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STEREOSTRUCTURE AND FORMATION MECHANISM OF A NEW SUBSTITUTED BENZOFURAN FROM PHOMENONE.

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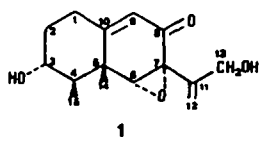
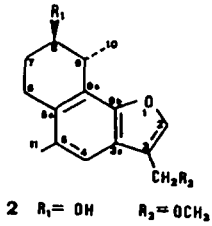
Abstract: Phomenone, a known phytotoxic and mycotoxic sesquiterpene, afforded a new substituted benzofuran, by treatment with a H_2SO_4 in MeOH solution (10%). The structure of such compound, determined by spectroscopic and X-ray diffraction methods on its acetylderivative, is described. The formation mechanism of the new substituted benzofuran from the toxin is also discussed.

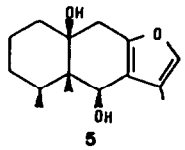
Investigation on a wilt disease of tomato (Licopersicon esculentum Mill.) caused by Phoma destructiva Plowr., led to the isolation and identification[1] of Phomenone (1), a known phytotoxic metabolite, whose role as a phytotoxin in wilted leaves of infected tomato plants has been recently demonstrated.[2] Phomenone is a sesquiterpene, having the eremofilane ring structure[3] related to PR toxin[4,5] a mycotoxin produced by Penicillium roqueforti, which is strongly toxic to mice and rats.[6,7] Recently a study on the structure-toxicity relationships of Phomenone and some derivatives in comparison with PR toxin has been also performed.[8] Many attempts were performed to modify selectively the epoxide function of the PR toxin and phomenone[9] (1), in order to confirm its preminent role in the biological activity of the eremophilanes. One of these experiments, i.e. the reaction of phomenone with a H_2SO_4 in MeOH solution (10%), afforded an unexpected product identified as the new substituted benzofuran 2 (or tetrahydro[1,2b]naphtofuran). This compound resulted to be very similar in the structure to Farfugin A (4), which is considered to be a suspected artifact of the 7-aneremophilane[10,11] 5, both being isolated from the natural extract of Farfugium japonicum.[12,13]



1

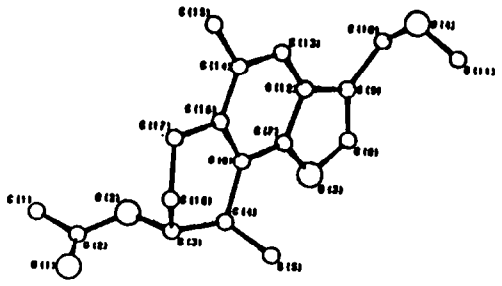


2 R_1= OH R_2= OCH_3
3 R_1= $OCOCH_3$ R_2= OCH_3
4 R_1= H R_2= H



5

Fig. 1



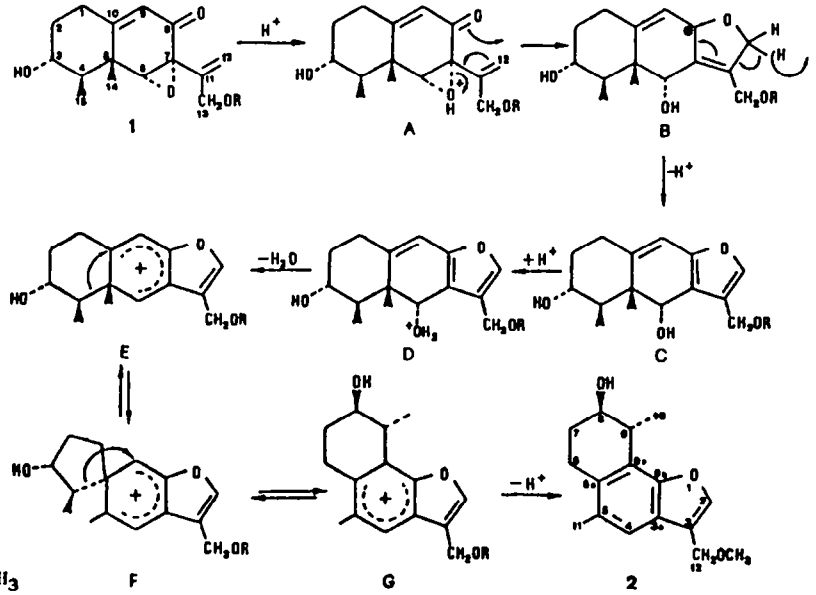
appeared to be in the range expected for the functional groups present in the molecule[14] (Fig.1). The furane and benzene ring are planar within the experimental errors; the highest deviation of the atoms of the rings from the least-square planes being 0.010 A. The dihedral angle between the two planes is 178.1°. The cyclohexene moiety is in half chair conformation with the two substituents in trans-diaxial conformation, the torsion angle C(5)-C(4)-C(3)-O(2) is -160°. The C(3) and C(4) atoms have the same chirality (R,R or S,S). This configuration was expected to be the preferred one, since in the diastereoisomers (R,S or S,R) repulsive interactions would occur because of the partial rigidity of the cyclohexene ring. The dihedral angles C(11)-O(4)-C(10)-C(9) and O(4)-C(10)-C(9)-C(12) are 70° and 64° respectively. Thus the conformation of the ether group is g+g+. Crystal packing is achieved through Van der Waals interactions, while only few intermolecular distances are less than 3.5 A.

A mechanistic interpretation of the rearrangement which afforded 2 arising from 1, follows. In order to investigate this transformation mechanism , the reaction was also performed in 10% solution of concentrated D_2SO_4 (99,5% deuterated) in CD_3OD (99,9% deuterated). Thus it was obtained a product whose R_f, IR and UV spectra were identical to 2, but with some differences in the PMR and MS data. MS gave a molecular peak at 263 m/e, a (M^+-H_2O) peak at 245 m/e and a (M^+-CD_3O) peak at 229 m/e; PMR spectrum showed only the disappearance of the signal at δ 3.38 , corresponding to the methoxy group. These data were consistent only with the incorporation in 2 of OCD_3 from CD_3OD solvent. On the basis of this result we postulated a transformation mechanism which is shown in the Scheme. We divided our mechanistic interpretation in two parts:

i) the formation of furanic ring as shown in the 1---> C sequence;

ii)the skeletal rearrangement of C into the 6,7,8,9-tetrahydro[1,2b]naphtofuran 2.

Scheme



R = H or CH_3

In the present paper we report the structural determination of 2 and its acetylderivative 3, by spectroscopic and X-ray diffraction methods. The mechanistic interpretation of the tetrahydro 1,2b naphtofuran 2 formation from phomenone (1), compared to the skeletal rearrangement of the furaneremophilane 5 into farfugin A[11,13] (4) is also discussed.

RESULTS AND DISCUSSION

The reaction of phomenone (1) with a H_2SO_4 in MeOH solution (10%) gave the substituted benzofuran 2 in a quite high yield. The structure of 2 was originally postulated on the basis of the spectroscopic analyses and then confirmed by X-ray diffraction analysis of its acetylderivative 3. In fact, the PMR spectrum of 2 showed the presence of two singlets at δ 7.30 and 7.44 (two protons), referred to the aromatic hydrogens, a singlet at δ 2.31, related to a methyl group attached to the aromatic ring and a singlet at δ 4.57, corresponding to a methylene group bound with an aromatic ring and a methoxy group. Finally, a singlet at δ 3.38 was consistent with the presence of a methoxy group. The IR spectrum of 2 showed the remarkable lack of the α,β-unsaturated cyclic ketone band, which was present in the IR spectrum of 1, moreover the UV spectrum had characteristic bands of a benzofuranic structure. The molecular formula of 3 determined by HRMS was $C_{18}H_{22}O_4$ (M^+ 302.1532 calculated 302.1512); other remarkable fragments were $C_{17}H_{19}O_3$ (M^+-OMe, 271.1319), $C_{16}H_{18}O_2$ (M^+-MeCOOH, 242.1438, base peak), $C_{15}H_{15}O_2$ (M^+-MeCOOH-Me, 227.1031) and $C_{15}H_{14}O$ (M^+-MeCOOH-OMe,210.1046). The spectroscopic data of 2 and 3 compared to those of phomenone (1) are summarized in Table I.

Because of the scarce availability of phomenone (1), the crystalline acetate 3 was analyzed by X-ray diffraction method.Such analysis provided the following results. Bond lengths and bond angles

Table I - Spectroscopic data of 2 and 3 compared to those of phomenone (1).

1[a]	2	3
UV (λ_{max}, ε): 248 (17000)	UV (λ_{max}, ε): 248 (9500) 278 (1050) 288 (1050)	UV (λ_{max}, ε) 248 (9500) 278 (1050) 288 (1050)
IR (ν, cm^{-1}): 1675, 1110 3350-3380.	IR (ν, cm^{-1}): 3550-3475	IR (ν, cm^{-1}) 1730, 1225.
MS (m/e): 264, 249, 246, 231	MS (m/e): 260, 242, 229	MS (m/e) 302, 271, 242.
^{1}H NMR (δ)	^{1}H NMR (δ)	^{1}H NMR (δ)
H -1 2.60	H -6 2.77	H -6 2.76
H^a-1 2.53	H^a-6 2.77	H^a-6 2.76
H^e-2 2.11	H^e-7 2.04	H^e-7 2.13
H^e-2 1.37	H^a-7 2.04	H^a-7 2.07
H^a-3 3.58	H^e-8 4.05	H^e-8 5.13
H -4 1.72	H -9 3.38	H -9 3.45
H -6 3.40	H -4 7.44	H -4 7.54
H -9 5.71	----	----
2H-12 5.24 and 5.20	H -2 7.30	H -2 7.33
2H-13 4.29 and 4.16	2H-12 4.57	2H-12 4.58
Me-14 1.25	Me-11 2.31	Me-11 2.34
Me-15 1.20	Me-10 1.37	Me-10 1.41
	OMe 3.38	OMe 3.40
		OCOMe 1.99

[a] See references 1 and 3.

In the first part we postulate the protonation of the oxirane ring of **1**, which affords **A**, followed by the formation of the carbocation **B**, strongly stabilized by resonance. Finally its deprotonation gives the compound **C**; its structure is very similar to that of furanoeremophilanes,[12] for which an interesting skeletal rearrangement, like to that of steroids[15] is reported in literature.[11] We can suggest an analogous rearrangement for the transformation of **C** into **2**. Our mechanistic interpretation, as reported in the Scheme, is supported by the following considerations: a) the compound **2** is optically active; b) the relative configurations at C-8 and C-9 in **2** correspond to those of C-3 and C-4 in **1**. Finally we cannot establish when the methoxylation at C-12 of **2** occurs but only that the methoxy group comes from the solvent as above reported.

To conclude we would suggest some interesting remarks. Firstly, the reported rearrangement supports the biogenetic hypothesis on the formation of furanic compounds from a precursor having a prenilic group, as reported in literature.[16] Furthermore, starting from the consideration that some natural substituted benzofurans are described to be artifact of furaneremophilanes[12,13] and that **C** (see Scheme), which is a furanoeremophilane, results to be an intermediate in the transformation of **1** into **2**, we are inclined to suppose that furanoeremophilanes could be artifacts of Phomenone-like substances. Finally, in our opinion the above discussed transformation turns out to give useful information about synthetic methods for the preparation of substituted furans or benzofurans starting from compounds with a carbon skeleton functionalized as Phomenone (**1**).

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EXPERIMENTAL

M.p. are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter in $CHCl_3$ solutions. IR spectra were recorded on a Perkin-Elmer 399 instrument ($CHCl_3$). UV spectra were measured on a Varian Cary 210 spectrophotometer ($CHCl_3$). ^1H NMR spectra were recorded on a 270 MHz Bruker and on a 500 MHz Bruker spectrometer ($CDCl_3$) using TMS as internal standard; chemical shifts are in ppm. Mass spectra were recorded on an AEI-902 mass spectrometer at 70ev. High resolution mass spectra were performed on a Kratos MS-50. Analytical and preparative TLC were performed on silica gel plates (Merck, Kieselgel 60 F_{254} 0.25 mm) Column chromatography was carried out on silica gel (Merck Kieselgel 60 0.063-0.2 mm).
Phomenone was purified, according to a published procedure[1], from 7-day-old shaked cultures of *P. destructiva*.

6,7,8,9-tetrahydro-3-methoxymethyl-5,9-dimethyl-8-hydroxy-nafto [1,2b]furan (2).
Phomenone (**1**) (37 mg) was added to a (10%) solution of conc. H_2SO_4 (370 µl) in dry MeOH (3.7 ml). The reaction, left at room temperature and monitored by TLC (EtOAc-n-hexane 7:3, v/v), was completed within 15'. The reaction mixture was neutralized with 0.4 N NaOH , diluted with H_2O (20 ml) and extracted with EtOAc (3x50 ml). The combined organic layers were dried on anhydrous Na_2SO_4 and evaporated under vacuum giving a crude residue (33 mg) which was purified by preparative TLC (EtOAc -n-hexane 7:3, v/v). The most abundant isolated product (24 mg, 65% yield) resulted to be an oil. $[\alpha]_D^{20}$ = +6.6 (c=0.9); UV, λ_{max} (ε) : 248 nm (9500), 278 nm (1050) and 288 nm (1050); IR, ν_{max} :3550, 3475 cm^{-1} ; ^1H NMR, δ :1.37 (3H, d, $J_{10,9}$=6.99 Hz, 10-Me), 2.04 (2H, m, 7-H_a and 7-H_e), 2.31(3H, d, $J_{11,4}$=0.74 Hz, 11-Me), 2.77 (2H, m, 6-H_a and 6-H_e), 3.38 (3H, s, OMe), 3.38 (1H, m, 9-H), 4.05 (1H, m, 8-H), 4.57 (2H, d, $J_{12,2}$=1.10 Hz 12-CH_2), 7.30 (1H, d, $J_{2,12}$=1.10 Hz, 2-H), 7.44 (1H, d, $J_{4,11}$=0.74 Hz, 4-H); MS, m/e: 260 (100%, M^+), 242 (75%, M^+-H_2O), 229 (28%, M^+-CH_3O). Found C,73.41; H,7.82. Calc. for $C_{16}H_{20}O_3$: C,73.82; H,7.74%.

6,7,8,9-tetrahydro-3-methoxymethyl-5,9-dimethyl-8-acethoxy-naphto[1,2b]furan (3).

A solution of 2 (10 mg) in dry pyridine (500 l) was treated with $(CH_3CO)_2O$ (500 µl) overnight at room temperature.The usual work-up gave a crude product (11 mg), which was purified by TLC preparative (n-hexane-EtOAc 6:4, v/v). The semicrystalline product (9.5 mg) was recrystallized from Et_2O: m.p. 102-104°C; $[\alpha]_D^{20}$=-4.0 (c=0.6); UV, λ_{max} (ε): 248 nm (9500), 278 nm (1050), 288 nm (1050); IR, ν_{max}: 1730 cm^{-1}; ^1H NMR, δ ; 1.41 (3H, d, $J_{10,9}$=7.35 Hz, 10-Me), 1.99 (3H, s, OAc), 2.07 and 2.13 (2H, two m, $J_{7,7}$=14 Hz and $J_{7,8}$=4.5 Hz, 7-$H_{a(e)}$ and 7-$H_{e(a)}$), 2.34 (3H, d, $J_{11,4}$=0.74 Hz, 11-Me), 2.76 (2H, m,$J_{6,6}$=19.7 Hz 6-H_a and 6-H_e), 3.40 (3H, s, OMe), 3.45 (1H, m, $J_{9,10}$=7.35 Hz and $J_{9,8}$=2.21 Hz, H-9), 4.58 (2H, d, $J_{12,2}$=1.10 Hz, 12-CH_2), 5.13 (1H, m, $J_{8,9}$=2.21 Hz, $J_{8,7}$=4.40 Hz and $J_{8,7}$=2.21 Hz, 8-H), 7.33 (1H, d, $J_{2,12}$=1.10 Hz, 2-H), 7.54 (1H, d, $J_{4,11}$=0.74 Hz, 4-H); MS, m/e: 302 (20%, M^+), 271 (20%, M^+-OMe), 242 (100%, M^+-MeCOOH).

6,7,8,9-tetrahydro-3-trideuteromethoxymethyl-5,9-dimethyl-8-hydroxy-naphto [1,2b]furan.

Phomenone (1) (30 mg) was added to a conc. D_2SO_4 solution (99.5% deuterated) (300 µl) in dry CD_3OD (99.9% deuterated) (3 ml). The reaction, monitored by TLC (EtOAc - n-hexane 7:3, v/v), was complete in 15' at room temperature. The reaction mixture was neutralized with 0.4N NaOH, diluted with H_2O (20 ml) and then extracted with EtOAc (3x50 ml). The combined organic layers dried on anhydrous Na_2SO_4 and evaporated under vacuum, gave a residue (24 mg) which was purified by preparative TLC. The most abundant product (20 mg), was an uncrystallizable oil. ^1H NMR, δ : 1.37 (3H, d, $J_{9,10}$=6.99 Hz, 10-Me), 2.04 (2H, m, 7-H_a and 7-H_e), 2.31 (3H, d, $J_{11,4}$=0.74 Hz, 11-Me), 2.77 (2H, m, 6-H_a and 6-H_e), 3.38 (1H, m, 9-H), 4.05 (1H, m, 8-H), 4.57 (2H, d, $J_{12,2}$=1.10 Hz, 12-CH_2), 7.30 (1H, d, $J_{2,12}$=1.10, 2-H), 7.44 (1H, d, $J_{4,11}$=0.74 Hz, 4-H); MS, m/e: 263 (100%, M^+), 245 (60%, M^+-H_2O), 229 (25%, M^+-CD_3O).

A CAD4 diffractometer, equipped with a PDP-8/E and a PDP-11/34 digital computers, was used for the determination of unit cell dimensions, data collection, structure determination and refiniment. A summary of crystal data for the present structure is given in Table II. An ω-2θ scan mode was used for the peak measurements; background counts were taken at the end of each scan. A total of 1628 indipendent reflections were collected in the θ range 1-70°; 874 (I>1σ(I)) were considered "observed" and used in the calculations. The structure was solved with MULTAN in the form programmed by Germain et al.[17] The map corresponding to the highest combined figure of merit revealed the position of all non hydrogen atoms were located with difference Fourier maps and included in the calculations in their stereochemically expected positions with an isotropic temperature factor equal to the B equivalent of the carrier atom. The structure was refined using full-matrix least squares procedure, minimizing the quantity $\Sigma w[|F_o^2 - F_c^2|]^2$ with w equal to $1/\sigma(F_o)^2$.Anisotropic temperature factors for C and O were used, while positional and temperature factors of H atoms were kept fixed. Refinement was ended when the maximum shift in the atomic coordinates and anisotropic temperature factors was less than 1/5 of the corresponding standard

Table II- Crystallographic data for 3

Molecular formula	$C_{18}H_{22}O_4$
Molecular weight (amu)	302.37
Crystal system	Monoclinic
Space group	P_{21}
Z (molecules/unit cell)	2
a (A)	9.314(1)
b (A)	9.727(2)
c (A)	9.622(1)
ß (deg)	112.38(1)
V (A^3)	806.1(4)
Density, by flotation (gcm^{-3})	1.24
Density, calculated (gcm^{-3})	1.246
Radiation	CuK_α,λ=1.5418 A
Measured reflection	1628
Reflection with I>1σ(I)	874
Final R value	0.065
Temperature (°C)	22, room temp.

deviations. The scattering factors for all atomic species were calculated according to Cromer and Waber.[18] All calculations were carried out using the SDP package of crystallographic programs. The final value for the weighted R factor was 0.065. The final atomic parameters are given in Table III.[14]

Table III - Final atomic parameters (x 10^4) for 3.

Atom	x/a	y/a	z/a	Beq(A2)[a]
C(1)	8692(14)	2516(14)	14866(10)	7.8(3)
C(2)	9287(11)	3462(12)	14023(9)	5.8(3)
C(3)	9056(9)	4162(11)	11569(9)	4.8(2)
C(4)	8729(9)	3379(12)	10118(9)	4.9(2)
C(5)	9652(10)	3978(14)	9248(8)	6.5(3)
C(6)	6999(8)	3355(11)	9156(8)	3.8(2)
C(7)	6409(9)	2469(10)	7916(8)	4.4(2)
C(8)	6256(11)	853(10)	6265(10)	5.5(3)
C(9)	4839(11)	1382(11)	5834(9)	5.6(3)
C(10)	3389(13)	945(13)	4467(11)	7.7(3)
C(11)	3808(15)	2374(15)	2691(11)	8.7(4)
C(12)	4888(9)	2430(0)	6913(8)	4.3(2)
C(13)	3856(9)	3303(11)	7155(9)	4.7(2)
C(14)	4318(8)	4201(10)	8374(8)	4.0(2)
C(15)	3138(10)	5115(13)	8642(10)	6.1(3)
C(16)	5898(8)	4229(10)	9349(8)	3.9(2)
C(17)	6412(9)	5227(11)	10662(9)	4.7(2)
C(18)	8161(11)	5501(10)	11312(9)	5.5(3)
O(1)	10248(9)	4368(9)	14549(7)	8.5(2)
O(2)	8599(6)	3264(7)	12534(5)	4.9(1)
O(3)	7297(6)	1494(7)	7552(6)	5.1(2)
O(4)	2846(8)	2067(9)	3422(7)	8.2(2)

[a] $Beq=(4/3)\sum_i\sum_j \beta_{ij}g_{ij}$ (g=metric tensor)

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