

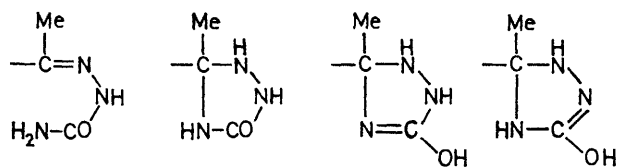
## Isomerism of Semicarbazones of 6-Hydroxy-4,7-dimethoxy- and 6-Hydroxy-4-methoxy-benzofuran-5-yl Methyl Ketone and Derivatives

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6-Hydroxy-4,7-dimethoxy- and 6-hydroxy-4-methoxy-benzofuran-5-yl methyl ketone (khellinone and visnaginone) semicarbazones can be obtained in either of two isomeric forms, depending of their mode of preparation. No *syn-anti*-isomerism could be detected, but the isomers obtained under acidic conditions were shown to be cyclic tautomers of the normal semicarbazones. This followed from n.m.r. experiments and from the results of van Slyke nitrogen determinations.

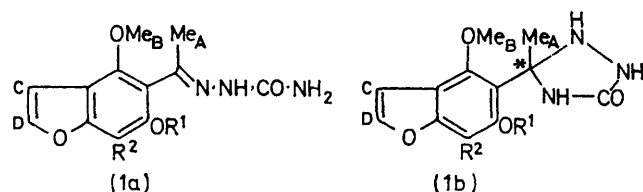
6-HYDROXY-4,7-DIMETHOXY- and 6-HYDROXY-4-METHOXYBENZOFURAN-5-YL METHYL KETONE (khellinone and visnaginone) derivatives can form two isomeric semicarbazones, depending whether these are prepared in buffered (sodium acetate) or acid ethanolic solution.



Some possible tautomeric forms of semicarbazones

Isomerism amongst semicarbazones has been discussed previously,<sup>1-5</sup> and it has been concluded from electronic spectral behaviour<sup>3</sup> that it is due to the presence of

has now been shown not to be due to the presence of *syn-* and *anti-*forms, but rather to the presence of cyclic tautomers.



The n.m.r. spectra of the isomeric semicarbazones formed from 6-*O*-isopropyl khellinone are shown in Figures 1 and 2. Data for other isomeric pairs are collected in the Table. Apart from small differences in the chemical shifts of similarly disposed protons, the spectra differ in that some resonances for those com-

M.p. and n.m.r. data for semicarbazones of khellinone and visnaginone derivatives

Compound <sup>a</sup>	M.p. (°C)	Solvent	Chemical shifts <sup>b</sup> ( <i>J</i> in Hz)							
			Me <sub>A</sub>	Me <sub>B</sub>	R <sup>2</sup>	H <sub>C</sub>	H <sub>D</sub>	R <sup>1</sup>	NH and/or NH <sub>2</sub>	
(1a; R <sup>1</sup> = Et, R <sup>2</sup> = OMe) <sup>c</sup>	168—171	(CD <sub>3</sub> ) <sub>2</sub> CO	2.21	3.94 and 4.04		7.04 (d, <i>J</i> 2.2)	7.80 (d, <i>J</i> 2.2)	1.29 (t, <i>J</i> 6.5)	4.08 (q, <i>J</i> 6.5)	6.16 (2H) and 9.16 (1H)
(1b; R <sup>2</sup> = Et, R <sup>2</sup> = OMe) <sup>d</sup>	187—190	CDCl <sub>3</sub>	2.23	3.96 and 4.06		6.88 (d, <i>J</i> 2.5)	7.32 (d, <i>J</i> 2.5)	1.32	4.04	5.60 (2H) and 7.30 (1H)
(1a; R <sup>1</sup> = Pr <sup>1</sup> , R <sup>2</sup> = OMe) <sup>e, e, f</sup>	190—192	CDCl <sub>3</sub>	2.16	3.91 and 4.06		6.83 (d, <i>J</i> 2.3)	7.55 (d, <i>J</i> 2.3)	1.23 (d, <i>J</i> 6.0)	4.47 (sept, <i>J</i> 6.0)	5.78 (2H) and 8.62 (1H)
(1b; R <sup>1</sup> = Pr <sup>1</sup> , R <sup>2</sup> = OMe) <sup>d, e, g</sup>	190—192	CDCl <sub>3</sub>	2.26	3.99 and 4.08		6.85	7.56 (d, <i>J</i> 2.5)	1.26 (two d) <sup>h</sup>	4.47 (sept, <i>J</i> 6.0)	5.60 (2H) and 7.38 (1H)
(1a; R <sup>1</sup> = Pr <sup>1</sup> , R <sup>2</sup> = H) <sup>c</sup>	193—194	CDCl <sub>3</sub>	2.12	3.97	6.76	6.79 (d, <i>J</i> 2.5)	7.43 (d, <i>J</i> 2.5)	1.32 (d, <i>J</i> 6.0)	4.48 (sept, <i>J</i> 6.0)	5.60 (2H) and 8.21 (1H)
(1b; R <sup>1</sup> = Pr <sup>1</sup> , R <sup>2</sup> = H) <sup>d</sup>	206—208	CDCl <sub>3</sub>	2.17	4.03	6.72 (d, <i>J</i> 1.0) <sup>i</sup>	6.82 (dd, <i>J</i> 2.5 and 1.0) <sup>i</sup>	7.44 (dd) <sup>i</sup>	1.31 (two d) <sup>h</sup>	4.49	5.35 (2H)

<sup>a</sup> Compound (1a; R<sup>1</sup> = Me, R<sup>2</sup> = OMe)<sup>e</sup> had m.p. 174—177°; compound (1b; R<sup>1</sup> = Me, R<sup>2</sup> = OMe)<sup>d</sup> had m.p. 188—189°.

<sup>b</sup> At 100 MHz, in p.p.m. from internal Me<sub>4</sub>Si. <sup>c</sup> Prepared with sodium acetate in ethanol and semicarbazide hydrochloride.

<sup>d</sup> Prepared with hydrogen chloride in ethanol and semicarbazide hydrochloride. <sup>e</sup> Mixed m.p. for (1a) and (1b) 170—175°; Found for (1a): C, 57.1; H, 6.0; N, 12.3. Found for (1b): C, 57.6; H, 6.1; N, 12.3. Calc. for C<sub>16</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>: C, 57.3; H, 6.25; N, 12.5%.

<sup>f</sup> Figure 2. <sup>g</sup> Figure 1. <sup>h</sup> Extra splitting due to diastereotopism; see text. <sup>i</sup> Mutual long-range coupling between R<sup>2</sup> and H<sub>C</sub> clearly present (double resonance).

*syn-* and *anti-*forms. Interconversion of isomers is relatively easy, and can be achieved smoothly by heat or by acids. However, in the case of several khellinone and visnaginone semicarbazone derivatives isomerism

<sup>1</sup> I. M. Heilbron and F. J. Wilson, *J. Chem. Soc.*, 1912, 101, 1482.

<sup>2</sup> F. J. Wilson and R. M. Macaulay, *J. Chem. Soc.*, 1924, 125, 841.

<sup>3</sup> M. Ramart-Lucas and M. Bruzau, *Bull. Soc. chim. France*, 1934, 1, 119.

pounds prepared in acidic media are duplicated; this is associated with the anisochromism<sup>6</sup> for potentially diastereotopic centres. In the ethyl derivative (1; R<sup>1</sup> = Et, R<sup>2</sup> = OMe) only a substantial broadening was observed, the doubling of the methylene quartet

<sup>4</sup> G. J. Karabatsos, J. D. Graham, and F. M. Vane, *J. Amer. Chem. Soc.*, 1962, 84, 753.

<sup>5</sup> V. I. Stenberg, P. A. Barks, D. Bays, D. D. Hammargren, and D. V. Rao, *J. Org. Chem.*, 1968, 33, 4402.

<sup>6</sup> K. Mislow and W. Raban, *Topics Stereochem.*, 1967, 1, 1.

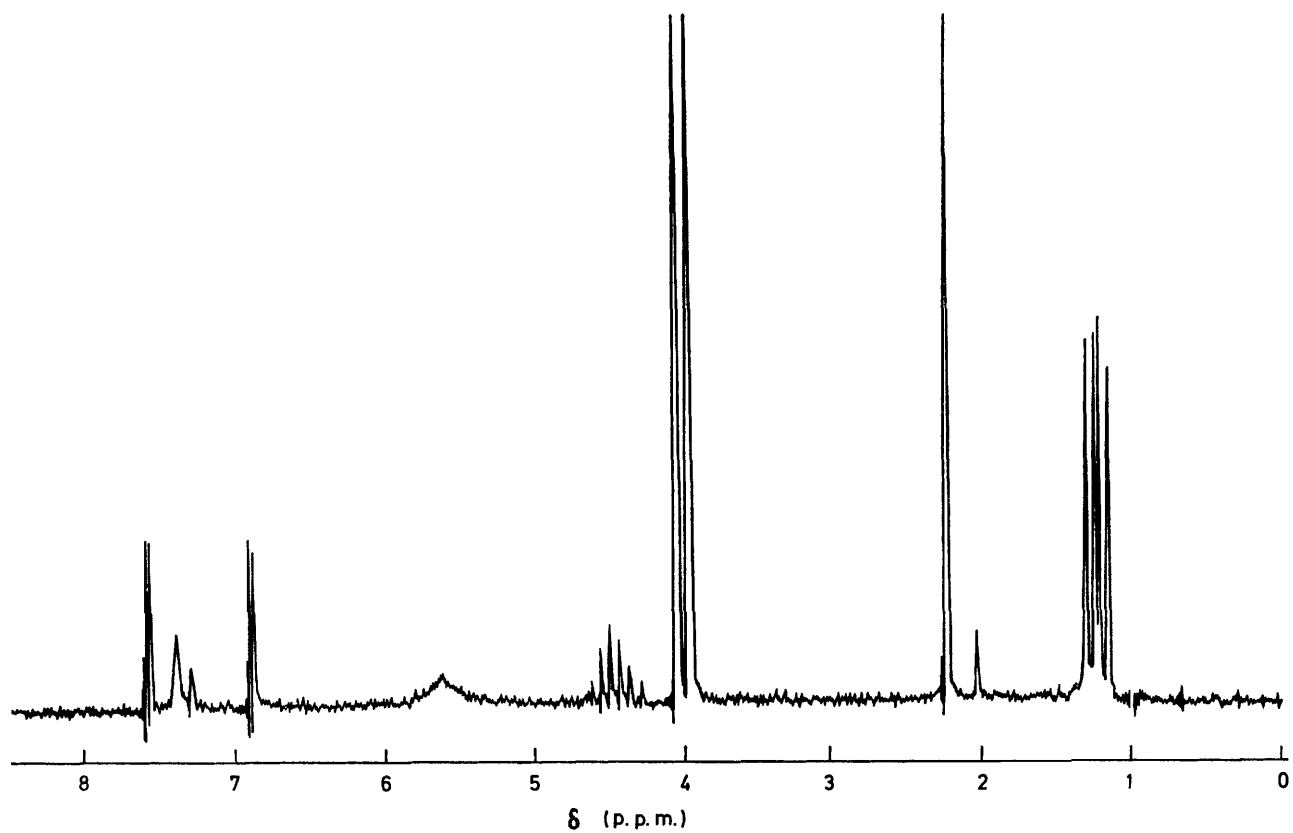


FIGURE 1 N.m.r. spectrum (100 MHz) of 6-O-isopropylkhellinone semicarbazone (1b;  $R^1 = Pr^1$ ,  $R^2 = OMe$ ) in  $CDCl_3$

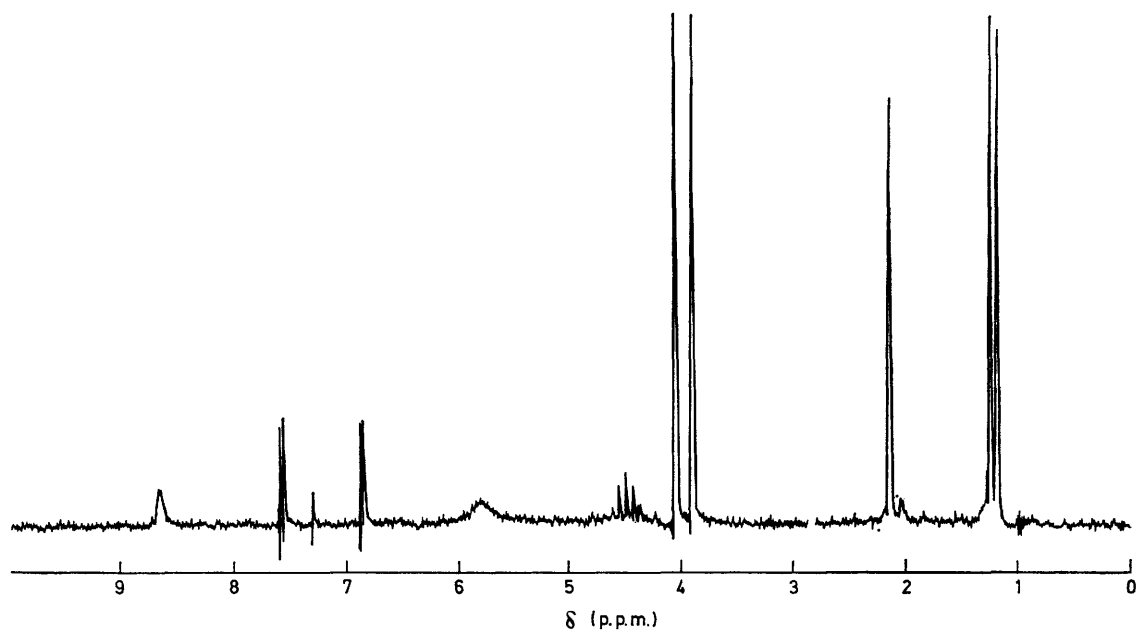


FIGURE 2 N.m.r. spectrum of 6-O-isopropylkhellinone semicarbazone (1a;  $R^1 = Pr^1$ ,  $R^2 = OMe$ ) in  $CDCl_3$

being unresolved even at 100 MHz. The fact that two doublets are found in the spectrum one of the isomers of the isopropylkhellinone derivative (1;  $R^1 = Pr^i$ ,  $R^2 = OMe$ ) (Figure 1) could perhaps be explained in terms of slow inversion of one of the nitrogen atoms in only one of the two *syn-anti*-isomers. Slow nitrogen inversion (with  $\Delta G^\ddagger$  ca. 20 kcal mol<sup>-1</sup>) has, however, only been observed<sup>7</sup> in nitrogen derivatives which either are angle-strained or have *N*-substituents bearing lone-pairs (*e.g.* Cl, Br, *etc.*). Normally the barrier for *N*-inversion is only 7–8 kcal mol<sup>-1</sup> in trivalent nitrogen derivatives. Moreover, in our case, the observed diastereotopism is retained even at temperatures as high as 150°.

Further arguments against possible *syn-anti*-isomerism are (a) the close relationship between the electronic spectra of both isomers, and (b) the slow interconversion between both isomers in trifluoroacetic acid (n.m.r.). An equilibrium mixture containing ca. 35% of the isomer (1b) is only reached after 150 h at 25°.

The observed isomerism can best be explained in terms of tautomeric ring closure [structures (1a and b)], as suggested<sup>8</sup> to us by Dr. R. S. Egan, the closed structure resulting in diastereotopism in the -OR<sup>1</sup> systems. The existence of ring-closed isomers has been suggested recently for several hydrazones of simple aliphatic aldehydes<sup>9</sup> and for thiocarbazone derivatives of simple<sup>10</sup> aromatic and aliphatic aldehydes and ketones, mainly

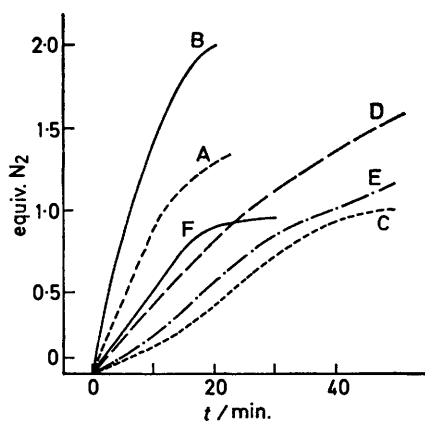


FIGURE 3 Relative rates of nitrogen liberation as followed by g.l.c. for khellinone semicarbazone isomers and some related compounds: (A) (1b;  $R^1 = Pr^i$ ,  $R^2 = OMe$ ), normal procedure at 25°; (B) (1a;  $R^1 = Pr^i$ ,  $R^2 = OMe$ ), normal procedure at 25°; (C) isomer (1b), modified procedure at 0°; (D) isomer (1a), modified procedure at 0°; (E) acetophenone semicarbazone, modified procedure at 0°; (F) L-glutamic acid (calibration curve), normal procedure at 25°

on the basis<sup>10</sup> of n.m.r. spectral shift and coupling data, and further work<sup>11</sup> has substantiated these claims. In order to obtain further information on

the nature of the isomerism in the khellinone semicarbazones, heteronuclear decoupling experiments were conducted, but the results were inconclusive.

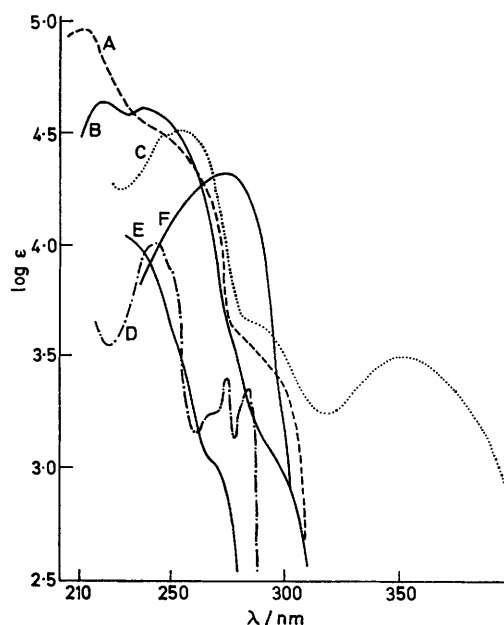


FIGURE 4 U.v. spectra of 6-*O*-isopropylkhellinone semicarbazones and related compounds: (A) (1a;  $R^1 = Pr^i$ ,  $R^2 = OMe$ ) in 100% methanol; (B) (1b;  $R^1 = Pr^i$ ,  $R^2 = OMe$ ) in 100% methanol; (C) khellinol (4-hydroxy-9-methoxy-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one) in 99.3% ethanol (ref. 13); (D) benzofuran in 95% ethanol (G. M. Badger and B. J. Christie, *J. Chem. Soc.*, 1956, 3438; R. A. Friedel, *Appl. Spectroscopy*, 1957, 11, 13); (E) mean absorption curve of the 'forme transparente' of an aromatic semicarbazone; (F) mean absorption curve of the 'forme absorbante' of an aromatic semicarbazone [(E) and (F) from ref. 3]

We have also examined the rates of liberation of nitrogen from the two isomers on treatment with nitrous acid,<sup>12</sup> in order to obtain further information on their structure. As might be expected for a ring-closed structure, isomer (1b;  $R^1 = Pr^i$ ,  $R^2 = OMe$ ) liberated nitrogen more slowly than the corresponding open-chain isomer (1a) (Figure 3).

One further aspect of the n.m.r. spectra requires comment. In the ring-closed isomer (1b) the methyl group is attached to a carbon centre which itself is attached to two nitrogen atoms. This would be expected to result in an upfield shift in comparison with isomer (1a). However this is not the case (Table). Conformational evidence obtained from electronic spectra reveals a possible explanation.

Figure 4 shows the relevant spectra together with those of some other closely related structures. *syn*- and *anti*-Forms of semicarbazones are characterised

<sup>8</sup> R. S. Egan, Chemical Physics Section, N.m.r. Laboratory, Abbott Laboratories, North Chicago, Illinois 60064, U.S.A., personal communication.

<sup>9</sup> W. Skorianetz and E. Sz. Kováts, *Tetrahedron Letters*, 1966, 5067.

<sup>10</sup> R. W. Lamon, *J. Org. Chem.*, 1969, 34, 756.

<sup>11</sup> W. R. Roderick and A. M. Von Esch, unpublished work.

<sup>12</sup> E. R. Hoffman and I. Lysyj, *Microchem. J.*, 1962, 45.

<sup>7</sup> Cf. S. J. Brois, *J. Amer. Chem. Soc.*, 1968, 90, 508; *Tetrahedron Letters*, 1968, 5997; D. Felix and A. Eschenmoser, *Angew. Chem.*, 1968, 80, 197; F. Montanari, I. Moretti, and G. Torre, *Chem. Comm.*, 1968, 1694; for benzophenone imines see J. B. Lambert, W. L. Oliver, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1965, 87, 5085; D. Y. Curtin and J. W. Hauser, *ibid.*, 1961, 83, 3474.

by typical differences in their possibilities for conjugation, resulting in a 'forme absorbante' and a 'forme transparente'.<sup>3</sup> In our case both isomers (1a and b) show nearly identical chromophoric behaviour, with no appreciable absorption above 300 nm. The spectrum<sup>13</sup> of khellinol (4-hydroxy-9-methoxy-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one) indicates that such absorption would have been expected if the semicarbazone system had been in conjugation with the benzofuran nucleus in one of the isomers. In fact the electronic spectra of our semicarbazones are similar to that of benzofuran itself. Thus even the non-cyclised isomer (1a) is not appreciably conjugated, indicating that an out-of-plane rotation of the semicarbazone system, as the result of di-*ortho*-substitution, is likely. In the light of this, prediction of the shift for the methyl group requires one to take into account possible diamagnetic contributions by the aromatic nucleus, which are not necessarily identical in both isomers.

#### EXPERIMENTAL

Details of preparation together with further spectral features will be published elsewhere. The Table gives the m.p.s observed for the several acyclic and cyclic semi-

carbazone tautomers. U.v. spectra were obtained with a Cary model 15 automatic spectrophotometer. N.m.r. spectra were taken with Varian HR-100 and A-60 instruments.

Nitrogen liberated by the van Slyke nitrous acid method was estimated as described<sup>12</sup> by Hoffman and Lysyj. Calibration was performed with L-glutamic acid. At room temperature, the normal procedure<sup>12</sup> applied to the open-chain isomer (1a) yielded slightly more than 2 equiv. of nitrogen in 20 min. However, the ring-closed isomer was much less soluble in the reaction mixture, so the procedure was changed in subsequent evaluations. Clear solutions were obtained in glacial acetic acid, in which interconversion between the khellinone derivatives is negligible (n.m.r.) under the conditions used. In the final procedure a saturated aqueous solution of nitrous acid was injected into a solution of the product in acetic acid, and the reaction was slowed down by working at 0 °C. The results were essentially the same.

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<sup>13</sup> W. Bencze, J. Eisenbeiss, and H. Schmid, *J. Chem. Soc.*, 1956, 923.