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5,6-DIMETHOXY-2-ISOPROPENYLBENZOFURAN FROM *LIGULARIA STENOCEPHALA* MATSUM. ET KOIDZ.

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Abstract—A new benzofuran derivative, 5,6-dimethoxy-2-isopropenylbenzofuran (**3a**) has been isolated from *Ligularia stenocephala* Matsum. et Koidz.

EUPARIN (**1**, R = OH)[1], tremetone (**2**, R = H, R′ = H),[2,4b] hydroxytremetone (**2**, R = OH, R′ = H; with 2ξ-isopropenyl),[2a,3] dehydrotremetone (**1**, R = H)[2a,3a,4a] and toxol (**2**, R = H, R′ = OH)[4] are the benzofuran derivatives occurring in plants of the Compositae family. The latter four ketones have been isolated from tremetol, the crude toxin of two plants, *Eupatorium urticaefolium* and *Aplopappus heterophyllus*, both of which cause the diseases known as trembles in cattle and milk sickness in humans.[2-4] The present paper reports the isolation and the constitution of a new benzofuran derivative isolated from *Ligularia stenocephala* Matsum. et Koidz. (Compositae).

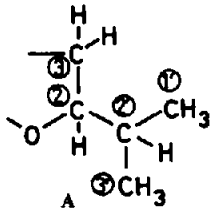
Benzene extraction of the roots, followed by separation by alumina column chromatography and sublimation, afforded a compound **3**, $C_{13}H_{14}O_3$, M^+ 218, m.p. 72·5–73°, $[\alpha]_{578}$ ±0°; UV (MeOH): 324 (sh), 314, 287, 278, and 215 mμ (log ε, 4·13, 4·21, 4·00, 4·02 and 4·18); IR (Nujol): 1612, 1550 and 890 cm^{-1}; NMR ($CDCl_3$):* δ 2·07 (3H, broad s, CH_3—C═C), 3·90 (6H, s, two OMe groups), 5·07 and 5·67 (each 1H, broad s, C═CH_2), 6·51 (1H, s, β-H of furan ring),[5] 6·94 (1H, s, aromatic H) and 7·00 (1H, s, aromatic H). This compound (**3**) is unstable in air and acids, and develops a pale blue colour during TLC when 2N-ceric sulphate reagent is sprayed.

The compound (**3**) in ethanol when shaken with 5% Pd–C absorbed two moles of hydrogen to give the tetrahydro derivative **4** (racemic), colorless liquid, M^+ 222, UV (MeOH): 302, and 234 mμ (log ε, ~4, ~4); IR (Nujol): 1619 cm^{-1}; NMR ($CDCl_3$): δ 0·95 and 1·01 (each, 3H, d, J = 6 Hz, $(CH_3)_2$—CH—), 1·92 (1H, multiplet, (Me_2)—CH—), 2·92 (2H, m, CH_2 group α to the aromatic ring), 3·74 (6H, s, two OMe groups), 4·41 (1H, m, —O—CH—), 6·34 (1H, s, aromatic H) and 6·65 (1H, s, aromatic H).

These spectral data suggest the presence of a benzofuran ring, two OMe groups and of an isopropenyl group for **3**. The formation of a dihydrobenzofuran ring together with an isopropyl group follows for **4**. The NMR spectrum of **3** shows the presence of one furan β-proton and of two isolated aromatic protons in a 1,4-relationship. Thus, two OMe and one isopropenyl groups must be attached to either position of 2, 5 or 6 of benzofuran ring.

Proton spin decoupling experiments (in $CDCl_3$, at 100 MHz) of **4** afford evidence for the presence of a partial structure (**A**). The multiplet at δ 1·92 (1H, C_2,-proton)

* s = singlet, d = doublet, m = multiplet etc.



A

collapsed to a doublet (J = 7 Hz) on double irradiation at the Me proton ($\delta \simeq 0{\cdot}98$) frequency. This doublet results evidently from the coupling between the proton concerned and an adjacent proton (C_2-proton). Double irradiation at δ 1·92 changed a pair of doublets of *gem*-dimethyl group into two separate signals at δ 0·95 and 1·01 (C_1,- and C_3,-protons). At the same time, this irradiation altered the pattern of multiplet at δ 4·41 (C_2-proton). Double irradiation at the latter frequency, in turn, changed the multiplet of the proton at δ 1·92 (C_2,-proton) into a distinct septet on one hand, and altered the pattern of multiplet at δ 2·92 (C_3-protons) on the other. The multiplet at δ 4·41 (C_2-proton) was reduced to a doublet (J = 7 Hz) on double irradiation at δ 2·92. (Fig. 1.)

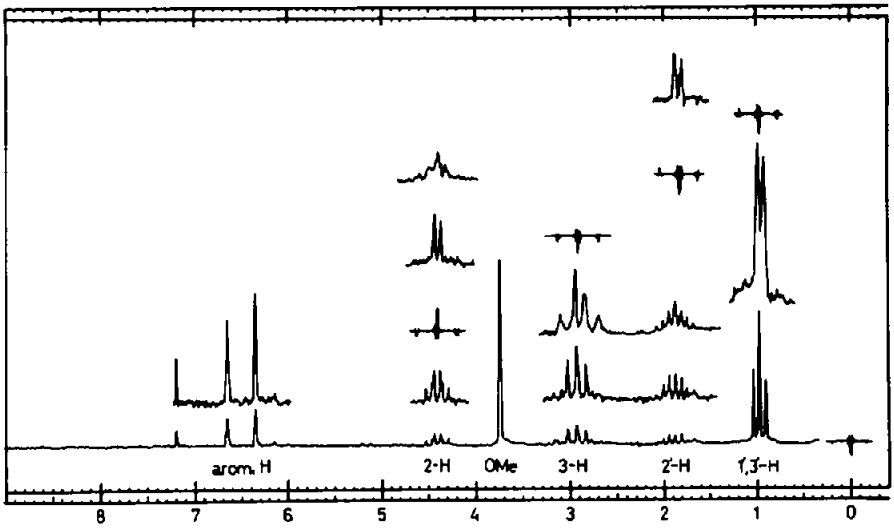


FIG. 1 The proton double resonance spectrum of the tetrahydro derivative **4**.

The above observations lead to the location of isopropyl group of **4** to the position 2. This was confirmed by the following evidence. By condensation of **3** with maleic anhydride, an adduct **5**, M^+ 316, m.p. ~180° (dec) was formed. The formation of the adduct indicates that the double bond of isopropenyl group is conjugated with a furan double bond. Thus, the nature of all C and O atoms is clarified for **3** and for **4**. The formula of 5,6-dimethoxy-2-isopropenylbenzofuran (**3a**) is given to the isolated natural compound **3**. The tetrahydro derivative **4** is, therefore, 5,6-dimethoxy-2-isopropyldihydrobenzofuran (**4a**).

Finally, the structure of **3** was fully established by the following synthesis. 4,5-Dimethoxy-2-hydroxybenzaldehyde (**6**)[6] was condensed under alkaline conditions with chloroacetone to give 5,6-dimethoxy-2-acetylbenzofuran (**7**), $C_{12}H_{12}O_4$, m.p. 118·5°, UV (MeOH): 339, 298 (sh), 263, and 222 mμ (sh) (log ε, 4·37, 4·15, 3·81 and 4·18), IR (Nujol): 1673 cm^{-1} (C=O). This ketone **7** was heated with triphenylmethylenephosphorane in refluxing THF to afford 5,6-dimethoxy-2-isopropenylbenzofuran (**3a**), $C_{13}H_{14}O_3$, m.p. 72°, identical (mixed m.p., IR, UV, VPC and TLC) with **3** (Chart I).

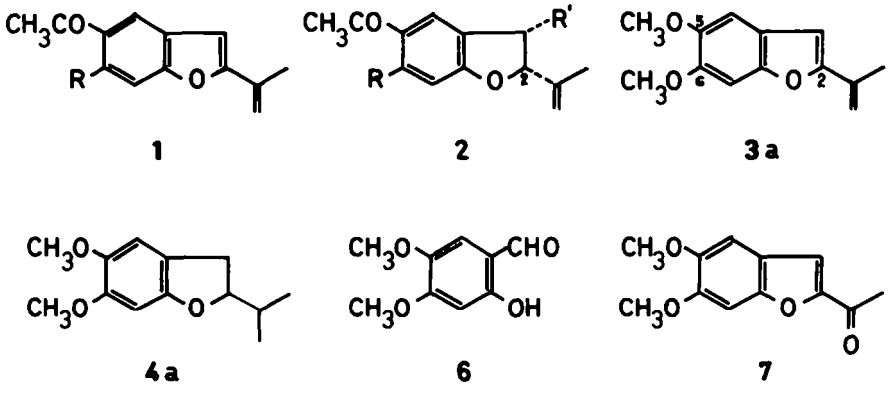


CHART I

The mass spectrum of **3** shows peaks at *m/e* 218 (M^+, base peak), *m/e* 203, *m/e* 175 and at *m/e* 160, together with other peaks at lower *m/e*. The formation of these fragments may be interpreted as shown in Chart II.[7]

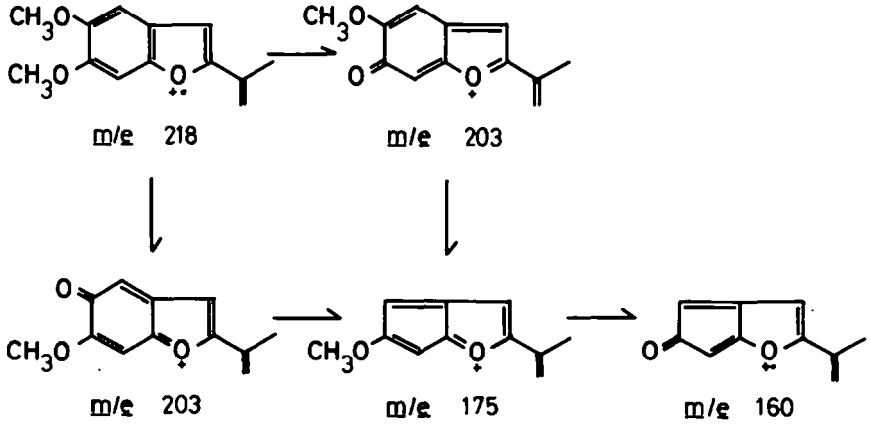


CHART II

5,6-Dimethoxy-2-isopropenylbenzofuran (**3a**) adds another example to benzofuran derivatives isolated from plants of Compositae family.

EXPERIMENTAL*

Isolation. Dried roots (3·8 kg) of *Ligularia stenocephala* Matsum. et Koidz. were extracted 3 times with boiling benzene. The combined extracts were chromatographed on a column of alumina (Merck, Act.-I, 500 g). Elution with benzene gave fractions containing substance of $R_f = 0{\cdot}4$ (TLC; Merck, silica gel G, developed with benzene). Evaporation of the solvent followed by sublimation (at 60°, 1 mmHg) afforded a benzofuran deriv, white needles (560 mg), which was recrystallized from pet. ether to give the analytical sample of **3**, m.p. 72·5–73°, $[\alpha]_{578}$ ±0° (c = 1·7, $CHCl_3$). (Found: C, 71·51; H, 6·63. Calc for $C_{13}H_{14}O_3$: C, 71·54; H, 6·47%.) UV, IR, NMR and mass spectral data are registered in the text.

Tetrahydro derivative (**4**). Benzofuran deriv **3** (8·4 mg) in EtOH (2 ml) was shaken at 30° with 5% Pd–C (15 mg) in H_2 to absorb two moles of H_2 within 1 hr. Filtration of catalyst and evaporation of solvent gave **4** (8·4 mg), colourless liquid, M^+ 222 ($C_{13}H_{18}O_3$ requires: 222). UV, IR and NMR spectral data are recorded in the text.

Condensation of **3** *with maleic anhydride.* A soln of **3** (33 mg) and maleic anhydride (21 mg) in warm benzene (2 ml) was heated under reflux for 14 hr and the adduct, which separated from the cooled mixture, was collected and crystallized 3 times from EtOH, forming colorless needles of **5** (6 mg), m.p. ~180° (dec), M^+ 316 ($C_{17}H_{16}O_6$ requires: 316), IR (Nujol): 1841, 1779 and 1619 cm^{-1}.

2-Acetyl-5,6-dimethoxybenzofuran (**7**). A soln of **6**[6] (2 g) in abs EtOH (6 ml) was treated with a hot soln of KOH (0·7 g) in MeOH (4 ml). The mixture was warmed to prevent crystallization. To this mixture chloroacetone (1·1 g) was added dropwise. The stirring was continued for 1 hr and an equal volume of water was added. Then, the alcohols were evaporated *in vacuo*. Extraction of the residue with CH_2Cl_2 and usual treatment gave an oily product, which was purified by column chromatography over silica gel (Davison. 100 g). The third component eluted with a mixture of benzene and ether (1:1) was recrystallized from a mixture of pet. ether and acetone (2:1) to afford **7** (0·9 g), colorless needles, m.p. 118·5°. (Found: C, 65·58; H, 5·49. Calc. for $C_{12}H_{12}O_4$: C, 65·44; H, 5·49%.) UV and IR spectral data are reported in the text.

5,6-Dimethoxy-2-isopropenylbenzofuran (**3a**). To a mixture of finely cut Li (130 mg) in anhyd ether (30 ml) was added with stirring under N_2 a soln of bromobenzene (1 g) in anhyd ether (10 ml) during 20 min. The mixture was stirred for an additional 20 min, when most of the Li had disappeared. At this point, triphenylmethylphosphonium bromide (2·5 g) was added and the mixture was stirred for 3 hr, then treated with the above **7** (116 mg) in one portion. The ether was distilled from the mixture, being simultaneously replaced by anhyd THF (40 ml). The soln was heated under reflux for 1·5 hr and then evaporated to dryness under reduced press. The tarry residue was extracted with ether and the extracts were washed with water, dried and evaporated, yielding a red tar, which was purified by preparative TLC (Merck, silica gel G). A component with $R_f = 0{\cdot}4$ (benzene) was extracted and crystallized from pet. ether to give light yellow needles, which on sublimation (60°, 1 mmHg) gave **3a** as white needles (20 mg), m.p. 72°. (Found: C, 71·77; H, 6·74. Calc. for $C_{13}H_{14}O_3$: C, 71·54; H, 6·47%.) The identity of this compound with **3** was confirmed by m.p., mixed m.p., IR, UV, VPC and TLC.

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