SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF α,β-UNSATURATED KETONES OF THE IMIDAZO[1,2-a]BENZIMIDAZOLE SERIES*

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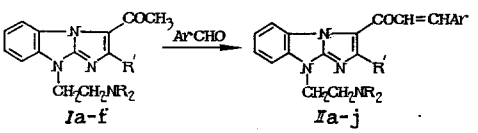
UDC 615.225.2+615.281]:547.785/.012.1

Chalcones and their heterocyclic analogs are known to possess an extremely wide spectrum of biological activity; they can be antihypertensive [18], antioxidant [19, 20], and coronary dilating [16]. The antibacterial and antifungal activities of chalcones are due, in the opinion of many workers (see, e.g., [13, 22]), to the presence of the α,β-unsaturated ketone group.

It has earlier been shown [1] that some α,β-unsaturated ketones of the imidazo[1,2-a]-benzimidazole series, which are readily obtained by condensing 3-acetylimidazo[1,2-a]-benzimidazoles with aromatic aldehydes in the presence of catalytic amounts of alkali, also possess hypotensive activity. Accurate evaluation of the latter was however hampered by the insolubility of the test samples in water. We have continued work on the synthesis of ketones of this type in the imidazo[1,2-a]benzimidazole series and examined their pharmacological activity. First, the possibility was examined of preparing water-soluble analogs of the abovementioned compounds by introducing dialkylaminoalkyl groups into the 9-position of the imidazobenzimidazole nucleus to give 3-(ω-arylacryloyl)-9-dialkylaminioethyl-2-phenyl(methyl)-imidazo[1,2-a]benzimidazoles (IIa-j), or a carbohydrate residue instead of the aryl radical of the α,β-unsaturated ketone group. In the latter case, the following C-glucosylated ketones were obtained: 3-[ω-(1,2,3,4-di-O-cyclohexylidene-D-gluco-1,2,3,4-tetrahydroxybutyl)acryloyl]-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (VIe), 3-[ω-(1,2,O-cyclohexylidene-3-O-methyl-α,D-xylofuranos-4-yl)acryloyl]-9-methyl-2-phenylimidazo[1,2-a]-benzimidazole (VIf), and 3-[ω-(1,2,O-isopropylidene-α,D-xylopyranos-4-yl)acryloyl]-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (VIg).

The synthesis of compounds (IIa-j) presented no difficulties, being readily effected by the crotonic condensation of the methyl ketones (Ia-f) with the appropriate aldehydes, as follows:



Ia-f IIa-j

Ia $R = C_2H_5$, $R' = C_6H_5$; b: $R = C_2H_5$, $R' = CH_3$; c: $R_2 = (CH_2)_5$, $R' = C_6H_5$;
d: $R_2 = (CH_2)_5$, $R' = C_6H_4$ Br-4; e: $R = C_2H_5$, $R' = C_6H_4$ Br-4;

f: $R_2 = (CH_2)_5$, $R' = C_6H_4CH_3$-4; IIa: $R = C_2H_5$, $R' = C_6H_5$, Ar=furyl;
b: $R = C_2H_5$, $R' = C_6H_5$, Ar=5-bromofuryl; c: $R = C_2H_5$, $H' = CH_3$,
Ar=5-bromofuryl; d: $R_2 = (CH_2)_5$, $R' = C_6H_5$, Ar=furyl; e: $R_2 = (CH_2)_5$,
$R' = C_6H_5$, Ar=5-bromofuryl; f: $R_2 = (CH_2)_5$, $R' = C_6H_4$ Br-4, Ar=furyl;
g: $R = C_2H_5$, $R' = C_6H_5$, $Ar = C_6H_4N(CH_3)_2$-4; h: $R = C_2H_5$, $R' = C_6H_4$Br-4;
$Ar = C_6H_4N(CH_3)_2$-4; i: $R_2 = (CH_2)_5$, $R' = C_6H_4CH_3$-4, $Ar = C_6H_4N(CH_3)_2$-4;
j: $R_2 = (CH_2)_5$, $R' = C_6H_4$ Br-4, $Ar = C_6H_4N(CH_3)_2$-4.

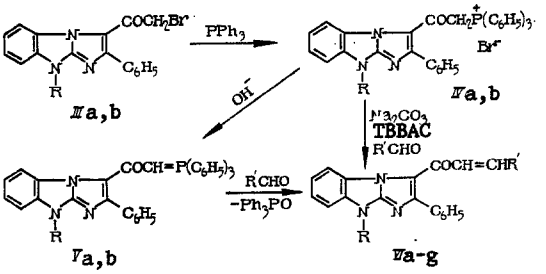
*Communication XX in the series "Studies on Imidazo[1,2-a]benzimidazoles." For communication XIX, see [2].

Research Institute for Physical and Organic Chemistry, Rostov University. Volgograd Institute of Medicine. Research Institute for the Biological Testing of Chemical Compounds, Moscow Region. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 19, No. 4, pp. 412-419, April, 1985. Original article submitted December 27, 1983.

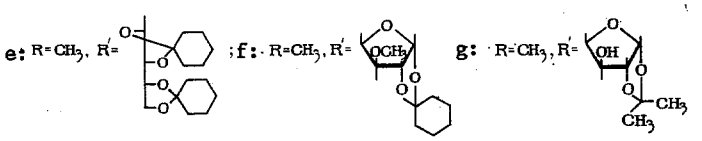
0091-150X/85/1904-0245$09.50

The ketones obtained (IIa-j) were insoluble in water, but treatment of their acetone solutions with conc. HCl gave the water-soluble hydrochlorides.

It was not possible to obtain the C-glucosylated ketones (VIe-g) in this way, as a result of the lability of the al-forms of the carbohydrate starting materials under the basic conditions required for the reaction. We therefore employed the Wittig olefination for their synthesis. The starting materials used in this case were the ketoalkyltriphenylphosphonium salts (IVa, b), formed in high yields by treating the bromoketones (IIIa, b) with PPh_3 in dry benzene:



III-Va: R = CH_3; b: R = C_4H_9; VIa: R = CH_3, R′ = 5-nitrofuryl;
b: R = C_4H_9, R′ = 5-nitrofuryl; c: R = CH_3, R′ = 5-nitrothienyl;
d: R = C_4H_9, R′ = 5-nitrothienyl



Thanks to the presence of the carbonyl group, salts (IVa, b) were readily converted to the ylids (Va, b), either in the presence of caustic alkali, or on treatment of their solutions with sodium carbonate or ammonia. The IR spectra of the ylids showed strong carbonyl absorption at 1520-1530 cm^{-1}, indicating strong delocalization of the negative charge on this group. In the original bromoketones (IIIa, b), C=O vibrations are seen at 1625-1640 cm^{-1}.

The ylids (Va, b) are extremely stable, yet quite reactive compounds. They react readily with a variety of aldehydes to give 86-96% yields of the α,β-unsaturated ketones (VIa-d). Some ketones of this type have previouly been obtained by the direct acylation of 3-unsubstituted-imidazo[1,2-a]benzimidazoles with the acid chlorides of the appropriate unsaturated acids, in yields of 20-53% [1, 9].

To introduce the carbohydrate residue, use was made of the phase transfer modification of the Wittig olefination [4], starting with the salt (IVa). The base used was Na_2CO_3, which did not cause the decomposition of the carbonyl derivatives of monosaccharides used as starting materials, and the catalyst used was tributylbenzylammonium chloride (TBBAC). At room temperature, the reaction was complete after 5-6 h. The yields of C-glucosylated ketones (VIe-g) were 60-85%. Unfortunately these together with their salts, were insoluble in water.

The structures of the compounds obtained (IIa-J) and (IVa-g) were confirmed spectroscopically. Their IR spectra showed two strong bands at 1590-1620 cm^{-1} for C=C and C=N stretching vibrations. Carbonyl group absorption, seen at 1635-1645 cm^{-1} for ketones (IIa-j) and (VIa-d), and at 1660-1670 cm^{-1} for ketones (VIe-g), were of low intensity in comparison with the C=C absorption, indicating that these were cis-oriented [12, 17]. The electronic spectra of (IIa-j) and (VIa-g) were similar to those of the previously obtained ketones [1], the high intensity of the long-wavelength band (λ_{max} 350-370 nm, $\varepsilon \sim 10^4$) making it impossible to obtain circular dichroism spectra for the C-glucosylated derivatives (VIe-g). At high field, the PMR spectra of chloroform solutions of the ketones (VIe-g) displayed a three-proton singlet for the N–CH_3 group at 3.6-3.7 ppm, and two groups of poorly resolved signals corresponding to the protons of the carbohydrate residue (δ 4-5 ppm) and the alkylidene protecting groups (δ 1.5 ppm), with the expected ratios of integral intensities. The spec-

TABLE 1. Compounds Synthesized

Compound	Mp, °C	Yield, %	Found, %				Empirical formula	Calc., %			
			C	H	Hal	N		C	H	Hal	N
Ia	82	90	73,7	6,8	—	14,8	$C_{23}H_{26}N_4O$	73,8	7,0	—	15,0
Ib	49	95	69,5	7,6	—	17,9	$C_{18}H_{24}N_4O$	69,2	7,7	—	17,9
Ic	117—8	97	74,5	6,8	—	14,4	$C_{24}H_{26}N_4O$	74,6	6,8	—	14,5
Id	134—5	94	62,0	5,5	17,4	12,1	$C_{24}H_{25}BrN_4O$	61,9	5,3	17,2	12,0
Ie	124	90	61,1	5,4	17,5	12,6	$C_{23}H_{25}BrN_4O$	60,9	5,5	17,7	12,4
If	118—9	88	75,1	7,2	—	13,8	$C_{25}H_{28}N_4O$	75,0	7,0	—	14,0
IIa	123—4	90	74,5	6,4	—	12,5	$C_{28}H_{28}N_4O_2$	74,3	6,2	—	12,4
IIa·HC	239—40	...	59,5	5,8	12,2	10,2	$C_{28}H_{28}N_4O_2 \cdot 2HCl \cdot 2H_2O$	59,8	6,1	12,6	10,0
IIb	147—8	88	63,0	4,9	14,5	10,5	$C_{28}H_{27}BrN_4O_2$	63,3	5,1	14,8	10,5
IIb·HC	238—9*	...	55,3	4,9	25,4	9,1	$C_{28}H_{27}BrN_4O_2 \cdot 2HCl$	55,6	4,8	25,0	9,3
IIc	113—4	70	58,6	5,2	16,6	11,9	$C_{23}H_{25}BrN_4O_2$	58,9	5,4	17,0	11,9
IIc·HC	245—6*	...	51,2	5,1	28,4	10,1	$C_{23}H_{25}BrN_4O_2 \cdot 2HCl$	51,0	5,0	27,9	10,3
IId	166—7	90	75,2	5,9	—	12,3	$C_{29}H_{28}N_4O_2$	75,0	6,1	—	12,1
IId·HC	205—6*	...	65,0	5,4	12,8	10,5	$C_{29}H_{28}N_4O_2 \cdot 2HCl$	64,8	5,6	13,2	10,4
IIe	177—8	85	64,3	5,1	15,1	10,1	$C_{29}H_{27}BrN_4O_2$	64,1	5,0	14,7	10,3
IIe·HC	220—2*	...	56,2	4,7	25,0	8,8	$C_{29}H_{27}BrN_4O_2 \cdot 2HCl$	56,5	4,7	24,5	9,1
IIf	157—8	87	64,2	5,1	15,0	10,5	$C_{29}H_{27}BrN_4O_2$	64,1	5,0	14,7	10,3
IIf·HC	242—3*	...	56,6	4,8	24,0	9,0	$C_{29}H_{27}BrN_4O_2 \cdot 2HCl$	56,6	4,7	24,5	9,1
IIg·HC	145—6*	80	62,2	6,4	17,0	11,2	$C_{32}H_{34}N_5O \cdot 3HCl$	62,5	6,2	17,3	11,4
IIh·HC	190—2*	86	55,1	5,5	26,3	10,3	$C_{32}H_{34}BrN_5O \cdot 3HCl$	55,4	5,4	26,8	10,1
IIi·HC	171—3*	78	63,5	6,2	16,3	10,8	$C_{34}E_{37}N_5O \cdot 3HCl$	63,7	6,3	16,6	10,9
IIj·HC	204—5*	89	55,8	5,4	26,0	9,7	$C_{33}H_{34}BrN_5O \cdot 3HCl$	56,1	5,3	26,4	9,9
IIIa	187—8*	37	58,4	3,7	21,3	11,6	$C_{18}H_{14}BrN_3O$	58,7	3,8	21,6	11,6
IIIb	137—8	42	61,4	5,0	19,3	10,4	$C_{21}H_{20}BrN_3O$	61,5	4,9	19,5	10,2
IVa	146—7	93	68,5	4,5	...	6,8	$C_{36}H_{28}BrN_3OP$	68,6	4,6	12,7	6,7
IVb	136—7*	86	69,4	5,0	11,5	6,5	$C_{39}H_{35}BrN_3OP$	69,6	5,2	11,9	6,3
Va	182,5—3	100	78,8	5,1	5,4**	7,4	$C_{36}H_{28}N_3OP$	78,7	5,1	5,6**	7,4
VIa	304—5*	93	67,0	3,7	—	13,7	$C_{23}H_{16}N_4O_4$	67,0	3,9	—	13,6
VIb	189*	89	68,6	5,0	—	12,5	$C_{26}H_{22}N_4O_4$	68,7	4,9	—	12,3
VIc	291—2*	96	64,2	3,7	7,2***	13,0	$C_{23}H_{16}N_4O_3S$	64,5	3,7	7,5***	13,1
VId	205	94	66,5	4,7	6,5***	11,7	$C_{26}H_{22}N_4O_3S$	66,4	4,7	6,8***	11,9
VIe	caramelan	75	67,7	6,8	—	6,8	$C_{35}H_{39}N_3O_5 \cdot 2H_2O$	68,0	6,9	—	6,8
VIf	173—6	85	69,9	5,9	—	8,2	$C_{30}H_{31}N_3O_5$	70,2	6,0	—	8,2
VIg	238—40	60	67,6	5,5	—	8,8	$C_{26}H_{25}N_3O_5$	67,9	5,7	—	9,1

Note. HC denotes hydrochloride; one asterisk, with decomposition; two asterisks, P content; three asterisks, S content.

trum of the ketone (VIf) also showed a signal with δ 3.27 ppm (s, 3H), corresponding to the protons of the 3-O-methyl group of the carbohydrate residue.

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a UR-20 instrument (East Germany), in vaseline oil or $CHCl_3$ and UV spectra on a Specord UV-VIS spectrophotometer (East Germany), in ethanol. PMR spectra were recorded on a Tesla BS-467 spectrophotometer (80 MHz) (Brno, Czechoslovakia), in chloroform, sample concentration 0.3-0.4 mole/liter, internal standard HMDS. The purity of the compounds was checked by TLC on alumina (eluent, chloroform). Information on the compounds obtained is given in Table 1.

2-Aryl-3-acetyl-9-dialkylaminoethylimidazo[1,2-a]benzimidazoles (Ia, c-f) were obtained by acylating the hydrochlorides of 2-aryl-9-dialkylaminoethylimidazo[1,2-a]benzimidazoles [10] with acetic anhydride in the presence of anhydrous sodium acetate, as described in [3].

3-Acetyl-9-diethylaminoethyl-2-methylimidazo[1,2-a]benzimidazole (Ib) was obtained by cyclizing 2-amino-3-acetonyl-1-diethylaminoethylbenzimidazolium bromide in acetic anhydride in the presence of anhydrous sodium acetate, as described for 9-alkyl-3-acetyl-2-methylimidazo[1,2-a]benzimidazoles [3].

3-Bromoacetyl-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (IIIa). To a solution of 0.47 g (3 mmole, 0.24 ml) of bromoacetyl chloride in 10 ml of dry benzene was added slowly with stirring a solution of 0.75 g (3 mmole) of 9-methyl-2-phenylimidazo[1,2-a]benzimidazole [8] in 10 ml of benzene. The mixture was stirred at ambient temperature for 30 min, then boiled for 4.5 h. The mixture was cooled, the solid dihydrochloride of the starting material filtered off, and washed repeatedly on the filter with benzene. The benzene solution was evaporated, and the residue was triturated with water, filtered off, and crystallized from alcohol to give 0.42 g of the ketone (IIIa) as colorless needles.

Similarly obtained was the bromoketone (IIIb), colorless cubic crystals (from alcohol).

The IR spectra of (IIIa, b), obtained in vaseline oil, showed absorption at 640 (C–Br) and 1640 cm^{-1} (C=O).

Oxoalkyltriphenylphosphonium Salts (IVa, b). To a hot solution of 5 mmole of the bromoketone (IIIa) or (IIIb) in 20-25 ml of dry benzene was added 0.78 g (3 mmole of PPh_3. The mixture became slightly warm, and was stirred until solution was complete, when it was left to stand at room temperature. After 2-3 h, the mixture, together with the solid which had separated, was boiled for 30-40 min, cooled, the solid filtered off, and washed with benzene and light petroleum. It was purified by recrystallization from alcohol.

Ylid (Va). To a suspension of 1.26 g of the phosphonium salt (IVa) in 15 ml of chloroform was added an aqueous solution of the inorganic base and the mixture shaken until the solid had dissolved completely. The chloroform solution was separated, washed with water, and evaporated. The residue was crystallized from ethyl acetate to give the ylid (Va) as large, bright yellow cubic crystals.

α,β-Unsaturated Ketones (IIa-j) and (VIa-g). A. To a hot alcoholic solution of equimolar amounts of the methyl ketone (Ia-f) and the appropriate aldehyde was added 1-2 drops of 50% KOH. The mixture was stirred thoroughly, boiled for 3-5 min, and kept at ambient temperature. When the reaction was complete (followed by TLC), either the solid which had separated was filtered off, washed with alcohol, and crystallized from a suitable solvent, or the solvent was removed and the residue chromatographed on an alumina column (eluent, benzene–chloroform 1:3); the orange-yellow fraction was collected. Thus obtained were ketones (IIa-j), and these were converted into their water-soluble hydrochlorides by acidifying their acetone solutions with conc. HCl to pH 1.0-2.0. The salts were purified by recrystallization from alcohol or alcohol and ether.

B. A suspension of 1 mmole of the phosphonium salt (IVa or b) in 7-10 ml of chloroform was shaken with 2-3 ml of 5% NaOH until the solid had dissolved completely. The chloroform layer was separated, washed with water, dried over anhydrous K_2CO_3, then mixed with a solution of 1 mmole of the hetarylaldehyde in 5 ml of chloroform. After 1 h, the chloroform was evaporated, and the residual ketone (VIa-d) crystallized from DMF.

TABLE 2. Effects of Ketone (II) Hydrochlorides on SAP (M ± m)

Hydrochloride of	Dose, mg/kg	Changes in SAP following administration of the compound, as % of the original levels, after				
		5 min	15 min	30 min	45 min	60 min
IIa	10,0	0	−3,0±1,0	−3,0±1,0	−9,0±3,0	−9,0±3,0
	20,0	−15,0±12,0	−17,0±8,0	−17,0±8,0	−11,0±7,0	−11,0±7,0
IIb	20,0	−8,0±3,0	−8,0±3,0	−14,0±5,0	−8,0±3,0	−8,0±3,0
	50,0	−24,0±8,0	−20,0±8,0	−18,0±6,0	−12,0±0,0	−2,0±2,0
IIc	0,1	+14.0±5,0	+18,0±12,0	+23,0±13,0	+21,0±10,0	+22,0±10,0
	0,25—0,5	Considerable variations in the SAP in the first 15 min, followed by 20-25% hypotension				
IId	20,0	−14,0±5,0	−9,0±3,0	−5,0±2,0	−5,0±2,0	−5,0±2,0
	50,0	−12,0±6,0	0	+12,0±6,0	+12,0±6,0	+12,0±6,0
IIe	20,0	−12,0±7,0	−6,0±5,0	0	−12,0±7,0	0
	50,0	0	0	−12,0±6,0	−18,0±8,0	−18,0±8,0
IIf	20,0	−9,0±7,0	−11,0±5,0	−13,0±6,0	−15,0±8,0	−15,0±6,0
	100,0	−8,0±6,0	−8,0±4,0	−18,0±5,0	−18,0±5,0	−18,0±5,0

C. To a hot solution of the ylid (Va) (0.55 g) in 10 ml of alcohol was added a solution of 1 mmole of 5-nitrofurfural or 5-nitrothiophen-2-aldehyde in 2 ml of alcohol. The mixture was stirred, boiled for 5 min, cooled, and the ketone (VIa or VIb) which seaprated was filtered off, washed with alcohol, and recrystallized from DMF.

D. A mixture of equimolar amounts of the phosphonium bromide (Va) and the al-form of the appropriate monosaccharide [4, 5, 14], 2 g of finely ground Na_2CO_3, and 20 mg of TBBAC in 20 ml of chloroform was shaken for 4-5 h at room temperature, until the al-form was no longer present in the reaction mixture (checked by TLC). The solid was then filtered off, and the chloroform solution containing the ketone (VIe-g) washed with water, dried over anhydrous Na_2SO_4, evaporated, and the residue chromatographed on an alumina column moistened with hexane (eluent, ether), and the fraction which did not contain triphenylphosphine oxide was collected.

EXPERIMENTAL (PHARMACOLOGY)

The ketones obtained were examined using tests designed to establish the presence of hypotensive, spasmolytic, antiarryhthmic, antiinflammatory, altiallergic, and antimicrobial activity.

The effects of the hydrochlorides of compounds (IIa-f) (administered intravenously as the aqueous solutions) on the systemic arterial pressure (SAP) were examined in acute experiments on nembutal-narcotized (50 mg/kg intraperitoneally) rats weighing 170-210 g. The tests showed (Table 2) that (IIa), (IIb), and (IIa-f) hydrochlorides had hypotensive effects, but these were less pronounced than those of dibasol. Unlike the other hydrochlorides, (IIc) hydrochloride had different effects on the SAP, depending on the dose. Thus, in small doses (0.1 mg/kg), it had hypertensive effects, but these were less pronounced than those of dibasol. Unlike the other hydrochloride, (IIc) hydrochloride had different effects on the SAP, depending on the dose. Thus, in small doses (0.1 mg/kg), it had a hypertensive effect, whereas in higher doses (0.25-0.5 mg/kg) its effect was hypotensive.

The levels of spasmolytic activity in (II) hydrochlorides, determined in isolated segments of rat small intestine by the method described in [11], were assessed by the minimum concentrations which reduced the intestinal spasm induced by $BaCl_2$ by 50% (EC_{50}). The EC_{50} values were determined graphically, from effect–concentration plots. It was found that (IIb) hydrochloride (EC_{50} $8.8 \cdot 10^{-4}$ mole/liter) was less active than spasmolytics such as dibasol (EC_{50} $1.0 \cdot 10^{-4}$ mole/liter) and papaverine (EC_{50} $8.9 \cdot 10^{-6}$ mole/liter) [7]. The salts of (IIa) (EC_{50} $8.9 \cdot 10^{-5}$ mole/liter) and (IId) (EC_{50} $9.2 \cdot 10^{-5}$ mole/liter) were more active than dibasol, but less so than papaverine. Examination of the hypotensive and spasmolytic activity of the test compounds shows that a vascular myotropic factor plays an important part in their mode of action on the SAP.

The salts of ketones (II) did not extend the refractory period in isolated rat auricles on low-frequency stimulation [6], showing that they possessed no antiarrhythmic effects.

TABLE 3. Effects of Salts of Ketones (II) on the Exudative Phase in Inflammation (M ± m)

Hydrochloride of	Dose, mg/kg	Volume of exudate, ml
Control	—	3,20±0,30
IIa	20,0	1,70±0,60
IIb	20,0	1,80±0,25
IIc	20,0	1,60±0,25
IId	20,0	1,50±0,32
IIe	20,0	1,60±0,21
IIf	20,0	2,00±0,29
Amidopyrine	10,0	1,70±0,67

Note. Results statistically significant with respect to the controls ($P < 0.05$).

TABLE 4. Minimum Bacteriostatic Concentrations (μg/ml)

Compound	Test culture							
	1	2	3	4	5	6	9	10
IV a	200	200	—	—	—	—	500	—
IV b	500	500	1000	1000	1000	1000	—	1000
V a	1000	1000	—	1000	—	—	—	—
VI b	—	1000	1000	1000	—	1000	—	1000
VI c	—	—	1000	1000	1000	1000	—	1000

The antiinflammatory effects of the compounds were assessed by their ability to suppress the exudative stage of inflammation. To determine the effects of the compounds on the exudative process, peritonitis was induced in rats by the intraperitoneal administration of 1 ml of 10% formalin solution. The test compounds were administered intramuscularly in a dose of 20 mg/kg, 30 min before administration of formalin and 3.5 h thereafter. Seven hours after the administration of formalin, the animals were killed and the amount of exudate measured.

The experimental results (Table 3) showed that (II) hydrochlorides had pronounced suppressive effects on the exudative stage of inflammation. The levels of antiinflammatory activity in these compounds were similar to those of such antiphlogistics as amidopyrine, although in doses twice as large as the latter.

The effects of (II) on the development of anaphylactic reactions in tissues were assessed in a model of passive dermal anaphylaxis in rats, under the conditions described in [15, 23, 24].

The test compounds were administered in doses of 1, 5, and 10 mg/kg in conjunction with a resolving dose of antigen. The activity of the compound was measured by comparing the intensity of the anaphylactic reaction in the experimental (3 rats) and control (3 rats) groups of animals and their activity with that of intal, which is widely used in clinical practice, in a dose of 10 mg/kg. In a dose of 15 mg/kg, (IIg) gave a statistically significant reduction ($P < 0.05$) in the intensity or the passive dermal anaphylactic reaction, but its level of activity was much lower than that of intal. This compound in lower doses, and the remaining compounds in all doses tested, had no effect on the extent of the dermal anaphylactic reaction.

Antihistamine activity, as determined by standard methods, by serial dilution in solid and liquid nutrient media. Dimethyl sulfoxide or alcohol was used as the solvent.

The test cultures employed were of the following organisms: Staphylococcus aureus 209-P (1), Staphylococcus buomko (2), Salmonella paratyphi "B" (3), Salmonella typhi 4446 (4), Shigella flexneri (5), Serratia marcescens (6), Bacillis subtilis (7), Klebsiella pneumoniae (8), Proteus morganii (9), Escherichia coli 0-20 (10).

Activity was measured as the minimum concentration of the drug which retarded the growth of the microorganisms. Compounds (VIa) and (VId) were inactive in doses up to 1000 mg/kg. The remaining compounds displayed some antimicrobial activity (Table 4), that of (IV) being greatest against Staphylococcus.

A fairly wide spectrum of antibacterial activity was shown by (IVb), but this was apparent only at high concentrations. Compounds (IV-VI) were without effect on the microorganisms Bacillus subtillis, Klebsiella pneumoniae, and hence these results are not given in the table.

These studies therefore lead to the conclusion that chalcones of the imidazo[1,2-a]-benzimidazole series display differing, moderate effects on arterial pressure, and possess spasmolytic properties which are not superior to those of amidopyrine. No antiarrhythmic or antiallergic properties are shown by the compounds, and their antimicrobial effects are apparent only at high concentrations.

LITERATURE CITED

1. V. A. Anisimova, N. I. Avdyunina, A. M. Simonov, et al., Khim. Geterotsikl. Soedin., No. 12, 1660-1665 (1976).
2. V. A. Anisimova and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 1, 68-70 (1980).
3. V. A. Anisimova and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 1, 121-125 (1976).
4. Yu. A. Zhdanov, Yu. E. Alekseev, V. G. Alekseeva, et al., Dokl. Akad. Nauk SSSR, 244, 1122-1124 (1979).
5. Yu. A. Zhdanov, Yu. E. Alekseev, et al., Zh. Obshch. Khim., 45, 1327-1333 (1975).
6. Ya. I. Zaidler, in: Modeling, Methods of Study, and the Experimental Therapy of Pathological Conditions [in Russian], Moscow (1967), Part 3, p. 191.
7. M. D. Mashkovskii, Drugs [in Russian], 8th edition, Moascow (1977), Part 1, pp. 383, 409.
8. A. M. Simonov and V. A. Anisimova, Khim. Geterotsikl. Soedin., No. 6, 1102-1104 (1968).
9. A. M. Simonov, V. A. Anisimova, and N. I. Avdyunina, Author's Certificate (USSR) No. 479,770, Otkrytiya, No. 29, 79 (1975).
10. A. M. Simonov, A. A. Belous, V. A. Anisimova, et al., Khim.-farm. Zh., No. 1, 7-10 (1969).
11. Ya. I. Khadzhai, G. V. Obolentseva, and A. P. Prokopenko, Farm. Toksikol., No. 2, 156 (1966).
12. R. L. Erskine and E. S. Waight, J. Chem. Soc., 3420 (1960).
13. W. B. Geiger and J. E. Conn, J. Am. Chem. Soc., 67, 112-116 (1945).
14. K. Iwarade, Bull. Chem. Soc. Japan, 16, 40-44 (1941).
15. S. Katayama, H. Shionoya, and S. Ohtake, Microbiol. Immunol. (Tokyo), 22, 89-101 (1978).
16. J. Koo, J. Org. Chem., 26, 4185 (1961).
17. R. Mecke and K. Noack, Ber. Chem. Ges., 93, 210 (1960).
18. German Patent No. 2,159,674 (1971); Chem. Abstr., 77, 140,078 (1972).
19. US Patent No. 2,728,784; Chem. Abstr., 50, 9043 (1956).
20. German Patent No. 919,128 (1954); Chem. Abstr., 52, 13,244 (1958).
21. J. J. Reyse, Br. J. Pharmacol., 3, 174-180 (1948).
22. E. Schraufstätter, Experientia, 4, 484-5 (1948).
23. H. M. Vijay, G. Lavergne, H. Huang, et al., Int. Arch. Allergy, 59, 277-82 (1979).
24. J. Wyczolkowska and C. Maslinski, Acta Allergol. (Kbh), 31, 175 (1976).