Antileukemic Compounds Derived by Chemical Modification of Macrocyclic Trichothecenes. 2. Derivatives of Roridins A and H and Verrucarins A and J

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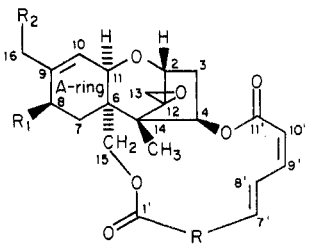
Various 8β-hydroxy, 16-hydroxy, and 9β,10β-epoxy derivatives of roridins A and H and verrucarins A and J have been prepared and tested in vivo against P388 mouse leukemia. The 9β,10β-epoxy derivatives and 16-hydroxy derivatives consistently exhibit very high activity. The 8β-hydroxy-9β,10β-epoxy and 16-hydroxy-9β,10β-epoxy derivatives of verrucarin A and roridin A exhibit extraordinary activity against P388. The 8β-hydroxy-9β,10β-epoxy and 16-hydroxy-9β,10β-epoxy derivatives of verrucarin A and roridin A exhibit extraordinary activity against P388.

A number of plant-derived and microbially produced natural products have served as prototypes for further drug development in the area of cancer chemotherapy. An example of this may be found with the trichothecene antibiotic complex,[1] of which one member, anguidine, has undergone clinical trials in humans.[2] The group at Bristol Laboratories has reported a study of structure–activity relationships (SAR) involving anguidine and its derivatives.[3]

Earlier, we reported[4] that the macrocylic trichothecene verrucarin A (1), which exhibits only low activity in vivo against P388 mouse leukemia, could be converted into 9β,10β-epoxyverrucarin A (2), which exhibits good activity in vivo against P388. The idea for this simple structural modification was based on the structure of baccharin (3),[5] a compound highly active against P388 in vivo, which was isolated from a Brazilian shrub.[5] This source has produced a series of baccharinoids[6] that are highly active in vivo and whose structures closely resemble those of the fungi-derived macrocyclic trichothecenes, verrucarins and roridins.[7] The baccharinoids can be classified as either 8β-hydroxyroridins (Chart I) or 9β,10β-epoxyroridins (Chart II). Thus, it appears that conversion of inactive roridins and verrucarins to either their 9β,10β-epoxy or 8β-hydroxy derivatives will result in the production of compounds

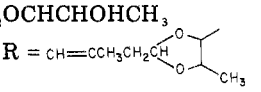
Chart I

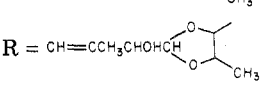


verrucarin A (1), $R_1 = R_2 = H$;
R = $CHOHCH(CH_3)CH_2CH_2OC{=}O$ (2′, 3′, 12′, 4′, 5′, 6′)

verrucarin J (4), $R_1 = R_2 = H$;
R = $CH{=}CCH_3CH_2CH_2OC{=}O$

roridin A (5), $R_1 = R_2 = H$;
R = $CHOHCHCH_3CH_2CH_2OCHCHOHCH_3$

roridin H (6), $R_1 = R_2 = H$; R = 

roridin J (7), $R_1 = R_2 = H$; R = 

baccharinol (8), $R_1 = OH$; $R_2 = H$;
R = $CH(O)CCH_3CHOHCH_2OCHCHOHCH_3$

8β-hydroxyverrucarin A (10), $R_1 = OH$; $R_2 = H$;
R = $CHOHCHCH_3CH_2CH_2OC{=}O$

8β-hydroxyroridin A (11), $R_1 = OH$; $R_2 = H$;
R = $CHOHCHCH_3CH_2CH_2OCHCHOHCH_3$

8β-hydroxyverrucarin J (17), $R_1 = OH$; $R_2 = H$;
R = $CH{=}CCH_3CH_2CH_2OC{=}O$

16-hydroxyroridin A (18), $R_1 = H$; $R_2 = OH$;
R = $CHOHCHCH_3CH_2CH_2OCHCHOHCH_3$

16-hydroxyverrucarin J (19), $R_1 = H$; $R_2 = OH$;
R = $CH{=}CCH_3CH_2CH_2OC{=}O$

16-hydroxyverrucarin A (25), $R_1 = H$; $R_2 = OH$;
R = $CHOHCHCH_3CH_2CH_2OC{=}O$

active against P388 in vivo. In this paper we report our SAR studies with verrucarins A (1) and J (4) and roridins A (5), H (6), and J (7).

Results and Discussion

The roridins and verrucarins used in this study were derived from a large-scale (760 L) fermentation of *Myrothecium verrucaria* (ATCC 24571).[8] Our previous experience[4] suggested that the 9β,10β-epoxy derivatives (cf. baccharin, 3) would exhibit higher activity than the 8β-hydroxy derivatives (cf. baccharinol, 8). Thus, treatment of verrucarin A (1) and roridin A (5) with *m*-chloroper-

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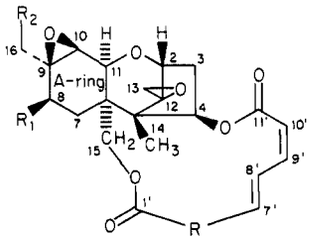
Table I. *In Vivo* P388 Mouse Leukemia Test Data for Macrocyclic Trichothecenes

compound	P388 dose,[a] mg/kg	T/C (survivors/total)[b]	MED[c] (T/C >125)
verrucarin A (1)	2	127	
verrucarin J (4)	0.8	150	
roridin A (5)	0.06	128	
roridin H (6)	12.5	131	
roridin J (7)	5	158	0.6
baccharin (3)	5.0	311	0.3
baccharinol (8)	2.5	185	1
8β-hydroxyverrucarin A (10)	1.25	132	0.5
8β-hydroxyroridin A (11)	0.2	156	0.025
8β-hydroxyverrucarin J (17)	1.25	181	0.15
9β,10β-epoxyverrucarin A (2)	8	210	0.12
9β,10β-epoxyroridin A (9)	10	205	0.15
9β,10β-epoxyverrucarin J (12)	8	172	0.5
9β,10β-epoxyroridin H (15)	32	172	4
9β,10β-epoxyroridin J (16)	12	101	
16-hydroxyverrucarin A (25)	4	252	<0.25[f]
16-hydroxyroridin A (18)	1.25	258 (1/6)	<0.16[f]
8β-hydroxy-9β,10β-epoxyverrucarin A (21)	20	321 (4/6)	<0.16[f]
8β-hydroxy-9β,10β-epoxyroridin A (22)	20	321[d] (3/6)[e]	<0.16[f]
16-hydroxy-9β,10β-epoxyverrucarin A (23)	6	203	<0.12[f]
16-hydroxy-9β,10β-epoxyroridin A (24)	6	321 (4/6)	<0.16[f]

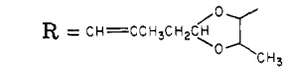
[a] The dose levels are those that exhibit the highest T/C values (days test animals live/days control animals live × 100). Higher dose levels generally are toxic. [b] "Cures" are mice surviving to day 30 postimplant. [c] Minimum effective dose, in milligrams per kilogram. [d] Gave a T/C = 321 at 20, 10, and 5 mg/kg and a T/C of 227, 229, 166, 160, and 150 at dose levels of 2.5, 1.25, 0.62, 0.31, and 0.16 mg/kg, respectively. [e] At a dose level of 10 mg/kg; at dose levels of 20 and 5 mg/kg, there were 2 out of 6 survivors for each test. [f] Minimum dose level tested; T/C's ≥ 150.

Chart II

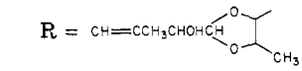


9β,10β-epoxyverrucarin A (2), $R_1 = R_2 = H$;
R = $CHOHCHCH_3CH_2CH_2OC{=}O$
baccharin (3), $R_1 = R_2 = H$;
R = $CH{-}CCH_3CHOHCH_2OCHCHOHCH_3$ (with O bridge)
9β,10β-epoxyroridin A (9), $R_1 = R_2 = H$
R = $CHOHCHCH_3CH_2CH_2OCHCHOHCH_3$
9β,10β-epoxyverrucarin J (12), $R_1 = R_2 = H$;
R = $CH{=}CCH_3CH_2CH_2OC{=}O$
9β10β:2′(*S*),3′(*R*)-diepoxyverrucarin J (9β,10β-epoxyverrucarin B) (14), $R_1 = R_2 = H$;
R = $CH{-}CCH_3CH_2CH_2OC{=}O$ (with O bridge)

9β,10β-epoxyroridin H (15), $R_1 = R_2 = H$;



9β,10β-epoxyroridin J (16), $R_1 = R_2 = H$;



8β-hydroxy-9β,10β-epoxyverrucarin A (21), $R_1 = OH$;
$R_2 = H$; R = $CHOHCHCH_3CH_2CH_2OC{=}O$
8β-hydroxy-9β,10β-epoxyroridin A (22), $R_1 = OH$;
$R_2 = H$; R = $CHOHCHCH_3CH_2CH_2OCHCHOHCH_3$
16-hydroxy-9β,10β-epoxyverrucarin A (23), $R_1 = H$;
$R_2 = OH$; R = $CHOHCHCH_3CH_2CH_2OC{=}O$
16-hydroxy-9β,10β-epoxyroridin A (24), $R_1 = H$;
$R_2 = OH$; R = $CHOHCHCH_3CH_2CH_2OCHCHOHCH_3$

oxybenzoic acid (MCPBA) yields the 9β,10β-epoxides **2** and **9**, respectively, which possess markedly increased activity in vivo against mouse P388 leukemia,[4] whereas conversion of verrucarin A to its 8β-hydroxy derivative (**10**) gives a derivative exhibiting only a modest increase in P388 activity in vivo.[4]

Treatment of verrucarin J with MCPBA produced 9β,10β-epoxyverrucarin J (**12**) (50% yield), 9α,10α-epoxyverrucarin J (**13**; α-isomer of **12**) (5% yield), and 9β,10β:2′(*S*),3′(*R*)-diepoxyverrucarin J (**14**). The latter diepoxide derivative was identical with 9β,10β-epoxyverrucarin B synthesized earlier in our laboratory.[4] Since the X-ray structure of verrucarin B has been reported,[9] we can assign the configuration of our epoxidation product, **14**, with confidence. The configurations of β-epoxide **12** and α-epoxide **13** were established by ^1H NMR spectroscopy; in **12**, $J_{10,11} = 4$ Hz (cis coupling), whereas in **13**, $J_{10,11} = 2$ Hz (trans coupling).[3,4]

In a similar fashion, roridin H was epoxidized with MCPBA to give the 9β,10β-epoxide (**15**) as the major product, accompanied by a trace of the 9α,10α-epoxide. Under the reaction conditions, the β-epoxide was partly transformed to products in which further epoxidation at the 7′,8′ and 2′,3′ positions had occurred. Upon epoxidation, roridin A behaved in a similar manner.[10] Under the same conditions, roridin J (**7**) produced 9β,10β-epoxyroridin J (**16**), accompanied by very minor amounts of side products.

Selenium dioxide hydroxylation of roridin A and verrucarin J gave principally the 8β-hydroxy derivatives **11** and **17**, respectively, accompanied by minor amounts of 16-hydroxyroridin A (**18**) and 16-hydroxyverrucarin J (**19**), respectively. Upon hydrolysis, **11** and **17** gave 8β-hydroxyverrucarol (**20**).[6] The structures of hydroxyl derivatives **11** and **17**–**19** were firmly established by ^1H and ^{13}C NMR spectroscopy.

Epoxidation of the 8β-hydroxy and 16-hydroxy derivatives of verrucarin A and roridin A led exclusively to the 9β,10β-epoxy derivatives **21**–**24**. Presumably, the neigh-

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boring hydroxyl group directs epoxidation (Henbest rule)[11] to the β-face of the A ring, which diminishes the extent of side reactions.

The P388 activity data (in vivo) of the semisynthetic products tested, as well as data for their parent compounds, are given in Table I. Conversion of the parent compounds into the 9β,10β-epoxides results in a very marked increase in P388 activity in vivo, with the single exception of roridin J (7). Unlike most of the other verrucarins and roridins, 7 exhibits substantial P388 activity in vivo (T/C = 158 at 5 mg/kg). However, upon conversion to the 9β,10β-epoxide 16, the activity seems to disappear (T/C = 100 from 0.6 to 15 mg/kg). However, insufficient material prevented testing at a higher dose level where there may be appreciable activity, as in the case of 9β,10β-epoxyroridin H (vide infra). Roridin H (6), whose structure is very similar to that of roridin J (7) shows a substantial increase in P388 activity upon transformation to 9β,10β-epoxide 15: T/C = 131 at 12.5 mg/kg for 6 and T/C = 172 at 32 mg/kg for 15 (Table I).

The 16-hydroxylated derivatives 23 and 24 are more potent than the isomeric 8-hydroxylated derivatives 21 and 22. The introduction of both an 8β-hydroxyl group and a 9β,10β-epoxide ring or, conversely, both a C16-hydroxyl group and a 9β,10β-epoxide group in the A ring of verrucarin A and roridin A results in a series of compounds (21–24) with extremely high activity against P388 mouse leukemia (Table I). 8β-Hydroxy-9β,10β-epoxyroridin A (22) is particularly notable because it exhibits T/C values of 227–321 over the dosage range of 1.25–20 mg/kg.

A principal effect of epoxidation of the 9,10-double bond in the macrocyclic trichothecenes is a diminishment in the toxicity of these compounds by an order of magnitude. Thus, verrucarins and roridins are toxic at dosage levels of a few milligrams per kilogram (intraperitoneally, in mice), whereas their 9β,10β-epoxides typically do not begin to exhibit significant toxicity until levels of 10 mg/kg and above are reached. It is in the dose region of 1–10 mg/kg that these epoxy derivatives exhibit marked activity in vivo against P388 mouse leukemia. Therefore, epoxidation of the 9,10-double bond has the effect of lowering toxicity toward normal cells without appreciably affecting toxicity toward neoplastic cells. This results in the observed high therapeutic index for these compounds. There might also be some increase in the intrinsic antileukemic properties of these compounds, but our data are insufficient to confirm this point.

Experimental Section

General Methods. Melting points were determined on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined in deuteriochloroform on an IBM FT-200 or a Varian XL-100 or FT-80 spectrometer with tetramethylsilane as an internal standard. The ^{13}C NMR signals (Table II) were assigned by using ^{1}H single-frequency off-resonance decoupling techniques, by using chemical-shift relations, and by comparison with literature data. Microanalyses were performed by Dr. Franz Kasler of the University of Maryland. Thin-layer chromatography (TLC) and preparative thick-layer chromatography were carried out on prepared silica gel (E. Merck or Analtech), and visualization was effected with short-wavelength UV light or sulfuric acid/ethanol/vanillin (20:3:1) spray. Flash chromatography was carried out on silica gel 60 (230–400 mesh, E. Merck on Whatman LPS-2). Medium-pressure liquid chromatography (MPLC) was carried out on either Licroprep 60 (E. Merck) or Whatman LPS-1 silica gel. High-pressure liquid chromatography (HPLC) was performed with an Altex Model 332 gradient liquid chromatograph. The starting macrocyclic trichothecenes were isolated from a large-scale liquid culture of *Myrothecium verrucaria* as described elsewhere.[8] P388 test data (Table I) were furnished by the National Cancer Institute. The compounds in Table I were tested on at least two separate occasions, and the reliability of the data was monitored by use of a control (CSC = 1 in each case). Testing was conducted intraperitoneally, qdi-9, as previously detailed.[12]

Hydroxylation of Verrucarin J. In 8 mL each of glacial acetic acid and acetic anhydride was dissolved 456 mg (0.92 mmol) of verrucarin J and 470 mg of selenium dioxide. The reaction mixture was stirred at 90 °C for 1 h. Filtration of black granular selenium metal gave an orange solution, which was carefully poured into 300 mL of saturated sodium bicarbonate solution. The solution was extracted with three 300-mL portions of methylene chloride, and the organic portion was dried with $MgSO_4$. The solvent was removed in vacuo to yield 440 mg of crude orange solid. The sample was then charged on a C-18 siloxane reverse-phase column and eluted with 50% water–methanol (air pressure) to remove most of the colloidal red selenium The sample was then subjected to flash chromatography on a silica gel (150 g) column with 60% ethyl acetate–hexane solvent system to give two components obtained as solids: 8β-hydroxyverrucarin J (17; 160 mg, 35%), mp 165–170 °C, and 16-hydroxyverrucarin J (19; 25 mg, 5%), mp >300 °C. Anal. Calcd for $C_{27}H_{32}O_9$: C, 64.79; H, 6.44. Found for 17: C, 64.52; H, 6.69. Found for 19: C, 64.78; H, 6.41.

Hydroxylation of Roridin A. This reaction was conducted in the same fashion as that described for hydroxylation of verrucarin J (vide supra) to give 8β-hydroxyroridin A (11), mp 237–239 °C, in 30% yield and 16-hydroxyroridin A (18), mp 206–207 °C, in 12.5% yield. Anal. Calcd for $C_{29}H_{40}O_{10}$: C, 63.49; H, 7.35. Found for 11: C, 63.58; H, 7.20. Found for 18: C, 63.64; H, 7.42.

Epoxidation of Verrucarin J. To a solution of 250 mg (0.52 mmol) of verrucarin J (4) in 2 mL of chloroform was added 119 mg (0.65 mmol) of 80–90% *m*-chloroperoxybenzoic acid (MCPBA; Aldrich Chemical Co.). After the solution was stirred for 12 h, the mixture was diluted with 30 mL of methylene chloride, washed with 15 mL of saturated sodium bicarbonate solution, and dried with magnesium sulfate; solvent was removed in vacuo. The crude product was separated by MPLC (2.6 cm, OD Michel-Miller column) with 30% ethyl acetate in hexane as the eluting solvent. Three products (all crystallized from methylene chloride–ether) were as follows, in order of elution from the column: 9α,10α-epoxyverrucarin J (13; 12 mg, 4.6%), mp 267–270 °C; 9β,10β-epoxyverrucarin J (12; 130 mg, 50%), mp 260–268 °C; 9β,10β:2′(*S*),3′(*R*)-diepoxyverrucarin J (14; 2 mg, 0.8%), mp >300 °C. Anal. Calcd for $C_{27}H_{32}O_9$: C, 64.79; H, 6.44. Found for 12: C, 64.70; H, 6.33. Found for 13: C, 64.83; H, 6.30.

Compound 14 was obtained in 60% yield by treatment of 12 with MCPBA in methylene chloride (2 days at room temperature) and was shown to be identical with 9β,10β-epoxyverrucarin B synthesized earlier by epoxidation of verrucarin B.[4]

Epoxidation of Roridin H (6). In 2 mL of methylene chloride was dissolved 100 mg (0.2 mmol) of roridin H (6), and 37.2 mg (0.24 mmol) of MCPBA was added. TLC analysis indicated incomplete epoxidation after 48 h. A further equivalent (31 mg) of MCPBA was added, and the reaction was allowed to continue for 12 h longer. Preparative TLC (25% ethyl acetate in hexane) on a 2-mm plate yielded three fractions. The highest eluting fraction, F1, was crystallized from ether–hexane to yield 5.2 mg (4.7%) of amorphous solid identified as 9α,10α-epoxyroridin H based on ^{1}H NMR spectroscopy (H-10 at δ 2.97, $J_{10,11}$ = 2.0 Hz). F2 was crystallized from methylene chloride–hexane to give 37.3 mg (34.0%) of 9β,10β-epoxyroridin H (15), mp 193–195 °C. F3 (49.3 mg) showed several spots upon TLC analysis (10% ethyl acetate in methylene chloride) and was separated into three components by HPLC (M-9 Whatman column) under gradient elution (5–25% ethyl acetate in methylene chloride). The second component was the major product (30.0 mg). ^{1}H NMR analysis

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Table II. ^{13}C and ^{1}H NMR Spectra of Macrocyclic Trichothecene Derivatives[a]

position	11	18
2	79.2, d (3.88) [4.8]	79.2, d (3.86) [4.9]
3	34.8, t (2.44, α) [15.4, 8.2]	35.0, t (2.47, α) [15.4, 8.2]
4	73.9, d (5.8, m)	74.3, d (5.8, m)
5	49.6	49.5
6	45.6	44.3
7	30.5, t	20.0, t
8	68.1, d (3.9, m)	23.2, t
9	143.0	143.7
10	120.6, d (5.50) [5.3]	118.0, d (5.72) [5.2]
11	67.1, d	66.7, d
12	65.0	66.0
13	47.7, t (2.98, AB) [4.0]	47.8, t (2.93, AB) [4.0]
14	7.5, q (0.81)	7.5, q (0.82)
15	65.1, t (4.43, AB) [12]	64.4, t (4.44, s)
16	18.8, q (1.84)	65.2, t (4.07)
1′	174.9	174.9
2′	75.6, d (4.11) [3.2]	75.6, d (4.05) [3.2]
3′	37.1, d	37.1, d
4′	33.1, t	33.1, t
5′	69.8, t	69.9, t
6′	84.0, d	84.0, d
7′	139.4, d (6.00) [15.6, 2.9]	139.4, d (6.00) [15.6, 2.8]
8′	126.1, d (7.65) [15.6, 11.4]	126.2, d (7.67) [15.6, 11.4]
9′	144.1, d (6.66) [11.4, 11.4]	144.0, d (6.66) [11.4, 11.4]
10′	117.4, d (5.79) [11.4]	117.5, d (5.80) [11.4]
11′	166.6	166.6
12′	14.8, q (1.08) [6.8]	14.8, q (1.08) [6.8]
13′	70.8, d	70.8, d
14′	18.3, q (1.19) [5.8]	18.3, q (1.19) [5.8]

position	22	24
2	78.8, d (3.98) [5.0]	78.8, d (3.95) [5.0]
3	34.6, t	34.8, t
4	73.7, d (5.8, m)	73.9, d (5.8, m)
5	49.1	49.2
6	46.2	46.0
7	27.0, t (2.0, m)	18.5, t (2.0, m)
8	69.0, d	25.1, t
9	60.5	59.7
10	60.8, d (3.30) [5.2]	60.1, d (3.40) [5.2]
11	66.8, d (3.54) [5.2]	67.1, d (3.62) [5.2]
12	64.6	64.4
13	47.6, t (2.98, AB) [4.0]	47.7, t (2.98, AB) [4.0]
14	7.5, q (0.77)	7.5, q (0.76)
15	64.2, t (4.36, AB) [12]	64.8, t (4.48, AB) [12]
16	18.5, q (1.52)	68.1, t
1′	174.9	174.9
2′	75.6, d (4.16) [3.2]	75.7, d (4.11) [3.2]
3′	37.2, d	37.2, d
4′	33.1, t	33.1, t
5′	69.9, t	69.9, t
6′	84.0, d	84.0, d
7′	139.7, d (6.00) [15.5, 2.8]	139.6, d (6.00) [15.5, 2.8]
8′	126.0, d (7.68) [15.5, 11.4]	126.0, d (7.72) [15.5, 11.4]
9′	144.4, d (6.67) [11.4, 11.4]	144.5, d (6.66) [11.4, 11.4]
10′	117.1, d (5.81) [11.4]	117.1, d (5.82) [11.4]
11′	166.6	166.6
12′	14.8, q (1.09) [6.8]	14.8, q (1.10) [6.8]
13′	70.8, d	70.8, d
14′	18.3, q (1.19) [6.0]	18.3, q (1.16) [6.0]

position	15	16
2	78.8, d (3.93) [5.0]	78.9, d (3.85) [5.0]
3	34.6, t (2.2, m)	34.6, t
4	73.9, d (6.00) [8, 4]	73.8, d
5	48.8	49.2
6	42.7	43.2
7	17.6, t (2.2, m)	18.5, t
8	26.3, t (2.2, m)	27.0, t
9	57.8	58.0
10	57.7, d (3.18) [5.4]	57.8, d (3.16) [5.2]
11	68.1, d (3.62) [5.4]	68.2, d (3.85) [5.2]
12	65.1	65.2
13	47.8, t (2.93, AB) [4.0]	47.6, t (2.94, AB) [4.0]
14	7.4, q (0.82)	7.5, q (0.78)
15	62.6, t (4.28, AB) [12]	63.3, t (4.25, AB) [12]
16	23.3, q (1.38)	23.2, q (1.36)

Table II (*Continued*)

position	15	16
1′	166.3	165.8
2′	118.5, d (5.88, br s)	119.8, d (5.84) [1.2]
3′	155.4	155.4
4′	47.8, t	79.8, d
5′	100.8, d (5.55) [8.0, 3.8]	103.3, d
6′	82.1, d	82.3, d
7′	135.0, d (5.84) [15.5]	134.6, d (5.82) [15.5]
8′	126.2, d (7.70) [15.5, 11.5]	126.1, d (7.64) [15.5, 11.5]
9′	143.2, d (6.58) [11.5, 11.5]	143.1, d (6.45) [11.5, 11.5]
10′	118.8, d (5.90) [11.5]	118.9, d (5.90) [11.5]
11′	166.3	166.2
12′	18.2, q (2.30) [1.2]	13.2, q (2.29) [1.2]
13′	76.8, d (3.68) [6.0]	76.5, d (3.60) [6.0]
14′	16.5, q (1.34) [6.0]	16.1, q (1.39) [6.0]

position	17	19	12
2	79.3, d	79.3, d	78.7, d
3	35.2, t	35.3, t	34.6, t
4	75.0, d (5.86, m)	75.0, d (5.85, m)	75.1, d (5.85, m)
5	49.1	49.1	48.8
6	45.3	43.7	42.7
7	31.3, t	20.6, t	17.7, t
8	68.3, d	23.3, t	26.4, t
9	142.4	143.2	57.7
10	121.2, d (5.88) [5.0]	118.3, d (5.62) [5.0]	57.5, d (3.10) [5.2]
11	67.3, d (3.90) [5.0]	66.9, d (3.85) [5.0]	67.9, d
12	65.4	65.4	65.0
13	48.0, t (3.02, AB) [4]	48.0, t (3.04, AB) [4]	47.8, t (2.98, AB) [4]
14	7.0, q (0.85)	7.0, q (0.84)	7.2, q (0.79)
15	64.0, t (4.38, AB) [12]	63.3, t	62.6, t (4.50, AB) [12]
16	18.8, q (1.86)	66.1, t	22.3, q (1.46)
1′	165.8	165.8	166.0
2′	118.1, d (5.86) [1.2]	118.8, d (5.84) [1.2]	117.9, d (5.82) [1.2]
3′	156.9	156.5	157.1
4′	40.3, t	40.4, t	40.2, t
5′	60.5, t	60.4, t	60.4, t
6′	165.5	165.5	165.4
7′	127.6, d (6.04) [15.5]	127.5, d (6.00) [15.5]	128.0, d (6.05) [15.5]
8′	139.0, d (8.05) [15.5, 11.5]	139.2, d (8.06) [15.5, 11.5]	138.7, d (8.04) [15.5, 11.5]
9′	139.6, d (6.60) [11.5, 11.5]	139.5, d (6.60) [11.5, 11.5]	140.1, d (6.64) [11.5, 11.5]
10′	125.4, d (6.14) [11.5]	125.5, d (6.13) [11.5]	125.1, d (6.09) [11.5]
11′	165.8	165.8	165.9
12′	17.3, q (2.03) [1.2]	17.3, q (2.28) [1.2]	17.2, q (2.32) [1.2]

position	21	23
2	77.4, d	78.7, d
3	34.4, t	34.7, t
4	75.2, d (5.78) [8, 4]	73.3, d (5.76) [8, 5]
5	48.7	49.3
6	45.8	44.1
7	25.9, t	16.7, t
8	65.5, d	21.6, t
9	59.4	60.5
10	59.1, d (3.33) [5.4]	53.8, d (3.40) [5.4]
11	66.8, d (3.99) [5.4]	66.8, d (3.99) [5.4]
12	64.7	64.7
13	46.7, t (2.94, AB) [4]	47.7, t (2.94, AB) [4]
14	7.0, q (0.82)	7.4, q (0.78)
15	62.0, t (4.43, AB) [12]	62.7, t (4.46, AB) [12]
16	18.7, q (1.56)	63.0, t
1′	173.5	174.9
2′	73.0, d (4.18) [3.5]	74.3, d (4.18) [3.5]
3′	32.5, d	33.4, d
4′	31.4, t	32.3, t
5′	61.0, t	61.1, t
6′	164.8	165.4
7′	127.3, d (6.04) [15.5]	127.7, d (6.04) [15.5]
8′	138.4, d (8.08) [15.5, 11.5]	138.8, d (8.08) [15.5, 11.5]
9′	138.4, d (6.73) [11.5, 11.5]	139.3, d (6.70) [11.5, 11.5]
10′	126.0, d (6.14) [11.5]	125.5, d (6.12) [11.5]
11′	165.6	166.1
12′	10.3, q (0.88) [6.8]	10.0, q (0.88) [6.8]

[a] All spectra were taken in deuteriochloroform solvent. The proton shifts are in parentheses, and J_{H-H} values (in hertz) are in brackets.

showed it to be 9β,10β:7′,8′-diepoxyroridin H (H-10 at δ 3.18, $J_{10,11}$ = 4.1 Hz), mp 259–261 °C. NMR spectra of the minor components, 2 and 1.5 mg each, indicated that they were also diepoxides, with extra epoxidation apparently present at the 7′,8′ double bond, since the normal dienic splitting pattern downfield was not observed. Anal. Calcd for $C_{29}H_{36}O_9$: C, 65.84; H, 6.87. Found for 9α,10α-epoxyroridin H: C, 65.69; H, 6.89. Found for **15**: C, 65.75; H, 6.92. Anal. Calcd for $C_{29}H_{36}O_{10}$: C, 63.96; H, 6.66. Found for 9β,10β:7′,8′-diepoxyroridin H: C, 64.10; H, 6.51.

9β,10β-Epoxyroridin J (16). To a solution of 198 mg (0.37 mmol) of roridin J (**7**) in 20 mL of methylene chloride was added 94 mg (0.60 mmol) of MCPBA. This mixture was stirred overnight at room temperature, diluted to 25 mL with methylene chloride, and washed twice with 15 mL of saturated sodium bicarbonate solution. The organic portion was dried with $MgSO_4$, and the solvent was removed in vacuo to yield 200 mg of crude product; TLC analysis showed it to be composed of a single major product with two other minor products. Preparative TLC on 2-mm plates with 30% ethyl acetate in hexane, followed by crystallization from ether–hexane, gave 90 mg (43% yield) of 9β,10β-epoxyroridin J (**16**), mp 175–179 °C. Anal. Calcd for $C_{29}H_{36}O_{10}$: C, 63.96; H, 6.66. Found: C, 63.75; H, 6.79.

9β,10β-Epoxides of 8β-Hydroxy and 16-Hydroxy Derivatives of Verrucarin A and Roridin A. Synthesis of 21–24. Epoxidation of alcohols **10**, **11**, **18**, and **25** carried out in the usual fashion (MCPBA/CH_2Cl_2 overnight) gave the following epoxides (yield, melting point), isolated by PTLC (EtOAc/hexane): **21** (71%, 152–153 °C); **22** (59%, mp 149–152 °C); **23** (47%, 294–298 °C); **24** (35%, mp 138–142 °C). Anal. Calcd for $C_{27}H_{34}O_{11}$: C, 60.66; H, 6.41. Found for **21**: C, 60.88; H, 6.30. Found for **23**: C, 60.79; H, 6.27. Anal. Calcd for $C_{29}H_{40}O_{11}$: C, 61.69; H, 7.14. Found for **22**: C, 61.85; H, 7.00. Found for **24**: C, 61.50; H, 6.98.

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Registry No. **1**, 3148-09-2; **2**, 74560-38-6; **3**, 61251-97-6; **4**, 4643-58-7; **5**, 14729-29-4; **6**, 29953-50-2; **7**, 74072-83-6; **8**, 63783-94-8; **9**, 74516-67-9; **10**, 74608-63-2; **11**, 87583-91-3; **12**, 87532-25-0; **14**, 74516-66-8; **15**, 87532-26-1; **16**, 87532-27-2; **17**, 87583-92-4; **18**, 87532-28-3; **19**, 87532-29-4; **21**, 87532-30-7; **22**, 87532-31-8; **23**, 87532-32-9; **24**, 87532-33-0; **25**, 74516-64-6; 9β,10β:7′,8′-diepoxyroridin H, 87532-34-1.

Book Reviews

Alkaloids: Chemical and Biological Perspectives. Volume 1. Edited by S. William Pelletier. Wiley, New York. 1983. xi + 398 pp. 16.5 × 24 cm. 0-471-08811-0. $60.00.

Any new series of books on the alkaloids, such as this, must expect to be compared to the classic series, "The Alkaloids", edited by R. H. F. Manske until his untimely death in 1977. The first volume in that series appeared in 1950 and the 17th appeared in 1979. The present series indeed has a difficult act to follow. The editor of the present series himself contributed three chapters to the Manske series. It is stated on the fly jacket: "Here is the first volume in an outstanding new series that provides unprecedented interdisciplinary coverage of material relating to the chemical and biological properties of alkaloids... Because no other series provides this interdisciplinary approach to alkaloids...". One hopes that the high standards of the Manske series will be maintained regardless of the reasons or justifications presented for this new series.

This first volume is composed of five chapters, and each one is concerned with a different subject. We will briefly look at each chapter in turn.

Chapter 1, entitled "The Nature and Definition of an Alkaloid", by S. William Pelletier is 31-pages long, containing 111 references and 10 sections. One of the author's colleagues is quoted in the beginning of the chapter as follows: "An alkaloid is like my wife. I can recognize her when I see her, but I can't define her." Finally, the author, after reviewing all of the types of compounds that apparently workers in the field agree are classified as alkaloids, suggests the following simple definitions: "An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms." While this chapter is interesting both from a historical perspective and as a brief summation of the field, it is unlikely that Pelletier's definition will affect the state of things.

Chapter 2, entitled "Arthropod Alkaloids: Distribution, Functions, and Chemistry", by Tappey H. Jones and Murray S. Blum contains 51 pages with 160 references, including several in 1982. There are 13 sections. Each of the heterocylic sections is divided into the three parts: "Distribution", "Function", and "Chemistry". These authors used a definition for alkaloids that was considered inappropriate in Chapter 1! The introduction contains some interesting and thought-provoking observations. Thus, arthropods have achieved an incredible degree of success in spite of great predatory pressure, and to a large measure this is due to the presence of potent defensive secretions, which are frequently alkaloids; since these animals, which account for 80% of all animal species, synthesize a wide variety of distinctive alkaloids, they will continue to be an outstanding source of nitrogenous compounds. The ability to utilize animal behavior in order to study the raison d'etre of these alkaloids presents zoologists with a luxury not generally available to those studying plant alkaloids. In the title at the top of each page, arthropod is misspelled.

Chapter 3, entitled "Biosynthesis and Metabolism of the Tobacco Alkaloids", by Edward Leete contains 67 pages and 388 references and is divided into 12 sections. Figure 1 shows the structures of 45 alkaloids of tobacco. Table 1 lists species other than Nicotiana in which nicotine and related alkaloids have been found and contains 85 entries. Table 2 lists 23 pages of tracer experiments relating to biosynthesis and metabolism of tobacco alkaloids. It is not difficult to believe the author's statement that tobacco has been more thoroughly examined than any other plant product. This chapter is clearly an exhaustive account for the expert but also provides much of interest to the nonspecialist.

Chapter 4, entitled "The Toxicology and Pharmacology of Diterpenoid Alkaloids", by M. H. Benn and John M. Jacyno contains 57 pages with 150 references and is divided into the three parts. Within Part 2, the properties of 64 alkaloids are discussed—this comprises the major part of the chapter. This treatment is uneven; sometimes detailed quantitative information is presented, whereas in other cases, perhaps by necessity, reference is made to a vague statement in the literature. Table 1 summarizes the acute toxicities of 42 diterpenoid alkaloids. Scrutiny of the pharmacological properties of the alkaloids is stated to reveal a broad range of symptoms, including impairment of the cardiovascular system (hypotension, cardiac arrhythmias), respiratory inhibition, muscular paralysis, and disturbances of the central nervous system. These effects appear to be due to the drugs acting as neurotoxins. Two main types can be characterized: those with aconitinelike (aconitiform) activity and those with curarelike (curariform) activity. This chapter is clearly of most interest to a relatively small group of specialists.

Chapter 5, entitled "A Chemotaxonomic Investigation of the Plant Families Apocynaceae, Loganiaceae, and Rubiaceae by Their Indole Alkaloid Content", by M. Volkan Kisakurek, Anthony J. M. Leeuwenberg, and Manfred Hesse comprises almost half the book with 166 pages. This chapter lists 754 references and was