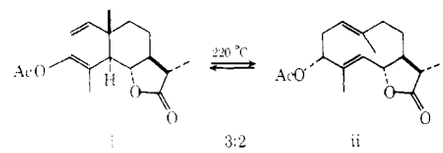
(d, 1 H, J = 3 Hz), 5.52 (d, 1 H, J = 3 Hz), 4.86 (m, 1 H), 4.72 (d, 1 H, J = 9 Hz), 4.56 (t, 1 H, J = 9 Hz), 1.71 (d, 3 H, J = 1 Hz), 1.42 (d, 3 H, J = 1 Hz).

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (CA 13689-04) from the National Cancer Institute and by the Alfred P. Sloan Foundation. We thank Mr. S. D. Burke and Mr. G. Majetich for many helpful comments and suggestions.

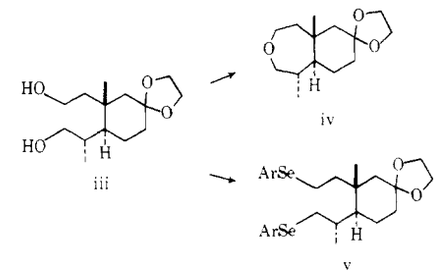
Registry No.—**1**, 28290-35-9; **2**, 553-21-9; **3**, 23527-07-3; **4**, 2225-79-8; **6**, 13902-54-0; **6** hydrazone, 61617-82-1; **7**, 60390-22-9; **8**, 61617-83-2; **9**, 61617-84-3; **10**, 61617-85-4; **11**, 61617-86-5; **12**, 61617-87-6; tosylhydrazine, 1576-35-8; *o*-nitrophenyl selenocyanate, 51694-22-5; diphenyl diselenide, 1666-13-3.

References and Notes

(1) (a) V. Herout, M. Suchý, and F. Šorm, *Collect. Czech. Chem. Commun.*, **26**, 2612 (1961); (b) A. S. Rao, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, **9**, 275 (1960).
(2) E. J. Corey and A. G. Hortmann, *J. Am. Chem. Soc.*, **87**, 5736 (1965). Recently a synthesis of dihydrocostunolide was reported [Y. Fujimoto, T. Shimizu, and T. Tarsuno, *Tetrahedron Lett.*, 2041 (1976)] which was based on the Corey use of the photolytic cleavage of a hexahydronaphthalene derivative.
(3) In 1967, N. H. Fischer and T. J. Mabry [*Chem. Commun.*, 1235 (1967)] reported the first example of the formation of a germacranolide from a



trans-1,2-divinylcyclohexane derivative (cf. i → ii). More recently T. C. Jain, C. M. Banks, and J. E. McCloskey [*Tetrahedron Lett.*, 841 (1970)] demonstrated the reversibility of the Cope rearrangement on dihydrocostunolide and costunolide.
(4) For a review of the Cope rearrangement see S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).
(5) A. S. Rao, A. Paul, D. Sadgopal, and S. C. Bhattacharyya, *Tetrahedron*, **13**, 319 (1961).
(6) J. B. Hendrickson and T. L. Bogard, *J. Chem. Soc.*, 1678 (1962).
(7) For a review of the Shapiro reaction, see R. H. Shapiro, *Org. React.*, **23**, 405 (1976).
(8) J. Meinwald, L. R. Smith, and G. E. Gream, *J. Org. Chem.*, **39**, 3461 (1974); E. Vedejs and R. A. Shepherd, *ibid.*, **41**, 743 (1976).
(9) E. Piers, M. B. Geraghty, R. D. Smillie, and M. Soucy, *Can. J. Chem.*, **53**, 2849 (1975).
(10) (a) K. B. Sharpless and M. W. Young, *J. Org. Chem.*, **40**, 947 (1975); (b) P. A. Grieco, Y. Masaki, and D. Boxler, *J. Am. Chem. Soc.*, **97**, 1597 (1975).
(11) Unpublished results of George Majetich, University of Pittsburgh.
(12) For the direct conversion of alcohols to alkyl aryl selenides, see P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, **41**, 1485 (1976).
(13) H. Bauer, *Ber.*, **46**, 92 (1913).
(14) Previous reports[10a,13] have reported *o*-nitrophenyl selenocyanate as light brown crystals, mp 139–141[10a] and 142 °C.[13] We have found that the brown, crystalline material obtained from the procedure of Bauer[13] can be sublimed [100 °C (0.2 mmHg)] providing yellow crystals of *o*-nitrophenyl selencyanate, mp 144 °C.
(15) The fact that treatment of diol **8** with only 1 equiv of *o*-nitrophenyl selenocyanate in the presence of 1 equiv of tri-*n*-butylphosphine gave monoselenide **9** was unexpected. We had previously observed[11] that treatment of diol iii under identical conditions gave the seven-membered ring ether



iv with no evidence of monoselenide formation. In addition treatment of iii with excess reagent gave the bisselenide v. At present, we do not have any reasonable explanation to account for these observations.
(16) K. B. Sharpless, K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chem. Scr.*, **8A**, 9 (1975); see also P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974).
(17) R. W. Doskotch and F. S. El-Feraly, *J. Org. Chem.*, **35**, 1928 (1970).
(18) The products were isolated by extraction of the aqueous layer with several portions of the indicated solvent. The combined organic extracts were washed with water followed by saturated brine. The organic layer was usually dried with either anhydrous sodium sulfate or anhydrous magnesium sulfate. Filtration followed by removal of the solvent in vacuo (water aspirator) employing a rotary evaporator provided the products.

Micordilin, a Complex Elemanolide from *Mikania cordifolia*[1a]

Werner Herz,*[1b] P. S. Subramaniam,[1b] Ramaswamy Murari,[1b] Nicholas Dennis,[1b] and John F. Blount[1c]

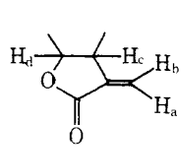
Department of Chemistry, The Florida State University, Tallahassee, Florida 32306, and Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received December 6, 1976

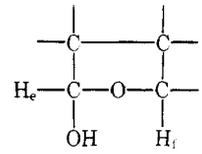
Micordilin, an intramolecular hemiacetal of a C-14-acetylated dialdehydic elemanolide, was isolated from the medicinal plant *Mikania cordifolia* (L. F.) Willd. Chemical transformations and NMR techniques eliminated all but two possible hemiacetal structures; a decision in favor of **5a** which also represents the absolute configuration was reached by x-ray analysis.

A group of interesting antitumor dilactones derived from germacranolides and elemanolides has been isolated from various *Mikania* (Eupatorieae, Compositae) species.[2-9] In the present communication we report isolation from the West Indian medicinal plant *Mikania cordifolia* (L. F.) Willd. of micordilin, a hemiacetal of the C-14-hydroxylated dialdehydic elemanolide **1**, and its structure determination as **5a**.

Micordilin, $C_{17}H_{20}O_7$ (high-resolution mass spectrum), mp 176–178 °C, was a conjugated γ-lactone (IR bands at 1770 and 1660 cm^{-1}, UV λ_{max} 212 nm). The NMR spectrum (Table I) exhibited the typical but very narrowly split H_a and H_b doublets of partial structure A at 6.13 and 5.62 ppm. The location



A



B

of the H_c multiplet at 3.12 ppm and the H_d triplet of doublets at 4.61 ppm was established by spin-decoupling experiments.

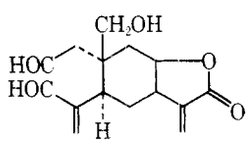
Partial hydrogenation (Pd/C, ethyl acetate) resulted in

Table I. NMR Spectra of Microdilin and Its Derivatives[a]

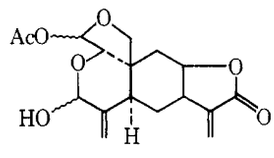
Registry no.	Compd	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14	H-15	Ac[b]
61701-92-6	**5a**	4.2[c]	5.5[d]	5.67	?	?	3.1c	4.58 m	?	6.13 br 5.62 br	4.2c[c,e]	5.00 d (2) 4.67 d (2)	2.10
61701-93-7	**5b**[f]	4.32	6.41	5.78	2.45 m	1.9 c[g] 1.4 m	3.12 m	4.61 td (5.5, 1.8)	2.53 dbr[g] (16, 1.5) 1.8 m	6.20 d (1) 5.69 d (1)	4.14[h]	5.09 d (2) 4.78 d (2)	2.12 2.09
	5b[c]	4.30	6.41	5.78	2.44 dq (12, ~2)	1.88 ddd (14, 7.5, 2) 1.34 m (14, 12, 10)	3.10 m (10, 7.5, 5, 5, 1, 1)	4.60 td (5.5, 1.8)	2.52 dbr (16, 1.5) 1.74 ddd (16, 5.5, 2)	6.19 d (1) 5.68 d (1)	4.19 dd[e,g] (12, 1.5) 4.04 d[g] (12)	5.07 d (2) 4.76 d (2)	2.12 2.07
61701-96-0	**6a**	4.2[c]	5.70	5.75	?	?	?	4.60 td	?	1.25 d (7)[b]	4.2[c,e]	5.10 d (2) 4.80 d (2)	2.10
61701-97-1	**7a**	4.02	5.46[c]	5.46[c]	?	?	?	4.5 m[c]	?	1.15 d (7)[b]	4.5 dbr (11)[c] 4.02 d (11)	0.95 d (7)[b]	2.10
61701-98-2	**7b**	4.22	6.36	5.60 d (1)	?	?	2.83 m[k]	4.54 m[c]	?	1.18 d (7)[b]	4.54 dbr[c] (11) 4.10 dbr (11)	0.98 d (7)[b]	2.12
	7b[j]	4.21	6.34	5.58 d (1)	2.5 c	1.95 m 1.78 m	2.83 qu[k] (7)	4.51 m[c]	2.59 dbr (16) 1.53 dm (16)	1.19 d (7)[b]	4.53 dbr[c] (11) 4.08 dbr (11)	0.98 d (7)[b]	2.09 2.06
61701-99-3	**8**[f]	4.32		5.99	2.5 c	1.9[c] 1.4	3.12 m	4.58 td (5, 1.5)	2.55[c] 1.9[c]	6.20 d (1.5) 5.68 d (1.5)	4.18[h]	5.30 d (2) 4.99 d (2)	2.10
	8[j]	4.34		6.01	2.53 m	1.9 m 1.41 m	3.1 m	4.58 td (5, 1.3)	2.58 m 1.90 dd (16, 5, 1)	6.22 d (1) 5.69 d (1)	4.25 dbr (11)[g] 4.11 d (11)[g]	5.30 d (2) 4.98 d (2)	2.10
61701-94-8	**9**	4.30		5.99	?	?	?	4.54 m	?	1.23 d (7)[b]	4.5 dbr[c] (11) 4.02 d (11)	0.95 d (7)[b]	2.08 1.25 m[l]

[a] Run in $CDCl_3$ using Me_4Si as internal standard on a Varian HA-60 NMR spectrometer unless otherwise specified. Chemical shifts are given in parts per million. Signals are denoted in the usual way: d, doublet; t, triplet; q, quartet; qu, quintet; m, multiplet; c, complex signal whose center is given; br, broadened singlet. Unmarked signals are singlets. Figures in parentheses are line separations or coupling constants in hertz. [b] Three-proton signal. [c] Overlapping signals. [d] Singlet after D_2O exchange. [e] Two-proton signal. [f] Run at 90 MHz on Bruker HFX-90 NMR spectrometer. [g] Clearly part of AB system. [h] Center of AB system. [i] Run at 300 MHz on Varian S-300 NMR spectrometer. [j] Run at 220 MHz on Varian S-220 NMR spectrometer. [k] One-proton signal, probably H-7. [l] H-4 and H-11.

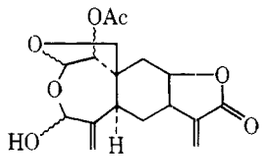
saturation of this double bond and formation of a dihydro derivative (**6a**) which exhibited a methyl doublet in place of the H_a and H_b doublets and lacked the UV absorption char-



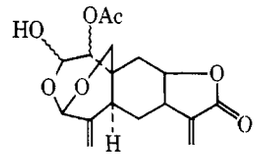
1



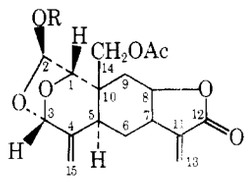
2



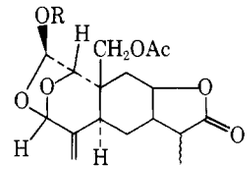
3



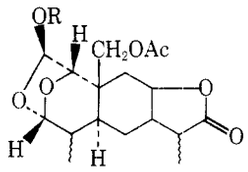
4



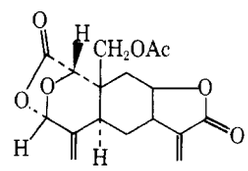
5a, R = H
b, R = Ac



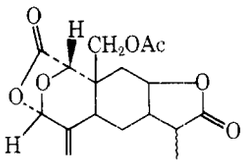
6a, R = H
b, R = Ac



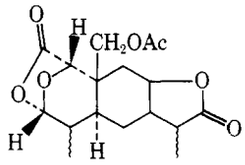
7a, R = H
b, R = Ac



8



9



10

acteristic of A. The presence of a second, unconjugated double bond was suggested by two low-field doublets (J = 2 Hz) at 5.00 and 4.67 ppm (5.10 and 4.80 ppm in **6a**). Further hydrogenation produced tetrahydromicordilin by saturation of this double bond (second new methyl doublet, disappearance of the second pair of doublets).

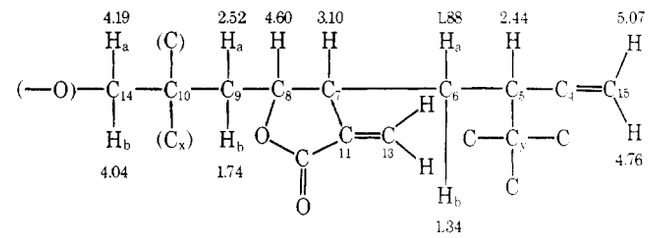
Micordilin and its derivatives contained an acetate function (IR band at 1740 cm^{-1}, NMR signal near 2.1 ppm, mass spectral peaks at m/e 60), but no other methyl group. Since the NMR spectrum displayed two singlets near 5.5 and 5.67 ppm and since other ester functions were absent, it was originally surmised that one of these singlets might represent a proton under the acetate. This surmise was not borne out by subsequent work.

The presence of a hydroxyl group indicated by an IR band at 3580 cm^{-1} was confirmed by acetylation of micordilin and tetrahydromicordilin to **5b** and **7b**, respectively. The reaction was accompanied by a downfield shift of the 5.5 ppm singlet to 6.41 ppm. Such unusually high paramagnetic shifts are characteristic[10] of hemiacetal hydrogen (H_e of partial formula B). This assignment was confirmed by oxidation of micordilin, dihydromicordilin, and tetrahydromicordilin to dehydro derivatives **8**, **9**, and **10**, a reaction which resulted in disappearance of the 5.5 ppm singlet and formation of a second lactone group. The size of the new lactone ring was not immediately obvious from the IR spectra; if the acetate were invariably associated with the carbonyl band of lowest frequency (at 1738, 1750, and 1745 cm^{-1} in dehydromicordilin, dehydrodihydromicordilin, and dehydrotetrahydromicordilin, respectively), the frequencies of the two remaining carbonyls (1770 and 1750 cm^{-1} in dehydromicordilin, 1780 cm^{-1} double strength in dehydrodihydro-, and 1795 and 1780 cm^{-1} in dehydrotetrahydromicordilin) suggested that the new lactone might be a γ-lactone.

The oxidations were also accompanied by a downfield shift of the 5.67 ppm singlet to about 6.00 ppm which was therefore identified with H_f of B rather than with the proton under the acetate. The multiplicity of H_e and H_f suggested the absence of vicinal hydrogens.

Six oxygens had thus been accounted for; the absence of aldehyde or keto groups revealed by the CD curves of **7a** and **7b** therefore led to the conclusion that the seventh oxygen was ethereal. Since the NMR spectra of micordilin, **5b**, and 8 displayed a three-proton multiplet near 4.2 ppm, it was surmised that this multiplet represented the proton or protons on the termini of the ether function together with the proton or protons under the acetate and that, on biogenetic grounds, two of the protons responsible for the multiplet arose from the grouping $-CH_2O$. In fact, inspection of the 220-MHz spectra of **5b** and 8 and spin decoupling revealed that the 4.2 ppm multiplet actually consisted of a singlet at 4.3 ppm superimposed on an AB system ([J] = 12 Hz) one of whose protons was additionally coupled to a proton at 1.74 ppm.

The high-field region of the NMR spectra was exceedingly difficult to unravel. Extensive spin-decoupling experiments at 90 and 270 MHz and inspection of the 300-MHz spectrum of **5b** finally permitted expansion of A into partial structure C (numbering based on final structure assignment) where H-5 was long-range coupled to each H-15 proton ($J_{5,15} \sim 2$ Hz) and vicinally coupled to two geminally coupled protons on C-6

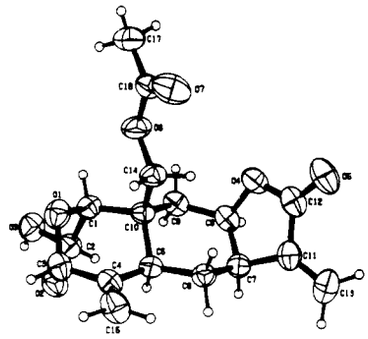


C

($J_{5,6a} \sim 2$, $J_{5,6b}$ = 12 Hz), where H-6a and H-6b were coupled to H-5 and to H-7 ([$J_{6a,6b}$] = 14, $J_{6a,7}$ = 7.5, $J_{6b,7}$ = 10 Hz), where H-8 was vicinally coupled to two geminally coupled protons on C-9 ($J_{8,9a}$ = 1.8, $J_{8,9b}$ = 5.5, [$J_{9a,9b}$] = 16 Hz) as well as to H-7 (vide supra) and where, as mentioned previously, one of the C-9 protons, namely H-9b, was long-range coupled to H-14 ($J_{9b,14}$ = 1.5 Hz).

Now C contains 12 of the 15 carbon atoms of microdilin (exclusive of the acetate); the remaining three carbon atoms are of the type HCO where the three protons are H_e and H_f of partial structure B and the proton responsible for the singlet at 4.30 ppm. This requires that C_y and C_x of formula C be identical, i.e., that C-5 and C-10 be linked. Thus four possible structures **2**–**5** can be written (relative stereochemistry at C-4, C-6, C-7, and C-10 based on coupling constants). Although H-1 and H-2 are vicinal in each of the formulas, the NMR spectra require that $J_{1,2} \sim 0$.

Structures **2**–**5** are hemiacetals of the C-14-hydroxylated dialdehydic elemanolide **1** which could not be differentiated on the basis of the evidence presented so far. The infrared spectra of the dehydro derivatives (vide supra) suggested that **5a** was more likely to be correct; likewise, a comparison of the CD curves suggested that oxidation of dihydromicordilin had not produced an α,β-unsaturated lactone as required by formulas **2** and **3**, thus again favoring **5a**. On the other hand,



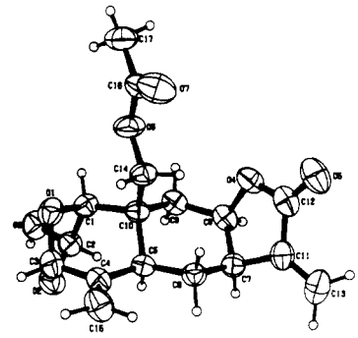


Figure 1. Stereoscopic view of micordilin.

Table II. ^{13}C NMR Spectra of Micordilin and Selected Derivatives[a]

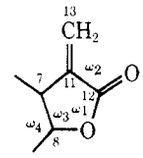
Carbon no.	5a[b]	8[c]	7a[b]
1	82.04 d	74.95 d	81.63 d
2	93.29 d	171.56	92.91 d
3	104.18 d	105.32 d	107.59 d
4	144.33	139.07	39.79 d
5	35.70 d	38.16 d	34.29 d
6	23.96 t	24.02 t	26.34 t
7	35.45 d	37.78 d	36.69 d
8	75.34 d	74.95 d	76.48 d
9	27.07 t	26.94 t	28.82 t
10	38.19	38.16	37.61
11	141.22	141.09	40.23 d
12	169.20[d]	169.22[d]	169.63[d]
13	108.19 t	113.85 t	8.88 q
14	61.88 t	61.09 t	63.03 t
15	120.88 t	121.56 t	11.38 q
1′	169.93[d]	170.04[d]	169.80[d]
2′	20.38	20.56	20.40
1″			178.24
2″			20.84

[a] Recorded in Me_2SO-d_6 (in which solvents all protonic signals of **5a** and **7a** were clearly identifiable at 270 MHz) with Me_4Si as internal standard using a Bruker HFX-270 instrument operating at 67.905 MHz. Unmarked signals are singlets. [b] All assignments made by single frequency off-resonance decoupling except for the singlets which were assigned by chemical shift criteria and by comparison of the three spectra. [c] Assignments made by chemical shift criteria and comparison with the spectra of **5a** and **7a**. [d] Assignments may be interchanged.

Table III. Crystal Data for Micordilin

Formula $C_{17}H_{20}O_5$, monoclinic
a = 7.585 (4) Å
b = 10.465 (3) Å
c = 10.730 (3) Å
β = 105.34 (3)°
Space group $P2_1$, Z = 2 d_{calcd} 1.359 g cm^{-3}

Table IV. Lactone Ring Torsion Angles of Micordilin



C(11)–C(12)–O(4)–C(8)	ω_1	−6°
C(13)–C(11)–C(12)–O(5)	ω_2	−14°
O(4)–C(8)–C(7)–C(11)	ω_3	−30°
C(9)–C(8)–C(7)–C(6)	ω_4	−36°

oxidation of **5a** and **6a** was accompanied by a definite, though relatively small, downfield shift of the C-15 protons (~0.3 ppm), an observation which seemed more in keeping with **2** and **3** than with **4** and **5**. Lastly, the chemical shift of H_f in partial structure B (~5.7 ppm) and in the derived lactones (~6 ppm) seemed more appropriate for H-2 in **3** and **4** and H-3 in **5** than for H-1 in **2**; if **2** were correct, H-2 would also have to be assigned an abnormally high shift of 4.3 ppm.

Structures **2** and **3** were eventually eliminated by examination of the ^{13}C NMR spectra of micordilin, dehydromicordilin, and acetyltetrahydromicordilin which are listed in Table II. If micordilin were **2** or **3**, dehydromicordilin would have a carbonyl group α to the exo-methylene group attached to C-4, in which case the signals of C-4 and C-15 would be shifted downfield relative to micordilin.[11,12] Inspection of Table II reveals no such shift. Hence the small downfield shift of H-15 in going from micrordilin to dehydromicordilin is due to its being located in the deshielding region of the newly introduced carbonyl group.[13] However, the ^{13}C NMR studies failed to distinguish between the remaining structures **4** and **5**.

Since further chemical work was precluded by the small quantity of micordilin which remained at our disposal, we decided to resolve our dilemma by crystallographic methods. This led to a decision in favor of **5**, with the stereochemistry of the hemiacetal defined as in **5a**.

X-Ray Analysis of Micordilin. Crystal data for micordilin are listed in Table III. Figure 1 is a stereoscopic drawing of the molecule which establishes structure and stereochemistry as **5a**. Tables V, VI, and VII containing bond lengths, bond angles, and torsion angles are available as supplementary material.

Although the absolute stereochemistry of micordilin was not determined by x-ray diffraction, Figure 1 represents the absolute configuration if H-7 is α as in all sesquiterpene lactones of authenticated stereochemistry. This is in harmony with the observation of a negative Cotton effect (θ_{257} −3430) associated with the n → π^* transition of a cis-fused lactone closed to C-8 whence H-7 and H-8 should be α on the basis of an empirical rule[14] which appears to be applicable to elemanolides of the type of **5a**. Indeed, the lactone ring torsion angles listed in Table IV show that for micordilin the chirality of the C=C–C=O group which has been related to this Cotton effect[16] is negative (ω_2 = −14°) and paired with the sign of the C(α)–C(β)–C(γ)–O torsion angle (ω_3) as has been noted previously[17] regardless of the validity of the rule, thus reinforcing our conclusion about the absolute configuration of micordilin. The x-ray study also correlates with the vanishingly small value of $J_{1,2}$ which complicated the interpretation of the NMR spectra, since the torsion angle H–C(1)–C(2)–H approximates 90°.

Experimental Section

Isolation of Micordilin. Above-ground plant material of *M. cordifolia* (L. F.) Willd., collected in the vicinity of Mayaguez, Puerto Rico, during the period Sept 1966–Jan 1967, wt 20.5 kg, was extracted with $CHCl_3$ and worked up in the usual manner.[18] The crude gum, wt 112 g, was taken up in the minimum amount of 1:1 benzene–$CHCl_3$ and adsorbed on 1.2 kg of silicic acid (Mallinckrodt, 100 mesh) set in benzene. The column was eluted in the following sequence, 1-L fractions being collected. Fractions 1–10 (benzene), 11–18 (Bz–$CHCl_3$, 4:1), 19–27 (Bz–$CHCl_3$, 3:2), 28–40 (Bz–$CHCl_3$, 1:1), 41–53 (Bz–$CHCl_3$, 2:3), and 54–63 (Bz–$CHCl_3$, 1:4) eluted nothing or gums which showed several spots on TLC and were discarded. Fractions 64–72 (Bz–$CHCl_3$, 1:4) and 73–75 ($CHCl_3$) gave gums showing a major spot corresponding to micordilin. Fractions 76–87 ($CHCl_3$) solidified on trituration with ether. Recrystallization from ethyl acetate afforded 7.8 g of micordilin, mp 174–177 °C. Fractions 88–90 ($CHCl_3$), 91–99 ($CHCl_3$–ether, 19:1), and 100–110 ($CHCl_3$–ether, 9:1) eluted impure micordilin. Combination of these with fractions 64–75 and rechromatography over 0.5 kg of silic acid afforded an additional 6.2 g of pure micordilin in the $CHCl_3$ fractions.

Micordilin, when recrystallized from ethyl acetate or acetone–hexane, formed colorless, thick rhombs some of which were single crystals and melted at 176–178 °C; UV λ_{max} 212 nm (ϵ 11 000); IR bands at 3580, 1770, 1740, 1667, 970, and 910 cm^{-1}; ORD curve (MeOH, *c* 0.19) Φ_{290} +346°, Φ_{250} +6230°, Φ_{240} +10 000°, Φ_{277} +17 600° (max); CD curve $[\theta]_{300}$ −57, $[\theta]_{275}$ −1830, $[\theta]_{257}$ −3430, $[\theta]_{240}$ −800, $[\theta]_{233}$ +3300 (last reading).

Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99; O. 33.30; mol wt, 336. Found: C, 60.64; H, 6.13; O, 33.32; mol wt (MS), 336.

Acetylmicordilin (5b). A mixture of 105 mg of **5a**, 1 mL of pyridine, and 1.5 mL of acetic anhydride was held at 80 °C for 3 h, evaporated to dryness in vacuo, diluted with ice water, and extracted with $CHCl_3$. Evaporation of the washed and dried extract furnished a gum which was purified by passing it through a column of 8 g of silicic acid (eluent $CHCl_3$). Recrystallization from ethyl acetate–hexane afforded 78 mg of **5b** which had mp 203–205 °C; UV λ_{max} 212 nm (ϵ 6900); ORD curve (EtOH, 0.193) Φ_{450} +245°, Φ_{400} +490°, Φ_{300} +980°, Φ_{250} +8830°, Φ_{230} +19 800°, ϕ_{224} 20 600° (max); CD curve $[\theta]_{270}$ −2200, $[\theta]_{252}$ −4150, $[\theta]_{240}$ −2250, $[\theta]_{235}$ 0, $[\theta]_{230}$ +3200 (last reading).

Anal. Calcd for $C_{19}H_{22}O_8$: C, 60.31; H, 5.86; O, 33.83. Found: C, 60.41; H, 5.81; O, 33.65.

Dehydromicordilin (8). To an ice-cold solution of 0.25 g of **5a** in 6 mL of purified acetone was added dropwise, with stirring, 0.4 mL of Jones reagent. Stirring was continued at 5 °C for 15 min and at room temperature for an additional 15 min. Excess oxidant was destroyed by careful addition of a few drops of MeOH. The mixture was diluted with ice water and extracted with $CHCl_3$. The washed and dried extracts were evaporated. The residue (one major, three minor spots on TLC) was chromatographed over 14 g of silicic acid, the eluate (six fractions of $CHCl_3$) being monitored by TLC. The fractions containing the major spot were combined, evaporated, and recrystallized from acetone–isopropyl ether. This afforded 96 mg of **8**. The material which retained an impurity (ca. 2%) of slightly lower R_f which could not be removed by rechromatography or further recrystallization melted at 202–204 °C; UV λ_{max} 206 nm (ϵ 12 400); IR bands at 1770, 1750, 1738, 1668, 978, and 972 cm^{-1}; ORD curve (MeOH, *c* 0.1) Φ_{275} −1450°, Φ_{250} +10 000°, Φ_{225} +39 200° (max), Φ_{220} +35 600° (last reading); CD curve $[\theta]_{300}$ −120, $[\theta]_{275}$ −2040, $[\theta]_{255}$ −3950, $[\theta]_{240}$ −4550, $[\theta]_{235}$ −3830 (last reading).

Anal. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43; O, 33.50. Found: C, 60.51; H, 5.28; O, 33.43.

Dihydromicordilin (6a). A solution of 0.336 g of **5a** in 40 mL of ethyl acetate was hydrogenated at atmospheric pressure with 10% Pd/C. Hydrogen uptake was stopped after absorption of 1 molar equiv of hydrogen. The solution was filtered and evaporated and the residual gum was chromatographed over silicic acid (solvent and eluate $CHCl_3$). The crystalline fractions were combined and recrystallized from $CHCl_3$–CCl_4: yield 0.25 g; mp 120–122 °C; IR bands at 3580, 1785, 1755, and 1745 cm^{-1} (bonded and nonbonded ester?).

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.64; H, 6.55; O, 33.10. Found: C, 60.56; H, 6.58; O, 32.98.

Dehydrodihydromicordilin (9). Oxidation of 0.4 g of **6a** with Jones reagent in the manner described for **5a** yielded a gum which gave crystals of **9** after recrystallization from THF: yield 0.36 g; mp 271–272 °C; IR bands 1780 (double intensity) and 1750 cm^{-1}; ORD curve (MeOH, *c* 0.1) Φ_{300} −1450°, Φ_{250} −4480°, Φ_{241} −5600° (min), Φ_{233} −4800°, Φ_{229} +224° (last reading); CD curve $[\theta]_{270}$ 0, $[\theta]_{250}$ −370, $[\theta]_{240}$ −2950, $[\theta]_{227}$ −6100, $[\theta]$ −3300 (last reading).

Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99; O, 33.80. Found: C, 60.79; H, 5.91; O, 33.06.

Tetrahydromicordilin (7a). A solution of 0.336 g of **5a** in 40 mL of ethyl acetate was hydrogenated with 0.3 g of 10% Pd/C in a Parr hydrogenator at 2 atm for 2 h until hydrogen uptake ceased. Evaporation of the filtered solution in vacuo gave a crystalline residue which showed a single spot on TLC. Recrystallization from ethyl acetate–hexane afforded 0.296 g of **7a** which melted at 210–212 °C and had IR bands at 3580, 1775, and 1738 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11; O, 32.91. Found: C, 59.89; H, 7.02; O, 33.38.

Acetyltetrahydromicordilin (7b). Acetylation of 0.125 g of **7a** in the manner described for **5a** gave, after dilution with ice water, a crystalline precipitate, wt 0.115 g. Recrystallization from acetone–isopropyl ether afforded **7b** which had mp 210–212 °C; IR bands at 1772 and 1740 cm^{-1} (double intensity); ORD curve (EtOH, *c* 0.1) Φ_{500} +185°, Φ_{350} +291°, Φ_{300} +450°, Φ_{250} +1030°, Φ_{223} +1900° (max), Φ_{204} +1300° (last reading); CD curve $[\theta]_{230}$ +760, $[\theta]_{218}$ +1780 (max).

Anal. Calcd for $C_{19}H_{26}O_8$: C, 59.67; H, 6.85; O, 33.47. Found: C, 59.17; H, 6.64; O, 33.30.

Dehydrotetrahydromicordilin (10). Oxidation of 0.20 g of **7a** with Jones reagent in the manner described for **5a** gave, after evaporation of the $CHCl_3$ extract, a solid residue. Two recrystallizations from acetone–hexane yielded 0.156 g of **10**: mp 272–274 °C; no strong UV absorption; IR bands at 1795, 1780, and 1745 cm^{-1}. Examination of the mother liquors by TLC revealed the presence of a compound with lower R_f which was not investigated.

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.12; H, 6.38.

X-Ray Analysis of Micordilin. A Hilger-Watts four-circle diffractometer was used to measure the intensity data (Ni-filtered Kα radiation, θ–2θ scans, pulse height discrimination). The approximate size of the crystal was 0.25 × 0.5 × 0.6 mm; no correction for absorption was made (μ = 9.0 cm^{-1}). A total of 1768 independent reflections were measured for $2\theta < 152°$, of which 1739 were considered to be observed. The structure was solved by a multiplet solution procedure[19] and refined by full matrix squares. In the final refinement anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were R = 0.039 and wR = 0.054 for the 1739 observed reflections. The final difference map had no peaks greater than ±0.3 e A^{-3}.

Registry No.—**10**, 61701-95-9.

Supplementary Material Available. Tables V, VI, and VII listing bond distances, bond angles, and selected torsion angles of micordilin (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Work at Florida State University supported in part by USPHS Grant CA-13121 through the National Cancer Institute. (b) The Florida State University. (c) Hoffmann-La Roche Inc.
(2) W. Herz, P. S. Santhanam, P. S. Subramaniam, and J. J. Schmid, *Tetrahedron Lett.*, 3111 (1967).
(3) W. Herz, P. S. Subramaniam, P. S. Santhanam, K. Aota, and A. L. Hall, *J. Org. Chem.*, **35**, 1453 (1970).
(4) P. J. Cox, G. A. Sim, J. S. Roberts, and W. Herz, *J. Chem. Soc., Chem. Commun.*, 428 (1973).
(5) W. Herz, P. S. Santhanam, H. Wagner, R. Höer, L. Hörhammer, and L. Farkas, *Chem. Ber.*, **103**, 1822 (1970).
(6) W. Herz, A. Srinivasan, and P. S. Kalyanaraman, *Phytochemistry*, **14**, 233 (1975).
(7) A. K. Kiang, K. Y. Sim, and S. W. Yoong, *Phytochemistry*, **7**, 1035 (1968).
(8) S. B. Mathur and C. M. Termin, *Phytochemistry*, **12**, 226 (1973).
(9) A chemical race of *Mikania micrantha* HBK gave the guaianolide mikanokryptin;[6] see W. Herz and P. S. Kalyanaraman, *Phytochemistry*, **14**, 1664 (1975), footnote 4. The stereochemistry assigned to mikanokryptin[6] has been confirmed by x-ray analysis (to be published).
(10) W. Herz, K. Aota, M. Holub, and Z. Samek, *J. Org. Chem.*, **35**, 261 (1970).
(11) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(12) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
(13) This was verified by construction of the Dreiding models after the structure had been settled as **5a**.
(14) W. Stöcklin, T. G. Waddell, and T. A. Geissman, *Tetrahedron*, **26**, 2397 (1970). A number of exceptions to this rule which arise from various factors which affect the chirality of the α,β-unsaturated lactone double bond system or are due to the presence of other chromophores have been pointed out.[15]
(15) (a) P. Sundararaman, R. S. McEwen, and W. Herz, *Tetrahedron Lett.*, 3809

(1973); (b) W. Herz and S. V. Bhat, *Phytochemistry*, **12**, 1731 (1973); (c) W. Herz and R. P. Sharma, *Phytochemistry*, **14**, 1561 (1975); (d) W. Herz and R. P. Sharma, *J. Org. Chem.*, **40**, 3118 (1975); **41**, 1115, 1248 (1976); (e) P. J. Cox, G. A. Sim, and W. Herz, *J. Chem. Soc., Perkin Trans. 2*, 459 (1975).

(16) A. F. Beecham, *Tetrahedron*, **28**, 5543 (1972).
(17) A. T. McPhail and G. A. Sim, *Tetrahedron*, **29**, 1751 (1973).
(18) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).
(19) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

One-Step Synthesis of 6*H*-Indolo[2,3-*b*][1,8]naphthyridines. A New Heterocyclic Ring System

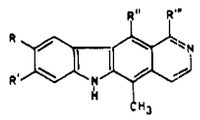
Antonio Da Settimo,* Gianpaolo Primofiore, Viviano Santerini, Giuliana Biagi, and Luigi D'Amico

Institute of Pharmaceutical Chemistry, University of Pisa, 56100 Pisa, Italy

Received October 22, 1976

The photolysis of 4-phenyltetrazolo[1,5-*a*][1,8]naphthyridines (**11**) in trifluoroacetic acid produces in high yield the corresponding 6*H*-indolo[2,3-*b*][1,8]naphthyridines (**2**). Compounds **2**, belonging to a hitherto unknown ring system, are interesting because of their structural resemblance to ellipticine and olivacine, two alkaloids which exhibit antitumor properties. Also the preparation of the parent nucleus **2g** is described.

Several alkaloids containing the indole nucleus as a part of a polycyclic system are very useful as curvative agents (see, e.g., reserpine, lysergic acid derivatives, the *Vinca* alkaloids, etc.). More recently the disclosure of potentially useful tumor inhibitory properties of certain 6*H*-pyrido[4,3-*b*]carbazoles such as ellipticine (**1a**), 9-methoxyellipticine (**1b**), and olivacine (**1c**) has prompted considerable interest[1] and several

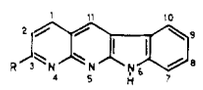


a : R = R' = R''' = H , R'' = CH_3
b : R = OCH_3 , R' = R''' = H , R'' = CH_3
c : R = R' = R'' = H , R''' = CH_3

1

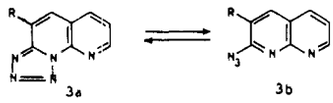
syntheses have been elaborated in attempts to make the above compounds and related substances available for evaluation as chemotherapeutic agents.[2]

Because of our interest in substances which might exhibit similar antitumor properties, we wish now to report on the one-step synthesis that was used to readily prepare some substituted 6*H*-indolo[2,3-*b*][1,8]naphthyridines (**2**), analogues and isosteres of the 6*H*-pyrido[4,3-*b*]carbazoles.



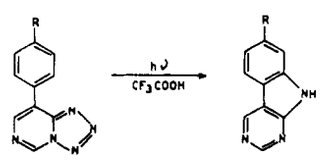
2

In the course of our studies on tetrazole derivatives of 1,8-naphthyridines, evidence was presented to demonstrate that the tetrazole ring structure **3a** is the dominant species in the solid state and in alkaline solution, while the open-chain azido form **3b** dominates in acidic solution.[3] Several tetrazole



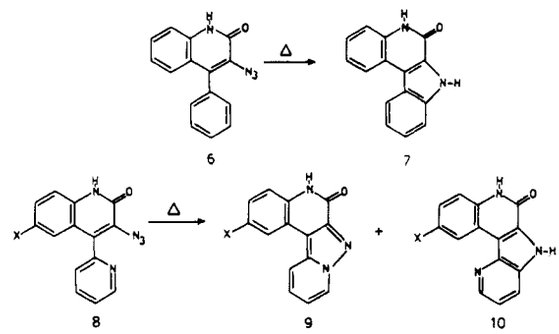
3a 3b

derivatives of 1,8-naphthyridine with a phenyl group in an adjacent position to the tetrazole nucleus were described.[3] Besides, it is well known that the photolysis of substituted 8-phenyltetrazole[1,5-*c*]pyrimidines (**4**) in trifluoroacetic acid produces in high yield the corresponding 9*H*-pyrimido[4,5-*b*]indoles (**5**).[4]



4 5

There has also been described the preparation in good yield of indolo[2,3-*c*]quinolone (**7**) by pyrolysis of 3-azido-4-phenylcarbostyril (**6**);[5] the pyrolysis of 3-azido-4-(2-pyridyl)carbostyrils (**8**) affords mixtures of the isomeric tetracyclic

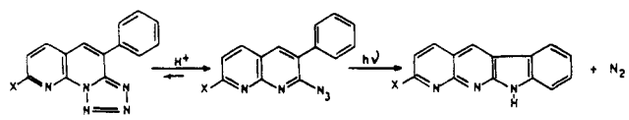


6 7 8 9 10

products **9** and **10**, resulting from nitrenoid cyclization reactions.[6]

The above researches suggested that similar processes might be of synthetic utility in yielding a number of compounds to evaluate for antitumor activity because of their structural resemblance to the pyridocarbazole system found in ellipticine.

We wish to report here an one-step, high-yield synthesis and the characterization of some 6*H*-indolo[2,3-*b*][1,8]naphthyridine derivatives (**2**), which represent a new heterocyclic ring structure. The title compounds **2** were prepared by photolysis of some 4-phenyltetrazolo[1,5-*a*][1,8]naphthyridines (**11**) in trifluoroacetic acid, yields ranging between 84 and 97%.



11a , X = NH_2
b , X = OH
c , X = Cl
d , X = OCH_3
e , X = OC_2H_5

11'

2a , X = NH_2
b , X = OH
c , X = Cl
d , X = OCH_3
e , X = OC_2H_5

The tetrazolonaphthyridines **11** were previously described,[3] except **11d**, which was prepared in the same manner as **11e**. The naphthyridinoindoles **2** are very high melting, crystalline, yellow to yellow-brown solids (mp above 320 °C), slightly soluble in many usual organic solvents. The most soluble product was 3-amino-6*H*-indolo[2,3-*b*][1,8]naphthyridine (**2a**). The structure of this compound was proved by analytical and NMR spectral data. In fact, the NMR spectrum