcd. for $C_{24}H_{26}O_9$ 458.1576; 416.1777 ($M^+-2\ H_2C=C=O$, 26), calcd. for $C_{22}H_{24}O_8$ 416.1471; 398.1412 ($M^+-H_2C=C=O-CH_3COOH$, 14), calcd. for $C_{22}H_{22}O_7$ 398.1365; 356.1181 ($M^+-2\ H_2C=C=O-CH_3COOH$, 24), calcd. for $C_{20}H_{20}O_6$ 356.1260; 177.0592 (47), calcd. for $C_{10}H_9O_3$ 177.0552; 153.0546 (42), calcd. for $C_8H_9O_3$ 153.0552; 137.0620 (100), calcd. for $C_8H_9O_2$ 137.0602; and 43.0203 (63), calcd. for C_2H_3O 43.0184.

Compound **2c** was prepared by reacting a 2:1 mixture of hexamethyldisilazane and trimethylchlorosilane with **2a** in pyridine for 15 minutes at room temperature (22). High resolution eims *m/z* (rel. intensity, %): 590.2776 (M^+, 16), calcd. for $C_{25}H_{46}O_7Si_3$ 590.2817; 500.2025 (M^+–TMSOH, 6), calcd. for $C_{26}H_{36}O_5Si_2$ 500.2227; 297.1363 (100), calcd. for $C_{14}H_{25}O_3Si_2$ 297.1519; and 209.0954 (12), calcd. for $C_{11}H_{17}O_2Si$ 209.1086. For literature values, see ref. 10.

IDENTIFICATION OF ISOLIOVIL (**3a**).—Separation of F216 (7.559 g) by column chromatography on silica was described previously (6); 72 fractions of 100 ml each were collected using an ethyl acetate-benzene step gradient. Evaporation of fractions 33–36 yielded a crystalline solid (0.835 g) (**3a**) which was triturated with ethyl acetate and recrystallized from methanol; mp 170–172°, $[\alpha]^{23}D-47.9$ (*c*. 0.22, ethanol); eims, *m/z* (rel. intensity, %): 376 (M^-, 34), 358 (M^+-H_2O, 28), 340 ($M^+-2\ H_2O$, 7), 206 (41), 153 (66), 138 (51) and 137 (100).

Acetylation of **3a** (acetic anhydride/pyridine at room temperature) gave isoliovil tetraacetate (**3b**) as an amorphous solid. ^1H nmr, table 1; ^{13}C nmr, table 2; eims, *m/z* (rel. intensity, %): 424 (M^+-2 AcOH, 62), 382 (M^+-2 AcOH–$H_2C=C=O$, 83), 340 (M^+-2 AcOH-2 $H_2C=C=O$, 38), 247 (12), 216 (19), 203 (26), 153 (52) and 137 (100). High resolution ms, *m/z* 424.1545, calcd. for $C_{24}H_{24}O_7$, 424.1522; 382.1455, calcd. for $C_{22}H_{22}O_6$ 382.1416; 340.1321, calcd. for $C_{20}H_{20}O_5$, 340.1311; 247.0981, calcd. for $C_{14}H_{15}O_4$, 247.0970; 195.0661, calcd. for $C_{10}H_{11}O_4$ 195.0657; 153.0569, calcd. for $C_8H_9O_3$, 153.0552; and 137.0605, calcd. for $C_8H_9O_2$, 137.0603.

Isoliovil was silylated as described for **2c**. Eims of **3c** gave *m/z* (rel. intensity, %): 644 (M^-, 56), 649 (M^+-CH_3, 25), 592 (M^++H–TMS, 5), 574 (M^+-TMSOH, 9), 599 (M^+-TMSOH–CH_3, 8), 486 (M^++2H-2TMSOH, 19), 485 (M^++H–2TMSOH, 46), 484 (M^+-2TMSOH, 93), 456 (30), 411 (12), 339 (34), 324 (35), 298 (71), 297 (100), 260 (10), 247 (17), 234 (14), 225 (16), 210 (47), 209 (75), 179 (16), 171 (20), 157 (32) and 73 (73).

ACKNOWLEDGMENTS

We thank Barry Jones and Milton Axley for technical assistance. Partial support to JLM was provided through contract no. NO1-CM-97296, Division of Cancer Treatment, National Cancer Institute.

Received 11 May 1981

LITERATURE CITED

1. H. Erdtman, in "Modern Methods of Plant Analyses," K. Paech and M. V. Tracey, eds., Springer Verlag, Berlin, 1955, Vol. III, pp. 428–449.
2. H. Erdtman and K. Tsuno, *Phytochemistry*, **8**, 931 (1969).
3. R. B. Mujumder, R. Srinivasan and K. Venkataraman, *Indian J. Chem.*, **10**, 677 (1972).
4. C. L. Lee, Y. Hirose and T. Nakatsuka, *Mokuzai Gakkaishi*, **21**, 249 (1975).
5. R. W. Miller, R. G. Powell, C. R. Smith, Jr., E. Arnold and J. Clardy, *J. Org. Chem* , **46** 1469 (1981).
6. J. L. McLaughlin, R. W. Miller, R. G. Powell and C. R. Smith, Jr., *J. Nat. Prod.*, **44**, 312 (1981).
7. O. R. Gottlieb, *Fortschr. Chem. Org. Naturst.*, **35**, 1 (1978).
8. R. C. Cambie, G. T. M. Pang, J. C. Parnell, R. Rodrigo and R. J. Weston, *Aust. J. Chem.*, **32**, 2741 (1979).
9. K. Sudo and A. Sakakibara, *Mokuzai Gakkaishi*, **23**, 151 (1977).
10. R. Ekman, *Holzforschung*, **30**, 79 (1976).
11. A. M. Duffield, *J. Heterocycl. Chem.*, **4**, 16 (1967).
12. S. Nishibe, M. Chiba, A. Sakushima, S. Hisada, S. Yamanouchi, M. Takido, U. Sankawa and A. Sakakibara, *Chem. Pharm. Bull.*, **28**, 850 (1980).
13. K. Freudenberg and L. Knof, *Chem. Ber.*, **90**, 2857 (1957).
14. G. M. Barton, *Wood Fiber*, **2**, 144 (1970).
15. J. E. Batterbee R. S. Burden, L. Crombie and D. A. Whiting, *J. Chem. Soc. C*, **1969**, 2470.
16. R. Andersson, T. Popoff and O. Theander, *Acta Chem. Scand.*, **B29**, 835 (1975).
17. G. Rücker and B. Langmann, *Tetrahedron Lett.*, **1978**, 457.
18. D. Takaoka, N. Takamatsu, Y. Saheki, K. Kono, C. Nakaoka and M. Hiroi, *Nippon Kagaku Kaishi*, **1975**, 2192; *Chem. Absts.*, **84**, 71488k (1976).
19. S. Roy, R. Guha and D. P. Chakraborty, *Chem. Ind. (London)*, **1977**, 231.
20. D. P. Chakraborty, S. Roy, S. P. S. Roy and S. Majumber, *Chem. Ind. (London)*, **1979**, 667.
21. J. Grimshaw, in "Rodd's Chemistry of Carbon Compounds," 2nd Ed., S. Coffey, ed., Elsevier Publishing Company, Amsterdam, 1976, Vol. III, part D, p. 268.
22. C. C. Sweely, R. Bentley, M. Makita and W. W. Wells, *J. Am. Chem. Soc.*, **85**, 2497 (1963).