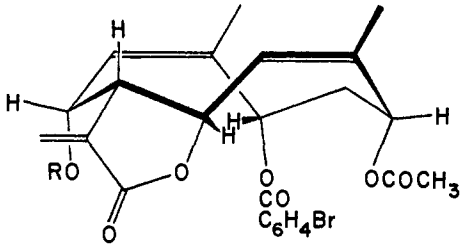
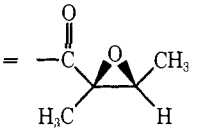
epoxide ring at C-1–C-10 in **6**. Evidence for a C-9 carbonyl in **6** was found in the disappearance of the doublet at τ 5.54 (J = 3 Hz, proton on carbon bearing oxygen), assigned to the C-9 proton signal in the spectrum of **10**, and the appearance of a new doublet at τ 4.36 (J = 3.5 Hz), which corresponds to a doublet of doublets at τ 4.36 (J = 3, 1 Hz) in the spectrum of **10**. This indicated that eupacunin has a C-1 hydroxyl group which undergoes allylic rearrangement,[6] on oxidation, to give the 1,10-epoxy 9-ketone grouping. Methanolysis of **10** (NaOMe) led to selective loss of the angeloyl group. This indicated that the angeloyl group in **10** is vicinal[7] to the C-9 hydroxyl group and is located at C-8 (in **10** *and* **1**).

Eupacunoxin [**2**; $C_{22}H_{28}O_8$; mp 171–172°; $[\alpha]^{25}D$ +27° (c 1.00); nmr (acetone-d_6) τ 6.95 (q, J = 5.5 Hz), 8.33 (s), 8.82 (d, J = 5.5 Hz) (epoxybutanoate)] was methanolyzed to methyl α-methyl-*trans*-α,β-epoxybutanoate and triol **9**, indicative that **2** differed from **1** solely in the ester function.

Unequivocal proof of the structure, stereochemistry, and absolute configuration of eupacunin was achieved by X-ray crystallographic analysis of eupacunin *o*-bromobenzoate (**11**), $C_{29}H_{31}BrO_8$, mp 184–186°, and eupacunoxin *m*-bromobenzoate (**12**), $C_{29}H_{31}BrO_9$, mp



11, R = angeloyl



191–192°. Eupacunin *o*-bromobenzoate (**11**) crystallized in the monoclinic space group $P2_1$ with a = 9.380 (4), b = 9.129 (4), and c = 17.309 (5) Å, β = 94.36 (5)°, and z = 2. The X-ray diffraction data were recorded on a Hilger and Watts' computer-controlled four-circle diffractometer with Cu Kα irradiation; 1769 significant independent intensities were obtained by the diffractometer measurements. The crystal structure was elucidated by Patterson and Fourier methods, and the atomic coordinates were subsequently adjusted by least-squares calculations incorporating corrections for anomalous dispersion; R is 11.8%. Eupacunoxin *m*-bromobenzoate crystallized in the orthorhombic space group $P2_12_12$ with a = 10.185 (5), b = 31.736 (12), c = 9.324 (5) Å, and z = 4. The X-ray diffraction data were collected and treated as above, except that Mo Kα radiation was used, and 1770 independent significant reflections were obtained; R is 11.3% for **12**.

Although a considerable number of sesquiterpene lactones have been found to show significant cytotoxicity toward KB carcinoma cell culture, eupacunin is one of the few which shows significant *in vivo* tumor inhibitory activity.[8] In view of the recent demonstration of the potential importance of nucleophilic additions of biologically important sulfhydryl groups for the tumor inhibitory activity of related compounds,[9] and of the inhibition of the sulfhydryl enzyme phosphofructokinase by eupacunin,[10] investigations are in progress to determine the significance of various structural features in relation to the biological activity of eupacunin.

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(7) S. M. Kupchan, P. Slade, R. J. Young, and G. W. A. Milne, *Tetrahedron*, **18**, 499 (1962).
(8) J. L. Hartwell and B. J. Abbott, *Advan. Pharmacol. Chemother.*, 7, 117 (1969).
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Liatrin, a Novel Antileukemic Sesquiterpene Lactone from *Liatris chapmanii*[1,2]

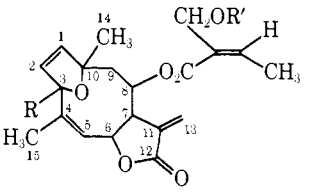
Sir:

In the course of a continuing search for tumor inhibitors from plant sources, it was found that chloroform extracts of *Liatris chapmanii* (Compositae)[3] showed significant inhibitory activity against cells derived from human carcinoma of the nasopharynx (KB) carried *in vitro*.[4] We report herein the isolation and structural elucidation of an antileukemic sesquiterpene lactone, liatrin (**1**).[5] Liatrin numbers among a very small group of sesquiterpene lactones which show significant *in vivo* tumor inhibitory activity,[6] and appears to be but the second recognized naturally occurring germacranolide *cis,cis*-diene (*cf.* ref 1).

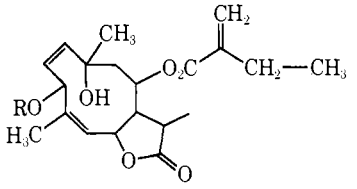
The active principle was isolated from *L. chapmanii* by fractionation involving successive solvent partitions and alumina and silicic acid chromatography, guided at each step by the KB assay.[4] Liatrin (**1**) [$C_{22}H_{26}O_8$; mp 130–132°; $[\alpha]^{24}D$ −142° (c 1.93, $CHCl_3$); uv end absorption (EtOH) 220 nm (ϵ 19,420); ir (KBr) 2.92 (OH), 5.67 (α,β-unsaturated γ-lactone), 5.76 (ester), 5.84 (α,β-unsaturated ester), and 6.03 μ (C=C); *m/e* 418 (M^+), 400 [M − 18 (H_2O)], 375 [M − 43 ($COCH_3$)], 358 [M − 60 (CH_3COOH)], 343 [M − 75

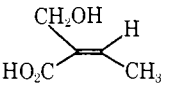
(1) Tumor Inhibitors. LXVIII. Part LXVII: S. M. Kupchan, M. Maruyama, R. J. Hemingway, J. C. Hemingway, S. Shibuya, T. Fujita, P. D. Cradwick, A. D. U. Hardy, and G. A. Sim, *J. Amer. Chem. Soc.*, **93**, 4914 (1971).
(2) Supported by grants from the National Cancer Institute (CA-11718 and CA-11760) and American Cancer Society (T-275), and a contract with Chemotherapy, National Cancer Institute (NIH 71-2099).
(3) Whole plant gathered in Florida in 1962. The authors acknowledge with thanks receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture (USDA), Beltsville, Md., in accordance with the program developed with the USDA by the Cancer Chemotherapy National Service Center (CCNSC).
(4) Cytotoxicity (KB) and *in vivo* activity were assayed under the auspices of the CCNSC, by the procedures described in *Cancer Chemother. Rep.*, **25**, 1 (1962).
(5) Liatrin showed significant tumor inhibitory activity against P-388 lymphocytic leukemia in mice.
(6) *Cf.* J. L. Hartwell and B. J. Abbott, *Advan. Pharmacol. Chemother.*, 7, 117 (1969).

(CH_3COOH, CH_3)], 277 [M − 141 ($CH_3CH{=}C(CH_2OAc)CO$)], 260 [M − 158 ($CH_3CH{=}C(CH_2OAc)COOH$)], 141 [$CH_3CH{=}C(CH_2OAc)CO$]] gave, on acid hydrolysis, an amorphous deacetylated product **2**, which was reconverted to **1** on acetylation and also could be converted to a bromoacetate (**3**): $C_{22}H_{25}BrO_8$; mp 135–137°; high-resolution mass spectrum M^+, calcd, 496.0733; found, 496.0721. Alkaline hydrolysis of **1** gave sarracinic acid (**4**),[7,8] identified by comparison of ir spectrum and mixture melting point with those of an authentic sample.[9] High-resolution mass spectrometry of **1** showed the presence of peaks at *m/e* 260.1047 ($C_{15}H_{16}O_4$) and 141.0576 ($C_7H_9O_3$), corresponding to the loss of acetylsarracinic acid from the molecular ion, and to acetylsarracinoyl ion, respectively. The presence of a hydroxyl group (ir 2.92 μ) in **1** was confirmed by a sharp D_2O-exchangeable proton singlet at τ 7.24 in the nmr spectrum. The stability of **1** toward treatment with acetic anhydride–pyridine indicated that the hydroxyl group was tertiary, and the remaining oxygen was assumed to be ethereal. The tertiary hydroxyl and ethereal oxygen functions were shown to constitute a hemiketal function by sodium borohydride reduction (at −15 to −5°), which yielded a diol (**5**): uv end absorption (EtOH) 210 nm (ϵ 14,700); ir (KBr) 2.92, 5.72, 5.83, and 6.15 μ; nmr ($CDCl_3$) τ 8.95 (t, J = 7.5 Hz, $-CH_2CH_3$), 8.91 (d J = 7.5 Hz, $>CHCH_3$), 8.50 (s, $>C(OH)CH_3$),



1, R = OH; R′ = Ac
2, R = OH; R′ = H
3, R = OH; R′ = $-COCH_2Br$
8, R = H; R′ = Ac





5, R = H
6, R = *o*-bromobenzoyl
7, R = *p*-bromobenzoyl

4

8.14 [s, $-C{=}C(CH_3)-$], 7.75 (q, J = 7.5 Hz, $-CH_2CH_3$), and 7.30 (quintet, J = 7.5 Hz, $>CHCHCH_3$); *m/e* 346 (M − 18), 263 (M − 101), and 83. The diol **5** yielded a mono-*o*-bromobenzoate (**6**), $C_{27}H_{31}BrO_7$, mp 181–182°, and a mono-*p*-bromobenzoate (**7**), $C_{27}H_{31}BrO_7$, mp 156–158°.

The 100-MHz nmr spectra of **1** and deoxyliatrin (**8**) [ir ($CHCl_3$) 5.71, 5.82, 6.04, 6.08 μ; *m/e* 402 (M^+), 387, 261, 141, 81; obtained by treatment of **1** with dimethylaminoborane] exhibited well-resolved signals,

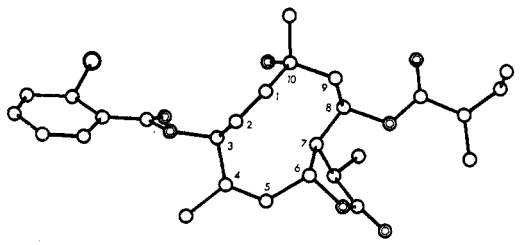


Figure 1. Molecular structure of the *o*-bromobenzoate derivative **6** as found in the crystal. The central ring is numbered to correspond to the structural formula given in the text. Oxygen atoms are represented by double circles, and the bromine atom by the larger circle.

and spin-decoupling experiments supported postulation of the indicated structures (apart from stereochemistry). The nmr ($CDCl_3$) assignments for **1** are as follows: τ 4.21 (*H*-1, d, J = 5.6 Hz), 3.64 (*H*-2, d, J = 5.6 Hz), 4.35 (*H*-5, d of d, J = 1.5, 6.5 Hz), 4.12 (*H*-6, m), 6.53 (*H*-7, m), 4.78 (*H*-8, t, J = 3.5 Hz), 7.63 (*H*-9, d, J = 3.5 Hz), 4.31 (*H*-13a, d, J = 2.3 Hz), 3.70 (*H*-13b, d, J = 2.3 Hz), 8.61 (*H*-14, s), 8.09 (*H*-15, m), and 7.24 (C-3-O*H*, s). The nmr spectrum of **8** is similar to that of **1**, the only significant difference being the presence of ABX-type signals for an allylic proton on carbon bearing ether oxygen [τ 4.79 (C-3-H_X, d of d, J = 1.5, 2.5 Hz)] and two olefinic protons [τ 4.32 (C-1-H_A, d of d, J = 1.5, 6.0 Hz), 3.92 (C-2-H_B, d of d, J = 2.5, 6.0 Hz)].

Unequivocal proof of the structure, stereochemistry, and absolute configuration of liatrin was achieved by X-ray crystallographic analysis of **6**. Crystals of the *o*-bromobenzoate (**6**) are orthorhombic with space group $P2_12_12_1$ and a = 11.25 (2), b = 26.63 (5), and c = 8.96 (2) Å. There are four molecules in the unit cell. 1150 independent nonzero reflections were measured in a single octant by automatic single-crystal counter diffractometry using monochromatic Mo Kα radiation. The structure was solved by the heavy atom method and refined by block-diagonal least-squares techniques.

The absolute configuration of the molecule was established using Hamilton's R factor ratio test.[10] With anisotropic thermal parameters adopted only for the bromine atom the R factors for the two possible enantiomeric structures were 0.123 and 0.116 when $\Delta f''$ for bromine was included in the structure factor calculation. The determination is significant at the 0.005 significance level. Refinement of the parameters for the preferred enantiomer with anisotropic thermal behavior assumed for all atoms led to a final R of 0.086. Despite the rather low ratio of observations to parameters this is a significant improvement by the same R ratio criterion. A view of the structure of **6** as found from the analysis is given in Figure 1. The same basic conformation of the central ten-membered ring system is found also in each of two crystallographically independent molecules in the asymmetric unit of the *p*-bromobenzoate **7**, which we have also examined, so that it is presumably a molecular characteristic only slightly influenced by crystal packing forces.

In view of the recent demonstration of the potential importance of nucleophilic additions to unsaturated

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systems for the tumor-inhibitory activity of related compounds,[11,12] investigations are in progress to determine the significance of various structural features in relation to the biological activity of liatrin.

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Thallium in Organic Synthesis. XXVI. Direct Conversion of Oximes into Aldehydes and Ketones with Thallium(III) Nitrate (TTN)[1]

Sir:

There has been considerable recent interest in the development of mild techniques for the conversion of oximes and their derivatives into aldehydes and ketones.[2] A variety of hydrolytic, oxidative, and reductive procedures have been described, only one of which appears to be of general applicability.[3]

We wish to describe in this communication a new method for the direct conversion of oximes into aldehydes and ketones by treatment with thallium(III) nitrate (TTN).[4] The following general procedure illustrates the manipulative simplicity of the method. A solution of TTN in methanol was added to a stirred solution of an equimolar amount of the oxime in methanol at room temperature. Reaction was rapid and nonexothermic, and was complete within a few minutes. The precipitated thallium(I) nitrate was removed by filtration, and the filtrate was shaken with dilute sulfuric acid for a few minutes and then extracted with ether or chloroform. The extract was dried, concentrated, and filtered through a short column of alumina or silica, using benzene or chloroform as eluent. Evaporation of the solvent followed by distillation or crystallization gave the pure aldehyde or ketone. Representative conversions are summarized in Table I.

From an examination of the reactions of a wide range of oximes with TTN under a variety of conditions, the advantages and limitations of the present method can be summarized as follows. (1) Reaction proceeds on the free oxime and prior conversion into a derivative is unnecessary (*cf.* ref 2). (2) Reaction proceeds virtually instantaneously at room temperature, and yields of pure products are uniformly high. (3) Considerable variation in experimental conditions is possible, depending on the solubility characteristics of the starting oxime. Thus, deoximation occurs equally efficiently in aqueous solution, provided that a small amount of perchloric acid is added to stabilize the TTN. Alternatively, deoximation can be accomplished in high yield by stirring a solution of the oxime in benzene with a suspension of TTN. In the latter case the water of crystallization of TTN participates in the reaction.

(1) Part XXV: A. McKillop, D. Bromley, and E. C. Taylor, *J. Org. Chem.*, in press.
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Table I. Conversion of Oximes into Aldehydes and Ketones with TTN

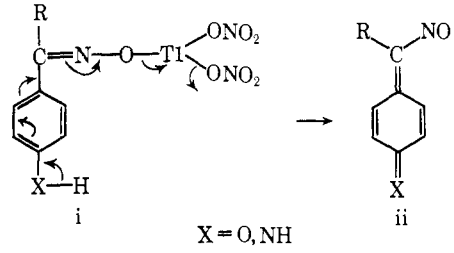
Ketone or aldehyde	Yield, %[a]
Ethyl methyl ketone	82
Pinacolone	74
Hexane-2,5-dione[b]	73
Cyclohexanone	92
2,2,6,6-Tetramethylcyclohexanone	78
n-Heptaldehyde	96
Furfuraldehyde	88
Benzaldehyde	88
Anisaldehyde	85
Mesitaldehyde	88
Cinnamaldehyde	88
Acetophenone	85
Benzophenone	86
4-Methoxybenzophenone	87
2,2′-Dithienyl ketone	72

[a] Calculated on pure recrystallized or redistilled material. [b] From hexane-2,5-dioxime.

(4) The procedure is unsuccessful when applied to aryl aldehydes or ketones which contain ortho or para substituted phenolic OH or aromatic NH_2 groups due to concomitant oxidation of the aromatic ring to quinone derivatives.[5] This limitation is, however, trivial and can be eliminated by acetylation of the OH or NH_2 group prior to formation of the oximes. (5) Treatment of monooximes of α-dicarbonyl compounds with TTN results in the formation of only 50–60% of the corresponding α-dicarbonyl compound. The remainder of the product consists of (as yet) unidentified products. (6) Oxythallation of α,β-unsaturated ketones is slow compared with isolated C=C bonds;[6] consequently, deoximation proceeds smoothly with α,β-unsaturated aldoximes and ketoximes. With oximes which contain an isolated C=C bond, however (*e.g.*, 1,2,5,6-tetrahydrobenzaldoxime), both deoximation and oxidative rearrangement[4] of the C=C bond occur, leading to mixtures of products.

Semicarbazone and phenylhydrazone derivatives of carbonyl compounds react analogously with TTN. Thus, treatment of the semicarbazone derivatives of cyclohexanone, acetophenone, and benzophenone at room temperature with TTN in methanol resulted in formation of the corresponding ketones in yields of 95, 86, and 82%, respectively. These reactions were slightly slower than those of the corresponding oximes, however, and required 1–5 min for completion. Regeneration of cyclohexanone and benzophenone from the corresponding phenylhydrazone derivatives was

(5) A. McKillop, B. P. Swann, and E. C. Taylor, *Tetrahedron*, 26, 4031 (1970). Failure of the reaction in these cases is due to rapid and preferential oxidation to a quinone methide (*i.e.* i → ii).



(6) A. McKillop, B. P. Swann, and E. C. Taylor, *Tetrahedron Lett.*, 5281 (1970).