

2',5'-Diazachalcones. I.

Preparation, structure, and antibacterial effects of some substituted 2',5'-diazachalcones

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Ten hitherto unknown 2',5'-diazachalcones variously substituted at the isocyclic residue have been prepared by means of a modified Claisen—Schmidt condensation of methylpyrazinyl ketone with aromatic aldehydes. The structure of the substances was verified by i.r. and ¹H-n.m.r. spectral data. The substances show antibacterial effects towards *Staphylococcus aureus*, *Bacillus subtilis*, and *Escherichia coli*.

Видоизмененной конденсацией по Клейзену—Шмидту метилпиразинилкетона с некоторыми ароматическими альдегидами было приготовлено десять новых 2',5'-диазахалконов с разными заместителями на изоциклическом остатке. Их структура была подтверждена интерпретацией ИК и ¹H-ЯМР спектров. Приготовленные соединения оказались активными по отношению к *Staphylococcus aureus*, *Bacillus subtilis* и *Escherichia coli*.

The present paper describes a new group of chalcones that contain two nitrogen atoms in one heterocycle. Azachalcones known so far, on account of the presence of the conjugated —CH=CH—HC=O system, show various biological effects, e.g. antibacterial [1—5], cardiovascular [6, 7], cytostatic [8, 9], etc. The effect of substituents (—OH, —OCH₃, —OC₂H₅) on the aromatic ring of 2',5'-diazachalcones upon antibacterial effects has been studied.

The new substances have been synthesized by a modified, diethylamine-catalyzed Claisen—Schmidt condensation of methylpyrazinyl ketone with aromatic aldehydes. The modification was applied because the original procedure [10, 11] was unsuccessful.

Experimental

The prepared substances were crystallized from absolute ethanol. For yields, elemental analyses, and melting points see Table 1.

The i.r. spectra ($4000\text{--}400\text{ cm}^{-1}$) were recorded using a double-beam UR-20 spectrophotometer (Zeiss, Jena) and applying KBr (1.5—2.0 mg of the sample/800 mg KBr) or Nujol techniques. The instrument was calibrated against a polystyrene foil.

The $^1\text{H-n.m.r.}$ spectra were obtained at 80 Hz. The measurements were run on solutions in DMSO-d_6 (internal standard hexamethyldisiloxane) with a Tesla BS 487 B spectrometer. The recorded chemical shifts were then calculated for tetramethylsilane. For i.r. and $^1\text{H-n.m.r.}$ spectral data see Table 2.

The antibacterial effects were tested by the method of Vincent using 1% solutions of the substances in 1,2-dimethoxyethane and standard microbial strains: *Staphylococcus aureus* OXFORD, *Bacillus subtilis*, and *Escherichia coli*.

2,5'-Diazachalcones (I—X)

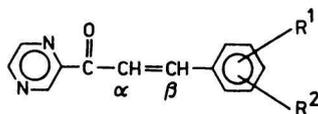
A mixture of methylpyrazinyl ketone (0.01 mol), the respective aldehyde (0.01 mol), and diethylamine (0.01 mol) in pyridine (4.4 ml) was boiled for 1 h. The mixture was cooled and poured onto ice, the pH being adjusted to 3—4 by the addition of a few drops of acetic acid. The mixture, from which a portion of the product precipitated immediately, was stored overnight in a refrigerator, the crystalline material was collected by filtration and recrystallized several times.

Results and discussion

Since the condensation of methylpyrazinyl ketone with aromatic aldehydes by means of the original Claisen—Schmidt procedure [10, 11] was unsuccessful the method was modified in that higher temperature (100°C) and longer reaction times were applied, and during the isolation of products the pH was adjusted to 3—4. This caused a favourable shift of the reaction equilibrium resulting in a substantial increase (by 40%) of the yields of the desired products. Also, diethylamine was used as the catalyst. The basicity of this amine is sufficient to assure smooth reaction without the formation of by-products. The obtained 2,5'-diazachalcones are crystalline, coloured from light-yellow to orange, water insoluble substances.

The structure of the prepared compounds was confirmed by i.r. and $^1\text{H-n.m.r.}$ spectra, the interpretation of which was based on published data observed for geometrically isomeric chalcones and azachalcones, mainly their hydroxy derivatives [12], while 2-hydroxychalcone was used as a reference substance. It follows from the literature [13] that a band at $990\text{--}960\text{ cm}^{-1}$ in the i.r. spectra is diagnostic of the presence of a *trans* azachalcone isomer. In the spectra of 2,5'-diazachalcones studied herein the characteristic band was shifted to $1003\text{--}972\text{ cm}^{-1}$ and was split in some cases. The band reflects off-plane deforma-

Table 1
Data for the prepared 2',5'-diazachalcones



Compound	R ¹	R ²	Formula	M	Calculated/found			Yield %	M.p. °C
					% C	% H	% N		
<i>I</i>			C ₁₃ H ₁₀ N ₂ O	210.22	74.26 74.46	4.79 5.00	13.32 13.56	82	106—107.5
<i>II</i>	2-OH	3-OH	C ₁₃ H ₁₀ N ₂ O ₃	242.23	64.52 64.64	4.17 3.88	11.58 11.25	48	214—220 (decomp.)
<i>III</i>	3-OC ₂ H ₅	2-OH	C ₁₄ H ₁₄ N ₂ O ₃	270.29	62.21 62.50	5.22 5.22	10.32 9.99	90	173—175
<i>IV</i>	3-OC ₂ H ₅	4-OH	C ₁₄ H ₁₄ N ₂ O ₃	270.29	62.21 62.36	5.22 5.10	10.32 9.94	49	189—191
<i>V</i>	2-OH	H	C ₁₃ H ₁₀ N ₂ O ₂	226.22	69.01 69.28	4.45 4.56	12.38 12.31	81	173—175
<i>VI</i>	3-OH	H	C ₁₃ H ₁₀ N ₂ O ₂	226.22	69.01 68.99	4.45 4.67	12.38 12.18	45	189—191
<i>VII</i>	4-OH	H	C ₁₃ H ₁₀ N ₂ O ₂	226.22	69.01 68.71	4.45 4.54	12.38 12.15	90	191—194
<i>VIII</i>	2-OH	3-OCH ₃	C ₁₄ H ₁₂ N ₂ O ₃	256.26	65.62 65.86	4.72 4.88	10.93 10.88	82	172—175
<i>IX</i>	3-OH	4-OCH ₃	C ₁₄ H ₁₂ N ₂ O ₃	256.26	65.62 65.67	4.72 5.00	10.93 10.70	33	212—214
<i>X</i>	4-OH	3-OCH ₃	C ₁₄ H ₁₂ N ₂ O ₃	256.26	65.62 65.90	4.72 4.84	10.93 10.90	81	183—185

Table 2

Spectral characteristics of the prepared 2',5'-diazachalcones

Compound	$^1\text{H-NMR } \delta, \text{ p.p.m.}$			IR $\bar{\nu}, \text{ cm}^{-1}$			
	—CH _A = CH _B —			—CH = CH—		$\nu(\text{C}=\text{O})$	
	α	β	$J_{AB}, \text{ Hz}$	$\gamma(\text{C—H})_{\text{trans}}$	$\nu(\text{C}=\text{C})$	<i>s-trans</i>	<i>s-cis</i>
I	8.08	7.85	16.0	a 983	1601	1655 sh	1673 (1698)
				b 985	1601	1652 sh	1672 (1697)
II	8.10	8.10	—	972	1593	—	1675
III	8.13	8.13	—	981	1593	1644 sh	1668
IV	7.87	7.80	16.3	1003	1587	1644 sh	1662
V	8.14	8.08	16.3	a 990	1601	1655 sh	1664
				b 991	1601	1654 sh	1664
VI	7.93	7.81	16.05	987	1606	—	1676
				997			
VII	7.88	7.79	16.1	a 987	1596	1655 sh	1674 (1668 sh)
				993			
VIII	8.11	8.11	—	b 987	1597	1654 sh	1673 (1665 sh)
				995			
IX	8.11	8.11	—	990	1592	1647 sh	1674
X	7.86	7.73	16.15	984	1598	1644 sh	1666
				a 978	1600	1655 sh	1667
988	d						
				b 979	1600	1654 sh	1666
				989			

d — doublet, sh — shoulder, a — in KBr, b — in Nujol.

tion vibrations of the hydrogen atoms of the vinylene group [14—16]. It follows that the prepared substances are *trans*-isomers.

From the point of view of conformation (*s-cis* and *s-trans* isomers) of chalcones and azachalcones diagnostically important region in their i.r. spectra is that at 1700—1600 cm^{-1} [17]. In the spectra of the substances under investigation two intense bands were present at 1676—1587 cm^{-1} . These were assigned to α,β -unsaturated ketone and characterized the vinylene and the keto group. The band at 1606—1587 cm^{-1} was that of C=C stretching vibrations and the one at 1676—1644 was assigned to C=O vibrations in the *s-cis* and *s-trans* forms of azachalcone (Table 2). The spectra obtained by both KBr and Nujol techniques showed that 2',5'-diazachalcones were the *s-cis* conformers; in some cases minor amounts of *s-trans* conformers were also detected, as a result of the presence of two nitrogen-containing heterocycle, instead of an isocycle, causing more pronounced energetical nonequivalency of the two possible conformers. The hydroxyl groups of the substances were associated, linked *via* intermolecular hydrogen bonds. The band at 1668 cm^{-1} present in the spectrum of 4-hydroxy-2',5'-diazachalcone showed a shoulder reflecting the C=O stretching vibration of the *s-cis* conformer, probably as a result of the formation of hydrogen bonds. The olefinic hydrogen atoms present in the molecules of azachalcones are reflected in the $^1\text{H-n.m.r.}$ spectra as a typical AB system of protons. The β -proton signal appears in the spectra of 2',5'-diazachalcones at a lower field than that of the α -proton (δH_β 8.13—7.73 and δH_α 8.14—7.86), due to the deshielding effect of the carbonyl group. The observed value of the coupling constants (16.3—15.9 Hz) corresponds to the *trans* arrangements of the olefinic hydrogens [17]. Thus $^1\text{H-n.m.r.}$ spectra confirmed the interpretation of the i.r. spectra of the prepared substances.

All compounds studied showed effects against *Staphylococcus aureus* OXFORD and *Escherichia coli*. Only 2-hydroxy-3-methoxy-2',5'-diazachalcone showed activity against *Bacillus subtilis*.

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