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A NEW DIHYDROBENZOFURAN FROM *LIATRIS PROVINCIALIS*

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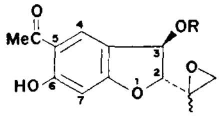
Key Word Index—*Liatris provincialis*; Compositae; epoxide of 2-isopropenyl-3-ethoxy-5-acetyl-6-hydroxy-2/β-dihydrobenzofuran.

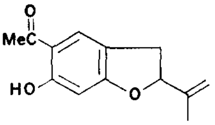
Abstract—A chloroform extract of *Liatris provincialis* Godfrey gave as a minor component a new dihydrobenzofuran, whose structure was established as I.

INTRODUCTION

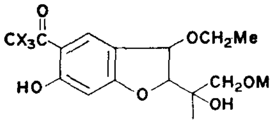
As part of a chemical study of the genus *Liatris* (Eupatorieae; Compositae) we have examined *Liatris provincialis* Godfrey, a plant endemic to a few countries in north Florida.[1] The present communication describes the structure determination of a new dihydrobenzofuran isolated in small amounts from the non-polar fraction of a chloroform extract of this plant. The results of our examination of the more polar sesquiterpene lactone fraction will be reported later.



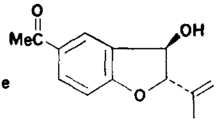
(I) R = CH₂Me
(VI) R = H



(II)



(III) X = D
(IV) X = H



(V)

RESULTS

The crystalline aromatic compound I, $C_{15}H_{18}O_5$, contained a hydrogen-bonded carbonyl group and a hydroxyl group (IR bands at 1635 and 3600–3000 cm^{-1}). The NMR spectrum confirmed the presence of the phenolic hydroxyl group (12·98 ppm, 1H, *s*) and revealed that the carbonyl resonance in the IR spectrum could be ascribed to a methyl ketone (2·58 ppm, 3H, *s*). The spectrum also contained signals due to two aromatic protons at 7·74 ppm (1H, *d*, $J = 1$) and 6·40 ppm (1H, *s*). These results, and particularly the chemicals shifts of all these protons, implied that I was a dihydrobenzofuran derivative.[2,3] This assignment was also supported by the UV spectrum, which had peaks at 319, 277, 242, 236, 223 and 218 nm (ε 7300, 13 500, 12 400, 12 800, 24 600 and 24 100 resp.) in good agreement with that reported for dihydroeuparin II.[3]

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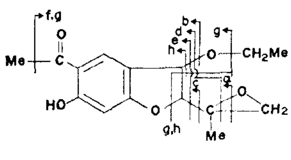
[1] R. K. Godfrey, *Am. Midland Naturalist* **66**, 466 (1966).

[2] T. Anthonsen and S. Chantharasakul, *Acta Chem. Scand.* **24**, 721 (1970).

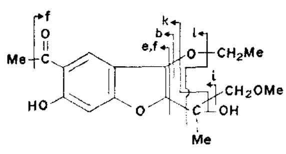
[3] F. Bohlmann and M. Grenz, *Chem. Ber.* **103**, 90 (1970).

As shown by double irradiation experiments the aromatic proton at 7·74 ppm, at lower field, hence *ortho* to the methyl ketone side-chain, was long-range coupled to a proton (broadened doublet, $J = 3$) at 4·95 ppm, which in turn was coupled to a proton at 4·61 ppm (sharp doublet). The magnitude of the coupling constant for the latter two signals (3 Hz) demonstrated that these protons were attached to vicinal carbon atoms and thus to C-3 and C-2 respectively. The NMR spectrum also indicated that I incorporated an ethoxyl group, conceivably attached to C-3, while a methyl singlet at 1·38 ppm and two doublets at 2·95 and 2·64 ppm, due to two protons coupled to each other (J 5 Hz), were ascribed to the C-2 substituent. On the basis of these data it seemed likely that the compound contained a terminal epoxide group and could be formulated as I. Reversal of the substituents, i.e. attachment of the ethoxyl group to C-2, seemed implausible on biogenetic grounds and was ruled out by considering the relative chemical shifts of the protons at C-2 and C-3.



(I)

a - H	M-31	m/e	247
b	M-45		233
b - H	M-46		232
c - H	M-58		220
c-2H	M-59		219
d	M-75		203
e + H	M-101		177
e	M-102		176
f	M-117		161
g + H	M-113		165
h	M-113		165

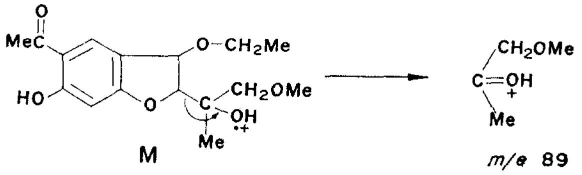


(IV)

b	alt	i	M-45	m/e	265
b-H_2O		i-H_2O	M-63		247
e+H			M-133		177
e			M-134		176
f			M-149		161
k-H			M-91		219
l+H			M-117		193

SCHEME 1. MS FRAGMENTATION OF I AND IV.

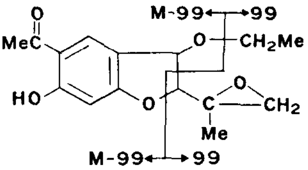
The MS fragmentation of I was in accordance with this formulation (see Scheme 1) The spectrum displayed peaks due to losses of a carbinol radical, in all probability derived from the epoxide group (cleavage *a*), of the C-2 substituent together with one or two hydrogens (M-58 and M-59, *c*) and of the C-3 substituent (M-45 and M-46, *b*). Furthermore, the fragmentation resulted in the formation of the diagnostically important dihydrobenzofuran and benzofuran ions of masses 177, 176 and 161 corresponding to the cleavages *e* and *f* in Scheme 1.



SCHEME 2. ORIGIN OF FRAGMENT *m/e* 89 IN MS of IV.

Attempted exchange of enolic hydrogens for deuterium in I by treatment with sodium and *O*-deteromethanol resulted in the formation of compound III, MW 313. The experiment was therefore repeated using sodium and methanol, which yielded IV, MW 310, $C_{16}H_{22}O_6$, evidently formed from I by addition of a molecule of methanol. This addition involved the epoxide group in I, since the two signals in the NMR spectrum ascribed to this group were replaced by a 3H singlet at 3·30 ppm (–OMe), a 2H singlet at 3·33 ppm (–O–CH_2–) and a broad signal at 2·28 ppm, exchangeable with D_2O and due to a hydroxyl hydrogen. These data are compatible with structure IV for the addition product. Support for this assignment also came from the MS of III and IV, which displayed a prominent peak at *m/e* 89 due to the C-2 substituent, $C_4H_9O_2$ (Scheme 2). The other important cleavage reactions of IV are summarized in Scheme 1.

The fragmentation pattern of I is more complex than that of III. Thus, some of the decomposition reactions of I seem to be governed by the proximity of the ethoxyl substituent to the epoxide group, which accords with previous findings that the fragmentation course of epoxides is highly sensitive to variations in substitution.[4,5] An interesting fragmentation process in I and absent in III, which gives rise to abundant ions of masses 99 ($C_6H_{11}O$) and 179 (M-99, $C_9H_7O_4$), obviously involves migration of an ethyl radical to the epoxide group. The reaction is complex and the cleavages shown in Scheme 3 are proposed to account for the formation of the two species.



SCHEME 3. ORIGIN OF FRAGMENT *m/e* 179 AND 99 IN MS OF I.

We now turn to the stereochemistry of I. The naturally occurring dihydrobenzofuran toxol, V, has most recently been reported to have the 2*S*, 3*R* configuration (*trans*).[6] The coupling constants for the vicinal C-2 and C-3 protons in the NMR spectra of V and its synthetic precursors were 3–4·5 Hz, while those in a series of synthetic 2*S*, 3*S* (*cis*) derivatives were 5–6 Hz.[6,7] The corresponding value for I wss 3 Hz, hence indicating a *trans* relationship at C-2, C-3. If the assumption be made that I is biogenetically closely related to toxol (*vide infra*), it would also possess the 2*S*, 3*R* configuration, while the stereochemistry of the epoxide in I remains unsettled.

A number of benzofuran and dihydrobenzofuran derivatives, obviously formed by condensation of hydroxyacetophenones with dimethylallyl pyrophosphate, have previously been isolated from different species of the Compositae.[2,3,7–11] Compound I is, to our knowledge, the first representative incorporating a terminal epoxide group. The biologically somewhat unusual ethyl substitutent at C-3 might conceivably have been introduced in the work-up procedure which involved treatment of the crude plant extract with ethanol under acidic conditions. Therefore we cannot completely exclude the possibility that the compound present in *Liatris provincialis* is IV rather than I.

EXPERIMENTAL

M.ps were determined in capillaries and are uncorrected. Rotations, in $CHCl_3$, were run on a Jasco ORD/UV-5 recording spectrophotometer; IR on a Perkin–Elmer model 257 instrument; NMR in $CDCl_3$ on a Bruker 90-MHz instrument; MS on an MS-902 high resolution mass spectrometer at 70 eV.

Extraction of Liatris provincialis *Godfrey*. Above ground parts, wt 10 kg, collected by Dr. R. K. Godfrey between Sopchoppy and St. James, Wakulla County, Florida, on 18 September 1971 (Godfrey voucher No. 70895 on deposit in herbarium of Florida State University) were extracted with $CHCl_3$ in a Soxhlet for 2 days. The extract was concentrated and the residue taken up in 3 l. of hot EtOH, diluted with 3·6 l. of hot

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[4] P. BROWN, J. KASSANYI and C. DJERASSI, *Tetrah. Suppl.* **8**, Part 1, 241 (1966).

[5] H. BUDZIKIEWICZ, C. DJERASSI and D. H. WILLIAMS, *Mass Spectrometry of Organic Compounds*, pp. 449–460, Holden-Day, New York (1967).

[6] L. H. ZALKOW, E. KEINAN, S. STEINDEL, A. R. KALYANARAMAN and A. BERTRAND, *Tetrahedron Letters* 2873 (1972). This reverses a previous assignment.[7]

[7] L. H. ZALKOW and M. GHOSAL, *J. Org. Chem.* **34**, 1646 (1969).

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[9] J. I. DEGRAW and W. A. BONNER, *J. Org. Chem.* **27**, 3917 (1962).

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[11] S. V. LOPEZ and B. R. GONZALES, *Anal. Quim.* **67**, 879 (1971).

H_2O containing 80 g of PbOAc and 20 ml HOAc, and allowed to stand. After 2 days, the supernatant liquid was filtered and concentrated at reduced pressure. The gum was taken up in $CHCl_3$ and dried. Removal of solvent yielded 102 g of material, which was chromatographed over 1·2 kg of silicic acid packed in benzene, 1–1 fractions being collected. Fractions 7–10, eluted with benzene, gave 565 mg of gummy solid, which was rechromatographed over silica gel (hexane–EtOAc 19:1:4:1) to give 178 mg of a cyrstalline material. This was recrystallized twice from isopropyl ether and petrol. affording I m.p. 111–112°, $[\alpha]_D - 65°$ (*c* 0·2, $CHCl_3$), UV (EtOH): 319 nm (ϵ 7300), 277 nm (ϵ 13 500), 242 nm (ϵ 12 400), 236 nm (ϵ 12 800), 223 nm (24 600) and 218 nm (ϵ 24 100); IR bands (KBr) 3600–3000 (hydrogen-bonded hydroxyl), 2980 (ether), 1635 (hydrogen-bonded ketone), 1590 and 1495 cm^{-1} (aromatic); MS (%, composition) 278 (M, 37, $C_{15}H_{18}O_5$), 247 (100, $C_{14}H_{15}O_4$), 233 (15, $C_{13}H_{13}O_4$), 232 (26, $C_{13}H_{12}O_4$), 220 (15, $C_{12}H_{12}O_4$), 219 (67, $C_{12}H_{11}O_4$), 203 (79, $C_{12}H_{11}O_3$), 191 (20, $C_{11}H_{11}O_3$), 179 (37, $C_9H_7O_4$), 177 (22, $C_{10}H_9O_3$), 176 (10, $C_{10}H_8O_3$), 165 (36, $C_9H_9O_3$), 165 (46, $C_8H_5O_4$), 164 (22, $C_9H_8O_3$), 161 (24, $C_9H_5O_3$), 99 (58, $C_6H_{11}O$). MW 278·1155. Calc. for $C_{15}H_{18}O_5$: 278·1153. Fractions 43–80, eluted with benzene–$CHCl_3$ and $CHCl_3$, being fairly homogeneous, were combined to give 33 g of a gummy material, which is currently being investigated. All other fractions contained mixtures.

Treatment of I *with sodium and* O-*deuteriomethanol.* 8 mg of I was refluxed under N_2 for 3 hr with a solution obtained from 3 ml *O*-deuteriomethanol and Na. The mixture was then kept at room temp. overnight, diluted with H_2O, acidified with 20% aq. H_2SO_4 and extracted with Et_2O. Chromtography over silica gel (hexane–EtOAc, 19:1 → 4:1) gave 6 mg of III. The NMR spectrum of III lacked the three-proton signal at 2·54 ppm. due to the $-COCH_3$ group, but was identical in all other respects to that of IV (*vide infra*); *m/e* (%): 313 (M, 10), 268 (44), 250 (79), 222 (31), 196 (21) 180 (96), 179 (36), 161 (34) and 89 (35).

Treatment of I *with sodium and methanol.* 5 mg of IV was obtained as a gum by treatment of 9 mg of I with Na and MeOH under the same conditions as described above for III. IV displayed IR bands (neat) at 3450 (hydroxyl), 2970 (ether), 1640 (hydrogen-bonded ketone), and 1490 cm^{-1} (aromatic); NMR 12·98 (1H, *s*), 7·72 (1H, *d*, $J \sim 1$), 6·39 (1H, *s*), 5·13 (1H, *dd*, $J \sim 1$ and 2·8), 4·62 (1H, *d*, $J = 2·8$), 3·64 (2H, $_1$, $J \sim 7$), 3·33 (2H, *s*), 3·30 (3H, *s*), 2·54 (3H, *s*), 2·28 (1H, broad), 1·28 (3H, *s*) and 1·25 (3H, *t*); *m/e* (%, composition); 310 (8, $C_{16}H_{22}O_6$), 265 (32, $C_{14}H_{17}O_5$), 247 (59, $C_{14}H_{15}O_4$), 219 (31, $C_{12}H_{11}O_4$), 193 (17, $C_{10}H_8O_4$), 177 (100, $C_{10}H_9O_3$), 176 (20, $C_{10}H_8O_3$), 161 (21, $C_9H_5O_3$) and 89 (31, $C_9H_4O_2$). MW 310·1420. Calc. for $C_{16}H_{22}O_6$: 310·1415.

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