Isolation and Structure Determination of the Second Toxic Constituent from *Tetradymia glabrata*

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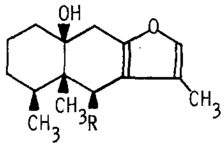
A new furanoeremophilane has been isolated and a derivative of it analyzed by x-ray crystallography. The two compounds are 10β-hydroxy-6β-isobutyrylfuranoeremophilane (II) and 6β,10β-dihydroxyfuranoeremophilane (III). Both have been shown to be hepatotoxins, LD_{50}^{IP} 400 and 113 mg/kg, respectively. Physical data are included in the publication with particular emphasis on NMR spectra correlation with x-ray structure. Compound III crystallized in a space group $P2_12_12_1$ with cell dimensions a = 21.322 (7) Å, b = 7.593 (2) Å, c = 8.387 (1) Å, with Z = 4. Counter data were refined by full-matrix least squares to a residual of 4.7%.

Recently Bohlmann[2] reported that plants belonging to the *genus Euryops, Senecio,* and *Othonna* (Senecioneae tribe) contain a variety of furanoeremophilane compounds. Further, Nagano,[3] Tada,[4] Ishii,[5] and Moriyama[6] have previously isolated a number of furanoeremophilanes from *Ligularia,* a member of the same tribe. In 1974, we reported[7] that another member of the Senecioneae tribe, *Tetradymia glabrata,* contained the furanoeremophilenic compound, I, which was subsequently shown to be one of the hepatotoxic substances responsible for the death of sheep feeding on the plant.

We now wish to report the isolation and characterization of a second hepatotoxic furanoeremophilenic compound, II, from the same plant. Compound III which is formed from the reductive cleavage of II is also reported. Its hepatotoxicity is greater than that of II and approximately equivalent to that of compound I. Included in this report is the x-ray structure analysis of compound III along with a discussion of the NMR spectra.



I R=H "Tetradymol"
II R=OOC-$CHMe_2$
III R=OH "βTetradymodiol"

Results

Isolation. New growth and flower buds were picked in June and kept chilled until extraction with hexane. From 13.6 kg of wet plant which was ground and extracted in hexane, 6 g (0.04%) of white, crystalline material (compound II) was won via chromatography and sublimation. Since the toxin was lethal to both sheep and mice, the latter was used to monitor for toxin during the isolation steps. Similar hepatocellular damage resulted from ingestion of the toxins by both types of animals.

Furanoeremophilanes reported earlier have been generally found in the roots of the plant while the compounds reported in this paper and earlier work[7] were isolated from the new growth.

Except for the following data, a detailed discussion of toxicity will be published elsewhere.

Compd	LD_{50}^{oral}	LD_{50}^{IP}
I	275	94
II	375	400
III		113

Characterization of Compounds II and III. Compound II, which was positive to the Ehrlich test, exists as a white solid, mp 100–100.5 °C, M^+ at m/e 320, has an $[\alpha]^{26}D$ −55.85 ± 0.35 (EtOH), and analyzed correctly for $C_{19}H_{28}O_4$. Its ir, uv, NMR, and MS spectra (cf. Experimental Section) indicated a tertiary hydroxyl, an ester, a *gem*-dimethyl group, a 3-methyl substituted furan and both a secondary and a tertiary methyl group. Lithium aluminum hydride reduction of II gave diol III and isobutyl alcohol in 77% yield. This diol was analyzed by x-ray crystallography (Figure 1) and isobutyl alcohol was identified by GC/MS analysis. Esterification of diol III with isobutyric anhydride produced ester II in 33% yield which was identical with the original ester in all physical and physiological properties. Tada[4] reported the physical properties of diol III as melting at 122 °C dec and $[\alpha]D$ +50°. In our laboratory it melted at 144–145 °C and $[\alpha]D$ +26.98 ± 0.15°.[8] Several attempts at reproducing Tada's reported rotation values have failed and always resulted in a value near 26°. Despite this difference in data, the structure shown in Figure 1 is identical with the one described by Tada. In addition all our spectral data agreed with Tada's results.

Discussion

Discussion of X-Ray Analysis. Results of the single crystal x-ray analysis of 6β,10β-dihydroxyfuranoeremophilane are shown as an ORTEP drawing in Figure 1. Bond distances, bond angles, and torsion angles are given in Tables I, II, and III, respectively.

It is readily apparent from Figure 1 that diol III has the necessary cis relationships at positions C-4, C-5, and C-10 to place it in the eremophilane class.

Discussion of NMR Spectra. The nuclear magnetic resonance spectra for furanoeremophilane compounds having the three rings in an "anthranoid" arrangement[7] are characterized by a spectrum having distinctive resonances for furan methyl group near 1.9 ppm (d), a tertiary methyl group near 1.1 (s), and a secondary methyl group having virtual coupling and thus appearing as a filled-in doublet near 0.70. Also a series of peaks appear between 2.0 and 4.0 which are the protons at positions C-6 and C-9. In our first paper[7] dealing with these compounds, we identified these peaks for compound I as two overlapping AB quartets with the upfield quartet resonances due to protons at C-6 having the smaller coupling constant ≈9 Hz. The downfield quartet resonances due to protons at C-9 have a larger coupling constant ≈16–17 Hz.[9]

Factors contributing to the different environments for the α and β protons for positions 6 and 9 include (a) a fairly planar central ring, (b) rigidity of the central ring, and (c) the β hydroxyl group at C-10. These ideas are further verified by the NMR spectra reported for compounds II and III (Table IV). Since these two compounds have an oxygen functionality at

Table I. Bond Distances in Angstroms with Standard Deviations in Parentheses

C(1)-C(2)	1.528 (7)	C(8)-C(9)	1.465 (5)
C(1)-C(10)	1.524 (6)	C(8)-O(1)	1.370 (4)
C(1)-H(1α)	0.86 (3)	C(9)-C(10)	1.569 (5)
C(1)-H(1β)	1.04 (3)	C(9)-H(9α)	1.06 (3)
C(2)-C(3)	1.523 (7)	C(9)-H(9β)	0.97 (3)
C(2)-H(2α)	1.05 (4)	C(10)-O(2)	1.454 (5)
C(2)-H(2β)	0.96 (4)	C(11)-C(12)	1.350 (6)
C(3)-C(4)	1.529 (6)	C(11)-C(13)	1.468 (6)
C(3)-H(3α)	0.96 (4)	C(12)-O(1)	1.376 (5)
C(3)-H(3β)	1.04 (3)	C(12)-H(12)	1.02 (3)
C(4)-C(5)	1.567 (5)	C(13)-H(13a)	1.05 (4)
C(4)-C(14)	1.523 (6)	C(13)-H(13b)	1.33 (4)
C(4)-H(4)	1.09 (3)	C(13)-H(13c)	0.77 (4)
C(5)-C(6)	1.560 (5)	C(14)-H(14a)	1.03 (4)
C(5)-C(10)	1.556 (5)	C(14)-H(14b)	1.02 (4)
C(5)-C(15)	1.543 (5)	C(14)-H(14c)	0.94 (4)
C(6)-C(7)	1.495 (5)	C(15)-H(15a)	1.00 (3)
C(6)-O(3)	1.458 (4)	C(15)-H(15b)	0.91 (4)
C(6)-H(6)	0.98 (3)	C(15)-H(15c)	0.95 (3)
C(7)-C(8)	1.331 (5)	O(2)-H(O-2)	0.87 (3)
C(7)-C(11)	1.439 (5)	O(3)-H(O-3)	0.82 (3)

position C-6, there is only one AB quartet in the spectrum resulting from the α and β protons at C-9. In these examples the coupling constant is between 15 and 22 Hz. However, in the absence of an oxygen function at C-10, such a simplistic analysis fails.[2]

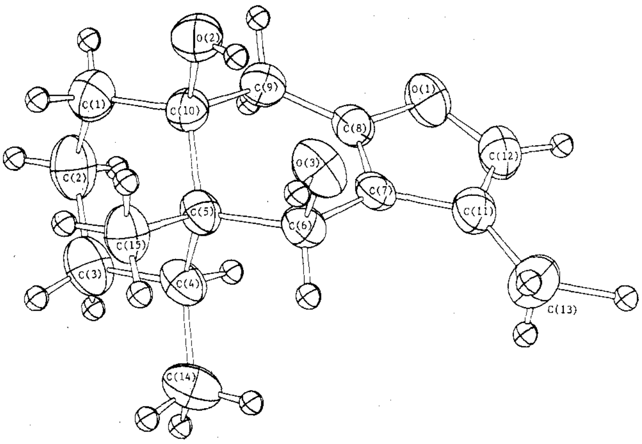


Figure 1. ORTEP drawing of tetradymodiol. Thermal ellipsoids have been scaled to include 50% probability; hydrogen atoms have been assigned an isotropic temperature factor of 1.0 for clarity.

Experimental Section

Infrared spectra were obtained using either a Beckman IR-4 or a Beckman IR-20. Nuclear magnetic resonance spectra were obtained on A-60, T-60, or HA-100 Varian spectrometers. Ultraviolet spectra were obtained on a Cary Model 14 and the mass spectra were collected from a Varian MAT CH-5 interfaced with a Varian Aerograph series 1700 gas–liquid chromatograph. Optical rotations were determined using a Bendix automatic polarimeter Model 1169.

Table II. Bond Angles in Degrees with Standard Deviations in Parentheses

C(2)-C(1)-C(10)	112.1 (4)	C(9)-C(8)-O(1)	120.4 (3)
C(2)-C(1)-H(1α)	112 (2)	C(8)-C(9)-C(10)	111.0 (3)
C(2)-C(1)-H(1β)	108 (2)	C(8)-C(9)-H(9α)	108 (2)
C(10)-C(1)-H(1α)	108 (2)	C(8)-C(9)-H(9β)	119 (2)
C(10)-C(1)-H(1β)	111 (2)	C(10)-C(9)-H(9α)	117 (2)
H(1α)-C(1)-H(1β)	104 (3)	C(10)-C(9)-H(9β)	102 (2)
C(1)-C(2)-C(3)	112.1 (4)	H(9α)-C(9)-H(9β)	100 (3)
C(1)-C(2)-H(2α)	117 (2)	C(1)-C(10)-C(5)	112.0 (3)
C(1)-C(2)-H(2β)	109 (2)	C(1)-C(10)-C(9)	109.4 (3)
C(3)-C(2)-H(2α)	98 (2)	C(1)-C(10)-O(2)	106.6 (3)
C(3)-C(2)-H(2β)	113 (2)	C(5)-C(10)-C(9)	112.9 (3)
H(2α)-C(2)-H(2β)	107 (3)	C(5)-C(10)-O(2)	110.0 (3)
C(2)-C(3)-C(4)	113.7 (4)	C(9)-C(10)-O(2)	105.7 (3)
C(2)-C(3)-H(3α)	114 (2)	C(7)-C(11)-C(12)	104.6 (3)
C(2)-C(3)-H(3β)	117 (2)	C(7)-C(11)-C(13)	128.5 (4)
C(4)-C(3)-H(3α)	101 (2)	C(12)-C(11)-C(13)	127.0 (4)
C(4)-C(3)-H(3β)	111 (2)	C(11)-C(12)-O(1)	111.9 (4)
H(3α)-C(3)-H(3β)	99 (3)	C(11)-C(12)-H(12)	129 (2)
C(3)-C(4)-C(5)	111.1 (3)	O(1)-C(12)-H(12)	119 (2)
C(3)-C(4)-C(14)	109.1 (3)	C(11)-C(13)-H(13a)	115 (2)
C(3)-C(4)-H(4)	105 (2)	C(11)-C(13)-H(13b)	126 (2)
C(5)-C(4)-C(14)	113.5 (3)	C(11)-C(13)-H(13c)	116 (3)
C(5)-C(4)-H(4)	113 (2)	H(13a)-C(13)-H(13b)	105 (3)
C(14)-C(4)-H(4)	105 (2)	H(13a)-C(13)-H(13c)	103 (3)
C(4)-C(5)-C(6)	110.5 (3)	H(13b)-C(13)-H(13c)	87 (3)
C(4)-C(5)-C(10)	108.0 (3)	C(4)-C(14)-H(14a)	120 (2)
C(4)-C(5)-C(15)	110.1 (3)	C(4)-C(14)-H(14b)	112 (2)
C(6)-C(5)-C(10)	110.3 (3)	C(4)-C(14)-H(14c)	113 (2)
C(6)-C(5)-C(15)	107.4 (3)	H(14a)-C(14)-H(14b)	100 (3)
C(10)-C(5)-C(15)	110.6 (3)	H(14a)-C(14)-H(14c)	102 (3)
C(5)-C(6)-C(7)	111.9 (3)	H(14b)-C(14)-H(14c)	109 (3)
C(5)-C(6)-O(3)	110.7 (3)	C(5)-C(15)-H(15a)	113 (2)
C(5)-C(6)-H(6)	105 (2)	C(5)-C(15)-H(15b)	113 (2)
C(7)-C(6)-O(3)	105.4 (3)	C(5)-C(15)-H(15c)	113 (2)
C(7)-C(6)-H(6)	116 (2)	H(15a)-C(15)-H(15b)	96 (3)
O(3)-C(6)-H(6)	108 (2)	H(15a)-C(15)-H(15c)	104 (3)
C(6)-C(7)-C(8)	121.0 (3)	H(15b)-C(15)-H(15c)	116 (3)
C(6)-C(7)-C(11)	131.2 (3)	C(8)-O(1)-C(12)	105.0 (3)
C(8)-C(7)-C(11)	107.5 (3)	C(10)-O(2)-H(O-2)	112 (2)
C(7)-C(8)-C(9)	128.6 (3)	C(6)-O(3)-H(O-3)	114 (2)
C(7)-C(8)-O(1)	111.0 (3)		

Table III. Torsion Angles in Degrees

C(1)–C(2)–C(3)–C(4)	−50.7	C(12)–O(1)–C(8)–C(9)	−178.4
C(2)–C(3)–C(4)–C(5)	54.2	O(1)–C(8)–C(9)–C(10)	−169.8
C(3)–C(4)–C(5)–C(10)	−56.3	C(6)–C(7)–C(8)–O(1)	174.5
C(4)–C(5)–C(10)–C(1)	58.2	C(9)–C(8)–C(7)–C(11)	177.7
C(5)–C(10)–C(1)–C(2)	−56.5	C(13)–C(11)–C(7)–C(6)	6.9
C(10)–C(1)–C(2)–C(3)	51.2	C(13)–C(11)–C(7)–C(8)	−178.8
C(5)–C(6)–C(7)–C(8)	25.4	C(13)–C(11)–C(12)–O(1)	178.8
C(6)–C(7)–C(8)–C(9)	−7.2	C(14)–C(4)–C(5)–C(6)	59.6
C(7)–C(8)–C(9)–C(10)	12.1	C(14)–C(4)–C(5)–C(10)	−179.7
C(8)–C(9)–C(10)–C(5)	−35.9	C(14)–C(4)–C(3)–C(2)	−179.9
C(9)–C(10)–C(5)–C(6)	55.0	C(15)–C(5)–C(6)–C(7)	−169.0
C(10)–C(5)–C(6)–C(7)	−48.4	C(15)–C(5)–C(10)–C(9)	173.7
C(7)–C(11)–C(12)–O(1)	−0.9	C(15)–C(5)–C(10)–C(1)	−62.3
C(11)–C(12)–O(1)–C(8)	0.5	C(15)–C(5)–C(4)–C(3)	64.5
C(12)–O(1)–C(8)–C(7)	0.0	O(2)–C(10)–C(1)–C(2)	−176.8
O(1)–C(8)–C(7)–C(11)	−0.6	O(2)–C(10)–C(5)–C(4)	176.5
C(8)–C(7)–C(11)–C(12)	0.8	O(2)–C(10)–C(5)–C(6)	−62.7
C(3)–C(4)–C(5)–C(6)	−177.1	O(2)–C(10)–C(9)–C(8)	84.4
C(4)–C(5)–C(6)–C(7)	70.9	O(3)–C(6)–C(7)–C(11)	78.9
C(8)–C(9)–C(10)–C(1)	−161.3	O(3)–C(6)–C(7)–C(8)	−94.9
C(9)–C(10)–C(1)–C(2)	69.4	O(3)–C(6)–C(5)–C(10)	68.7
C(4)–C(5)–C(10)–C(9)	−65.8	O(3)–C(6)–C(5)–C(4)	−171.9
C(1)–C(10)–C(5)–C(6)	179.0	C(14)–C(4)–C(5)–C(15)	−58.9
C(5)–C(6)–C(7)–C(11)	−160.8	C(15)–C(5)–C(10)–O(2)	56.0
C(6)–C(7)–C(11)–C(12)	−173.5	C(15)–C(5)–C(6)–O(3)	−51.9
O(2)–C(10)–C(6)–O(3)	4.4	C(14)–C(4)–C(6)–O(3)	−114.4

Table IV. NMR Data[a]

	I ($CDCl_3$)	II ($CDCl_3$)	III (C_6D_6)
C-4 Me	0.80 d[d] (7)[b]	0.95 d[d] (7)	1.04 d (6)
C-5	0.95 s	1.05 s	1.08 s
C-11 Me	1.88 d (1)	1.85 d (1)	1.90 d (1)
C-6 H	2.2	3.2 s	4.37 d (6)
	2.4 q (9)[c]		
C-9 H	2.1	2.75	2.35
	3.0 q (17)[c]	3.06 q (17)[c]	2.84 q (17.8)
C-12 H	7.04 s	6.98 s	6.97 s
i-Bu Me		1.07 (7)	
		1.3 (7)	
i-Bu H		2.45 m (7)	

[a] All data are reported in parts per million. [b] Coupling constant in hertz. [c] Major peaks of quartet. [d] Actually an A_3B splitting pattern.

Isolation of II. Fourteen kilograms of frozen plant, which had been harvested approximately 20 miles south of Park Valley, Utah, was ground and extracted with 5 gal of hexane in a stainless steel cone. This procedure was carried out in a cold room at 5 °C to minimize decomposition. Solvent of the liquid extract was removed under vacuum and the semisolid material chromatographed on silica el resulting in only a crude separation of toxic constituents from other components.

The silica gel column of 4 ft × 4 in. was packed with 1500 g, charged with 75 g of crude extract and eluted with the solvent series hexane, diethyl ether, and methanol. Toxic compounds were eluted between 22% and 55% diethyl ether–hexane fractions.

Further purification was achieved using a 100-g alumina column which had been slurried and poured with a solvent containing 3% methanol in diethyl ether. Once settled, it was back eluted to hexane and charged with 1 g of crude material from the silica gel column. In the elution series hexane, diethyl ether, and methanol, compound II was eluted between 25% and 50% ether in hexane. At the end of the 50% ether fraction, another compound which as yet is unidentified is also found. Compound I and the above unknown are found in the 100% ether fraction.

Thin Layer Chromatography Results. Using prepoured Baker-flex silica gel 1B plates and solvent systems indicated, the following R_f values were obtained.

Compd	R_f
I[a]	0.28[b]
II	0.53[b]
III	0.50[c]

[a] Sulfuric dichromate. Ehrlich's reagent, and vanillin–sulfuric acid sprays were used for development. [b] Solvent system hexane–diethyl ether (1:1). [c] Solvent system hexane–diethyl ether–methanol (50:100:4).

Physical Data for 6β-Isobutyryl-10β-hydroxyfuranoeremophilane (II). The white crystals won from the wet plant by extraction, chromatography on silica gel and alumina, and sublimation melted at 100–100.5 °C, $[\alpha]^{MeOH}{}_D$ −56.11 ± 0.35°, λ_{max} 2150 Å (log ε 3.80). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.15; H, 8.61. Ir (CCl_4) 3590 and 1740 cm^{-1}; mass spectrum *m/e* 320, 232, 124 (base peak), and 71. $LD_{50}{}^{mice}$ oral was 350–400 mg/kg.

Preparation of 6β,10β-Dihydroxyfuranoeremophilane (III). A. Saponification of II. A solution of 100 ml of hexane, 1.32 g of II, 6.3 g of KOH, and 25 ml of H_2O was refluxed (60 °C) for 8 h. Separation and cooling the hexane portion gave crystals of diol III in 42% yield. These white crystals melted at 142–143 °C; $[\alpha]^{25}{}_D$ +26.98 ± 0.15° (EtOH); uv λ_{max} 2160 Å (log ε 3.79). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.87; H, 8.86. Found: C, 71.7; H, 8.8. Ir (KBr) 3350 (broad), 1650, and 1570 cm^{-1}; mass spectrum *m/e* 250, 231, and 124 (base peak).

The isobutyric acid garnered from the acidified water layer of the saponification by hexane extraction was proved identical with a known sample by mass spectrometry.

B. $LiAlH_4$ Reduction of II. Using 3 mmol of $LiAlH_4$ and 0.96 g of II in a standard reduction gave 0.580 g of diol III (77% yield) which was identical with III prepared by saponification. The isobutyl alcohol of the reaction was identified by GC–MS.

Preparation of II. A mixture of 250 mg of diol III, 7 ml of isobutyric anhydride, and 10 ml of anhydrous pyridine was placed in a stoppered flask at room temperature for 24 h. Extraction of the mixture with hexane which was subsequently washed with dilute HCl, dilute Na_2CO_3, and cold H_2O, dried, and evaporated gave a 33% yield of II after sublimation. Synthetic II was identical with original II according to its NMR, ir, uv, MS, mixture melting point, and elemental analysis.

Crystallographic Data Collection and Structure Analysis. Preliminary x-ray photographs of a crystal of diol III indicated the orthorhombic space group $P2_12_12_1$ with systematic absences of $h00$, $h \neq 2n$; $0k0$, $k \neq 2n$; and $00l$, $l \neq 2n$. Unit cell dimensions, refined by least squares from 16 independent 2θ values obtained with a G.E. XRD-490 diffractometer, are given in Table V. The crystal used was mounted along the *b* axis and bounded by $\{0{\cdot}1{\cdot}0\}$, $(1{\cdot}0{\cdot}0)$, $(4{\cdot}0{\cdot}1)$, $(\bar{8}{\cdot}0{\cdot}\bar{1})$, $(\bar{2}{\cdot}0{\cdot}1)$, $(2{\cdot}0{\cdot}\bar{1})$, and $(\bar{2}{\cdot}0{\cdot}\bar{1})$; its approximate dimensions were 0.21 × 1.44 × 0.39 mm measured parallel to the *a*, *b*, and *c* axes, respectively. Ni filtered Cu Kα radiation and a scintillation counter detector were

Table V. Crystal Data for $C_{15}H_{22}O_3$

$a = 21.322\ (7)$ $\alpha = \beta = \gamma = 90°$
$b = 7.593\ (2)$
$c = 8.387\ (1)$
Space group $P2_12_12_1$ $Z = 4$
$\rho_c = 1.217$ g cm^{-3} $\rho_{meas} = 1.203$ g cm^{-3}
μ(Cu Kα) = 6.76 cm^{-1}

employed to collect intensity data out to a 2θ of 120° using automatic θ–2θ step scans. Of a total 1204 reflections scanned, 1053 were considered observed by the criteria $I > 3\sigma(I)$ and were included in structure refinement. Lorentz and polarization factors were applied in the normal manner,[10] and the data were corrected for absorption by the method of Tompa.[11] Weights were calculated by the method of Stout and Jensen:[12] $w(F) = [(K/4Lp\ I)(\sigma^2(I) + (0.03I)^2)]^{-1}$. Scattering factors used were as follows: for nonhydrogen atoms from Cromer and Mann;[13] and for hydrogen from Stewart, Davidson, and Simpson.[14]

The structure was solved by direct methods using the program MULTAN.[10] Positions of all nonhydrogen atoms were refined, first isotropically, then anisotropically, by full-matrix least squares minimizing $\Sigma w \Delta F^2$, and all hydrogen atoms were located from a subsequent difference Fourier map. Further refinement of positional parameters for all atoms and anisotropic temperature factors for the nonhydrogen atoms resulted in a final R factor of 4.7% ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$). The R factor for all data, including unobserved reflections, was 5.7%; the weighted R_w ($R_w = [\Sigma w \Delta F^2]^{1/2}/[\Sigma w F_o^2]^{1/2}$) was 5.9%: and the largest shift divided by the standard deviation was 0.27 at the end of refinement. A $\delta(R)$ normal probability plot[15] was calculated and was essentially linear with a slope of 2.11 and an intercept of 0.14. A final difference Fourier showed no peaks greater than ±0.2 eÅ^{-3}. Absolute configuration could not be determined from the data.

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Registry No.—I, 52279-13-7; II, 60410-89-1; III, 35101-40-7.

Supplementary Material Available. Dihedral angles, equations of planes, positional and thermal parameters, and standard deviations (2 pages). Ordering information is given on any current masthead page.

References and Notes

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(10) Computer programs used were by F. R. Ahmed and co-workers (NRC-2, Data Reduction; NRC-8, Fourier for Distorted and Undistorted Nets; and NRC-12, Scan of Interatomic Distances and Angles; National Research Council, Ottawa, Ontario, Canada), Busing and Levy (ORFLS), Carrol K. Johnson (ORTEP), and Germaine, Main, and Woolfson (MULTAN, 1972 version). These programs were locally modified for use with the XDS Sigma 7 computer. Other programs were written locally by G. D. Smith, C. N. Caughlan, and R. D. Larsen.

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Syntheses of [8][8]- and [8][10]Paracyclophanes[1]

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Coupling of 2,5-dimethylene-2,5-dihydrofuran with the *p*-xylylene derivative (**16b**) prepared from 10-bromomethyl-13-methyl[8]paracyclophane (**8b**) yielded the benzene–furan "hybrid" [2.2]paracyclophane (**18b**) whose furan moiety was converted to a tetramethylene chain affording [8][8]paracyclophane (**3b**). The same sequence of reactions applied to 12-bromomethyl-15-methyl[10]paracyclophane (**8a**) furnished [8][10]paracyclophane (**3a**). The uv and NMR spectra of these [*n*][*n*]- and [*m*][*n*]paracyclophanes reveal their unusually twisted benzene rings.

Preparations of the optically active triple- and quadruple-layered [2.2]paracyclophanes 1 and 2 with known absolute configurations have been reported from our laboratory;[2] these compounds have D_2 symmetry and are gyrochiral.[3] While substitution of both the outer benzene nuclei of 1 with equivalent polymethylene chains leads to **3b** with D_2 symmetry, substitution with different polymethylene chains gives **3a** with C_2 symmetry. Although the names of [*n*][*n*]- and [*m*][*n*]-paracyclophanes were proposed by Smith[4] for these types of compounds, none of them have yet been prepared. By analysis[5] of the uv spectra of [*n*]paracyclophanes 4 with short para

Chart I