STRUCTURE–ACTIVITY RELATIONSHIPS IN FLAVONOIDS.

4. VINYLOGOUS CHALCONES AND METADICHALCONES

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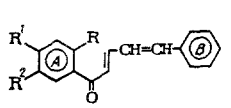
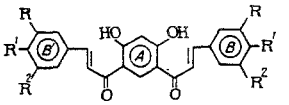
Examination of structure-activity relationships in chalcones has shown that the biological activity of these compounds is attributable to the interaction between structural fragments A and B via the propenone grouping. By influencing each other by the transfer of electronic effects via the conjugated system, each fragment makes its contribution to biological activity. The most important feature of all those determining the structural and biological properties of chalcones is therefore the propenone fragment.

We have shown experimentally that the structure of fragment A determines the type of biological activity, while fragment B, depending on the type and position of the substituents, either enhances or decreases this activity [4-7].

The observed structure-activity relationships in chalcones do not, however, provide any unambiguous information on the effects on biological activity of lengthening the conjugated chain. For this reason, we deemed it necessary to synthesize some compounds which are vinylogues of chalcone (Ia-h) and metadichalcones (IIa-f).



Ia-h



Ia-f

R = H (Ia, c, e, f, IIb, e), OH (Ib, d, g, h), OCH_3 (IIc, d), Br (IIf), COOH (IIa);

R^1 = H (Ia, b, d, f), OH (Ig, h, IIa, d), OCH_3 (Ie, IIb, c), Br (Ic), $N(CH_3)_2$ (IIe), OH (IIf);

R^2 = H (Ia, b, e, IIa-e), OCH_3 (If), Cl (Id), Br (Ic, g, IIf), Ae (Ih)

Cinnamylideneacetophenone (Ia) is the parent member of compounds known as chalcone vinylogs [9]. We obtained these compounds by alkaline condensation of cinnamaldehyde with acetophenones. The following acetophenones were employed: o-hydroxyacetophenone, p-bromoacetophenone, 2-hydroxy-5-chloroacetophenone, bromoresacetophenone, and resodiacetophenone. Table 1 gives the characteristics of the chalcone vinylogs obtained.

Antibacterial activity was determined by serial dilution in a solid nutrient medium, enabling the activity of the compounds to be measured against staphylococci and spore-forming bacteria. The unsubstituted cinnamylideneacetophenone (Ia) (the parent structure) failed to show activity against these cultures in concentrations of 10-400 μg/ml. Introduction of a hydroxyl group into the 2-position of fragment A (Ib) slightly increased the activity against spore-forming bacteria (70-80 μg/ml).

Attempts to obtain a compound containing two hydroxyl groups in positions 2 and 4 of fragment A were unsuccessful as a result of the rapid resinification of the reaction product both with basic and acidic catalysts.

The use of m-bromoacetophenone as starting material afforded 1-phenyl-5-(4-bromophenyl)-1,3-pentadien-5-one (Ic), which showed slight antistaphylococcal activity in concentrations of 240 μg/ml or more. If a hydroxyl group is present in the 2-position in fragment A, introduction of chlorine into the 5-position of the same fragment (Id) considerably enhances the antibacterial spectrum of activity, concentrations of 30 μg/ml or more suppressing the growth of spore cultures, this concentration in the case of staphylococci being 200 μg/ml.

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TABLE 1. Characteristics of Vinylogs of Chalcones and Metadichalcones

Compound	mp, °C	UV spectrum, nm		IR spectrum, cm^{-1}	
		band I	band II	C=C	C=O
Ia	102	347	260	1590	1650
Ib	148	366	259	1595	1640
Ic	136	352	267	1590	1660
Id	149	369	265	1600	1635
Ie	91	350	294	1605	1645
If	122	350	238	1605	1650
Ig	171	330	280	1610	1630
Ih	196	323	254	1585	1660
IIa	173	325*	250	1590	1640
IIb	180	328*	258	1600	1650
IIc	175	328*	250	1595	1655
IId	182	325*	255	1605	1645
IIe	180	325*	255	1595	1650
IIf	186	325	255	1590	1640

*Inflection

TABLE 2. Comparative Antistaphylococcal Activity of Chalcones $RR^1R^2C_6H_2$-$COCH{=}CHC_6H_5$ (IVa-d) and (IVg-h), and Their Vinylogs (Ia-d) and (Ig-h)

Compound	C, μg/ml	LD_{50}, mg/kg	Compound	C, μg/ml	LD_{50}, mg/kg
IVa	400	—	Ia	400	—
IVb	320	610	Ib	200	640
IVc	320	450	Ic	240	490
IVd	320	450	Id	200	500
IVg	40	180	Ig	20—30	250
IVh	320	650	Ih	300	750

Note. The values of R, R^1, and R^2 are the same as in their vinylogs (Ia-d) and (Ig-h).

Methylation of the hydroxyl group results in total loss of antibacterial activity (Ie, f). The greatest antistaphylococcal activity was seen with (Ig), 1-phenyl-5-(2,4-dihydroxy-5-bromphenyl-1,3-pentadiene-5-one. Fragment A in this compound has the bromoresorcinol structure. The high selectivity against staphylococci, which is apparent at concentrations of 20-30 μg/ml, is coupled with relatively low toxicity, the LD_{50} being 250 mg/kg.

Comparison of the biological activity of the vinylogs with that of the corresponding chalcones (IVa-d), (IVg-h), in which fragment A has the same structure, shows that increasing the length of the conjugated chain enhances the antibacterial activity (Table 2).

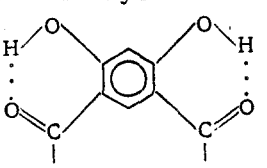
Metadichalcone [2, 8] and its derivatives (II) were obtained by condensing one mole of resodiacetophenone with two moles of the appropriate aldehyde in an alkaline medium. The characteristics of these compounds are shown in Table 1.

The UV spectra of the metadichalcones show characteristic absorption bands (I-II) at 220-400 nm, the short-wavelength band having the greater intensity and corresponding to $\pi \rightarrow \pi^*$ transitions. The latter considerably overlaps the $n \rightarrow \pi$ transition band, the absorption of which is therefore very weak.

According to [3], the intensity of the short-wavelength band is attributable to the $\Psi_0 \rightarrow \Psi_1$ transition, which is localized predominantly in the phenylpropenone fragments C_6H_5—CH=CH—CO—, and is regarded as an intramolecular charge-transfer band from the styryl fragments to the carbonyl groups.

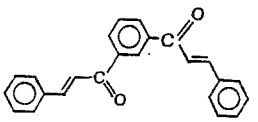
Dichalcones may be regarded as systems containing two chalcone chromophores (phenylpropenone fragments) bonded to a central aromatic ring in the meta-positions. Comparison of the metadichalcones with the corresponding chalcones, in which the structure of the aldehyde moiety is the same, shows that the short-wavelength maximum in metadichalcones undergoes a hypsochromic shift of 10 nm. The long-wavelength band in metadichalcones has a weak maximum, more like an inflection. In the corresponding chalcones the long-wavelength band on the other hand has a pronounced maximum. These observations may well be due to interaction of the two carbonyl groups [1].

The hydroxyl groups ortho- to the carbonyl groups influence each other by transmission of electronic effects along the conjugated chain, resulting in an increase in their acidity and a decrease in the electrophilicity of the carbonyl carbon. Simultaneously, six-membered chelate rings are formed on either side of the central aromatic ring by hydrogen bonding between the ortho-hydroxyl groups and the carbonyls:



fragment of the metadichalcone molecule

If no hydroxyl groups are present, chelate rings cannot be formed, with the result that the vinylene and carbonyl groups in metadichalcones are the S-cis-conformers, as reported in [3].



The interaction of the ortho-hydroxyl groups and the carbonyl groups to form chelate rings results in a change in the conformation of the left-hand propenone fragment. This assumption is in accordance with the results obtained for chalcones, in which fragment A is a resodiacetophenone residue.

We have shown [4] that chalcones obtained from bromoresacetophenone have the cis-configuration and the S-cis-conformation, and have high antimicrobial activity. Replacement of the bromine in the 5'-position of fragment A by the acetyl group gives structure (III), resulting in changes in both the configuration and the conformation. Chalcones derived from resodiacetophenone therefore have the trans-S-trans molecular structure. This feature apparently prevents penetration of the compound through the cell membrane of the microorganism, so that the antimicrobial activity of 2,4-dihydroxy-5-acetylchalcones is much lower than that of 2,4-dihydroxy-5-bromochalcones.

With respect to the number of rotational isomers, the metadichalcones should possess four (two for each propenone fragment). We have shown that 2,4-dihydroxy-5-acetylchalcones have the S-trans-conformation. Using these as model structures, as in similar instances [3], it may be assumed that in metadichalcones at least one of the propenone fragments has the trans-S-trans structure. Irrespective of the configuration and conformation of the second propenone fragment, the whole metadichalcone molecule will possess, as a result of the structural features enumerated above, even less ability to penetrate the cell membranes. This is clearly the reason for the observed extremely low antimicrobial activity of the metadichalcones (1000 μg/ml or more).

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