Investigation by means of Nuclear Magnetic Resonance Spectroscopy of Geometric Isomerism in some α-Benzamidocinnamates and their Related Azlactones

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Summary Determination of the magnitude of the benzamido-substituent effect on the signal of a *cis*-olefinic proton in the n.m.r. spectrum, leads to the assignment of the *trans*-configuration to the stable geometric isomers of the title compounds.

THE stable isomer of 4-benzylidene-2-phenyl-2-oxazolin-5-one obtained in the Erlemeyer-Plöchl synthesis has been variously claimed to be the *cis*- [1] or the *trans*- [2] isomer. Some n.m.r. spectroscopic results support the *cis*-configuration,[2] whilst the n.m.r. spectra both of the two isomers of ethyl α-benzamido-3,4-dimethoxycinnamate (IIa) and (IIb) and of other model compounds lead us to believe that the *trans*-assignment is correct.

The stable azlactone [(Ia) (m.p. 149·5—151°)][3] was converted with concentrated hydrobromic acid into the metastable geometric isomer [(Ib) (m.p. 147·5—148·5°)]. Hydrolysis of (Ia), followed by esterification, yielded [(IIa) (m.p. 118—119·5°)][3] and basic alcoholysis of (Ib) yielded (IIb) (m.p. 141—142°). In this conversion of azlactones into cinnamates no change occurs in the geometric configuration.[1,2] The n.m.r. spectral data are listed in the Table.

The [β-^{2}H]azlactones and esters were synthesized from 3,4-dimethoxy[α-^{2}H]benzaldehyde† in order to determine the exact value of the chemical shift of H_β. To determine the structures of (IIa) and (IIb) by n.m.r. spectroscopy it is necessary to know the magnitude of the substituent effect

† Prepared by reduction with $LiAlD_4$ (T. Axenrod, L. Loew, and P. S. Pregosin, *J. Org. Chem.*, 1968, **33**, 1274) of *N*-t-butyl-3,4-dimethoxybenzamide (m.p. 126—128°), followed by hydrolysis.

of the α-benzamido-group on the signal of H_β[2,5] (in *ortho*-substituted *N*-acylanilines there is a sharply increased deshielding of the proton *ortho* to the acylamine group[6]). In order to establish a reliable value for this effect, the n.m.r. spectra of the compounds (IV)‡ and (VI)§ were determined.

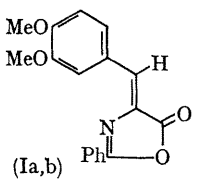
on the H_β signal as a result of the introduction of the α-benzamido-substituent, is included in the value of Δ.

Choice of (A) defines the position of the β-proton signals in the n.m.r. spectrum of (IV). The chemical shifts of H_β in (IIa) and (IIb) could be calculated by adding the chemical shifts of H_A (δ 6·01) and H_B (δ 6·80) to the value of the

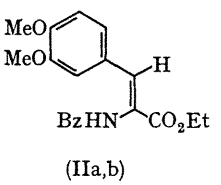
TABLE[a]

Compound	H_β	H(2)[b]	H(5)	H(6)		–NH	$-OCH_3$
(Ia)	7·15	8·14	6·93	7·56	[c]	—	3·94; 4·00
(Ib)	7·48	8·36	6·90	7·52	[c]	—	3·93; 3·99
(IIa)	7·44	7·11	6·79	7·10	[c]	7·7–8·1	3·64; 3·82
(IIb)	8·00	*ca.* 6·90	*ca.* 6·90	*ca.* 6·90	[d]	8·37	3·85; 3·88
(III)	5·82(H_B); 6·38(H_A)	—	—	—	[e]	—	—
(IV)	6·01; 6·80	—	—	—	[f]	—	—
(VI)	8·83(4-position)	—	—	—	—	8·7–9·0	—

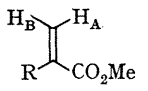
[a] The spectra were measured with a Varian A-60A ($CDCl_3$, *ca.* 38°). The chemical shifts are expressed in δ values (p.p.m.) relative to internal Me_4Si; [b] aromatic protons of the 3,4-$(MeO)_2C_6H_3$-ring; the protons of the Ph-ring appear in the range δ 7·7–8·3 (2 H) and δ 7·3—7·7 (3 H); [c] $J_{2,6}$ = 2 c./sec., $J_{5,6}$ = 8—9, and $J_{2,5}$ = 0 c./sec.; [d] 6·90 is the centre of a multiplet δ 6·85—6·95, corresponding to 3 H. [e] Varian spectra catalogue, spectrum No. 64. [f] Coupling of the δ 6·01-proton, probably with –NH (*J* = 1—2 c./sec.).



(Ia,b)

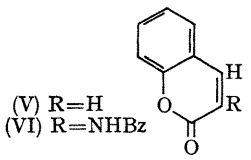


(IIa,b)



(III) R=H
(IV) R=NHBz

one geometric isomer only is shown



(V) R=H
(VI) R=NHBz

A comparison of the n.m.r. spectra of (III) and (IV) (Table) showed that there are two ways of estimating the benzamido-substituent effect in the *cis*- (Δ_{cis}) and in the *trans*-position (Δ_{trans}) with respect to H_β: (A) chem. shift H_A = δ 6·01 and H_B = δ 6·80, *i.e.* Δ_{cis} = + 0·98 and Δ_{trans} = − 0·37; (B) chem. shift H_A = δ 6·80 and H_B = δ 6·01, *i.e.* Δ_{cis} = + 0·19 and Δ_{trans} = + 0·42.

The n.m.r. spectrum of the 3-benzamidocoumarin (VII), when compared with that of the coumarin (V) is a test of these two possibilities. The 4-proton in coumarin resonates at δ 7·80[7]. Introduction of a 3-benzamido-group shifts this signal to δ 8·83, therefore Δ_{cis} = + 1·03; this value agrees well with the substituent effect calculated by method (A).

The change of the substituent effect of the $-CO_2R$-group

substituent effect of the β-dimethoxyphenyl group on H_β. By using Pascual's[5] substituent effect (+1·35) of an aryl-group on an olefinic proton in the α-position, values of δ 7·36 and δ 8·15 are obtained. From the good agreement with the values found (δ 7·44 and δ 8.00) it may be concluded that what has been established for compound (IV), is also true for (IIa) and (IIb): the proton at the lowest field is *cis* to the benzamido-group and the proton at higher field occupies the *trans*-position. It follows that in the stable ester (IIa) the dimethoxyphenyl-group is *trans* to the $-CO_2Et$ group; one of the methoxy-groups (δ 3·64) lies in the shielding region of the phenyl nucleus of the benzamido-group. In (IIb) the aryl-group is *cis* to $-CO_2Et$.

When the values of Δ_{cis} and Δ_{trans} [assumption (A)] are used to calculate, on the basis of the chemical shift of H_β in the *cis*- and *trans* methylcinnamates,[2] the shift of H_β in the corresponding α-benzamido-derivatives, good agreement with the n.m.r. data[2] is obtained; the *cis–trans* assignment should, however, be inverted.

Thus, we conclude that in the azlactone (Ia) the dimethoxyphenyl nucleus is *trans* to the oxazolone carbonyl. In addition to a strong deshielding effect of the oxazolone ring on H(2) and H(6), the n.m.r. spectra of the azlactones show that, under the deshielding influence of *cis* –N=C.Ph–, the H_β signal shifts more downfield than when it is *cis* to the >C=O.

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‡ Synthesis: α-benzamidoacrylic acid (T. Wieland, G. Ohnacker, and W. Ziegler, *Chem. Ber.*, 1957, **90**, 194) was converted into the silver salt, which gave with CH_3I in ether the methyl ester.

§ M.p. 176°; obtained as a by-product in the reaction of salicylaldehyde with hippuric acid (E. Erlenmeyer, jun., and W. Stadlin, *Annalen*, 1904, **337**, 283).

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