and spore-forming microorganisms. To determine the antimicrobial activity of the preparations, the following methods were used.

A. Method of Sample Testing. To determine the antimicrobial activity of the preparations samples of them (0.1 g/ml) were placed in recesses in meat peptone agar or sugar agar preliminarily inoculated by the corresponding microbial suspension. The dishes were incubated for 18 h at 37°C. The presence of the antimicrobial properties was determined from the diameter of the bactericidal action zone of the preparations (in mm) (Table 2).

B. Method of serial dilutions was carried out similarly as in the preceding case. Preparations having a pronounced antimicrobial action (compounds II-IV) in concentrations from 0.000001 to 0.1 g/ml were used. Control experiments with marketed antibiotics (penicillin, tetracycline) and solvent (dimethyl sulfoxide) were carried out in parallel.

It is seen from the results presented in Table 3 that compounds II-IV have pronounced antimicrobial properties with respect to the microbes tested. In the degree of activity with respect to suppurative infection inducers (Micrococcus, Staphylococcus aureus 209), compounds II-IV surpass the known antibiotics, penicillin by 10-100 times and tetracycline by 10 times.

It was found that the minimal inhibiting concentration of compounds II-IV against the suppurative infection inducers is 0.00001-0.0001 g/ml.

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SYNTHESIS OF 1,2-(2-DIMETHYLAMINOMETHYL-1-OXOPOLYMETHYLENE) BENZENES AND THEIR 4,5-DIETHOXY DERIVATIVES AND THEIR ANTI-INFLAMMATORY ACTIVITY

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Certain derivatives of 3-dimethylaminopropionylbenzene exhibit anti-inflammatory activity (AA) and are slightly toxic [2, 3]. Therefore, in order to study the relationship between the chemical structure and the AA, and also to search for new drugs, we synthesized and studied the cyclic analogs of these compounds (IIa-f), which were previously unknown or had not been examined for AA.

The hydrochlorides of β-aminoketones IIc-f were synthesized by the Mannich reaction of the corresponding ketones (Ic-f) with $Me_2NH{\cdot}HCl$ and paraform, while ketones Ie, f were obtained by heating the corresponding acids IIId, f) with polyphosphoric acid. Acid IIId was obtained by hydrogenation of unsaturated acid IIIc, synthesized by condensation of aldehyde (IIIb) with malonic acid in a pyridine solution in the presence of piperidine, while acid IIIf was obtained by reduction with amalagamated zinc and HCl of keto-acid (IIIe), synthesized by acylation of 1,2-diethoxybenzene (IIIa) with succinic anhydride in the presence of anhydrous $AlCl_3$.

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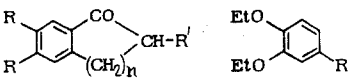

Ic-f IIa-f *IIIa-f*

$PhCOCH(R)CH_2NMe_2 \cdot HCl$
IVa,b

I, II: R^1=H(Ic-f), $CH_2NMe_2 \cdot HCl$(IIa-f);
Ic,d,IIa-d: R=H; n=1(a), 2(b), 3(c), 4(d);
Ie,f, IIe,f: R=OEt; n=1(e), 2(f);
IIIa-f: R=H(a), CHO(b), CH=CHCOOH(c), CH_3CH_2COOH(d), $COCH_2CH_2COOH$(e), $CH_2CH_2CH_2COOH$(f);
IVa,b: R=H(a), Me(b).

The characteristics of the new synthesized compounds are given in Tables 1 and 2. The results of the elemental analyses correspond to the calculated values.

The structure of the synthesized compounds was confirmed by the UV, IR and PMR spectral data. The UV absorption bands of the unsaturated acid IIIc are more intense and are shifted more to the long-wave side, compared with the bands of the hydrogenated analog IIId. The UV spectra of the saturated acids IIId, f differ little, while the UV spectra of ketones Ie, f are similar to the spectrum of the keto acid IIIe.

Compounds Ic, d [7], IIa [4], IIb [8], IIIa [10], IIIb [6] and IVb [1] have been described previously, compound IVa is a commercial product.

EXPERIMENTAL (CHEMICAL)

The UV spectra were run on a "Specord M40" spectrophotometer (Germany) in ethanol, the IR spectra – on a "Specord M80" spectrophotometer (Germany) in mineral, oil, and the PMR spectra – on a "Tesla BS-487C" spectrometer (CSFR, 80 Hz), using TMS as internal standard.

1,2-(1-Oxopolymethylene)-4,5-Diethoxybenzenes (Ie, f). A 50 g portion (0.4 mole) of 85% H_3PO_4 was mixed together with 100 g (0.7 mole) of P_2O_5, and 0.1 mole of the corresponding acid IId, f was added at 90°C. The mixture was stirred for 20 min at 110°C, poured onto ice, extracted with benzene, the extract was washed with an alkaline solution and the solvent was distilled of f.

Hydrochlorides of 1,2-(2-dimethylaminomethyl-1-oxopolymethylene)benzenes (IIc, d) and Their 4,5-diethoxy derivatives (IIe, f). A mixture of 50 mmoles of the corresponding ketons Ic-f, 4.5 g (55 mmoles) of $Me_2NH \cdot HCl$, 4.5 g (150 mmoles) of paraform, 2 drops of concentrated HCl and 20 ml of ethanol was boiled for 8 h, ethanol was evaporated, and the residue was recrystallized from acetone, and then from 2-propanol.

3,4-Diethoxycinnamic Acid (IIIc). A mixture of 29.1 g (150 mmoles) (150 mmoles) of aldehyde (IIIb), 18.2 g (175 mmoles) of malonic acid, 80 g of anhydrous pyridine, and 20 g of piperidine was heated for 6 h at 110°C, concentrated in vacuo, and the residue was poured into water and the mixture was acidified with HCl.

3-(3,4-Diethoxyphenyl)propionic Acid (IIId). A 2 g portion of Raney nickel was added to a solution of 25 g (106 mmoles) of acid IIIc in 200 ml of 15% KOH, hydrogenated in an autoclave for 3 h at 60°C and a hydrogen pressure of 90 atm, filtered and the filtrate was acidified with HCl.

4-Oxo-4-(3,4-diethoxyphenyl)butyric Acid (IIIe). A 16 g portion (120 mmoles) of anhydrous $AlCl_3$ was added in the course 30 min at 10-15°C to a mixture of 100 ml of anhydrous CH_2Cl_2, 16.6 g (100 mmoles) of compound IIIa and 11.0 g (110 mmoles) of succinic anhydride. The mixture was stirred for 3 h at 20°C, then poured onto ice, acidified with HCl, extracted with CH_2Cl_2, the extract was washed with water, and the solvent was distilled.

4-(3,4-Diethoxyphenyl)butyric acid (IIIf). A mixture of 300 ml (3 moles) of concentrated HCl, 15 g (56 mmoles) of acid IIIe and 15 g (230 mmoles) of granulated amalgamated zinc was boiled for 36 h, then cooled and extracted with benzene. The extract was washed with water, dried and distilled.

TABLE 1. Characteristics of Synthesized New Compounds

Compound	Yield, %	Mp, °C*	UV spectrum**		IR spectrum, $\nu_{C=O}$, cm^{-1}	Empirical formula
			λ_{max}, nm	log ε		
Ic	70	83—4	230 268 310	4,17 4,01 3,98	1680	$C_{13}H_{16}O_3$
If	77	75—6	234 274 313	4,24 4,10 3,93	1663	$C_{14}H_{18}O_3$
IIc	67	137—9	245 286	3,69 2,93	1670	$C_{14}H_{19}NO \cdot HCl$
IId	53	149—50	247 288	3,85 3,08	1684	$C_{15}H_{21}NO \cdot HCl$
IIe	60	163—5	233 272 316	4,15 3,97 3,92	1692	$C_{16}H_{23}NO_3 \cdot HCl$
IIf	75	142—4	234 278 314	4,05 3,92 3,77	1675	$C_{17}H_{25}NO_3 \cdot HCl$
IIIc	88	152—4	216 236 288 316	4,17 4,14 4,19 4,24	1680 1690	$C_{13}H_{16}O_4$
IIId	95	111—2	228 278	3,92 3,48	1696	$C_{13}H_{18}O_4$
IIIe	63	108—9	228 272 302	4,24 4,07 3,92	1660 1750	$C_{14}H_{18}O_5$
IIIf	89	—***	228 277	3,87 3,46	1700 1710	$C_{14}H_{20}O_4$

*Reacrystallized from 2-propanol.
**For compounds IIa, b λ_{max}, nm (log ε): 247(3.85), 290(3.19) and 249(3.99), 292(3.12), respectively.
***Bp 206-8°C at 1 mm.

TABLE 2. PMR Spectral Data (Deuteroacetone, δ, ppm) of Compounds Ie, f, IIc-f and IIIc-f.

Compound	CH_3	$(CH_2)_n$	$CHCO, CH_2CO$	CH_2Az	CH_2N	CH_3N	CH_3O	ArH, HC=
Ie[a]	1,40 t[b] 1,45 t[b]	—	2,33—2,56 m	2,75—2,98 m	—	—	3,95 q[b] 4,01 q[b]	6,60 s (3-H) 6,85 s (6-H)
Ie[a]	1,40 t[b]	1,92—2,25 m	2,34—2,60 m	2,65—2,95 m	—	—	4,03 q[b]	6,42 s (6-H) 7,25 s (6-H)
IIc	—		3,03—3,82 m			2,90 s	—	7,23—7,48 m (3,4,5-H) 7,80 d.d[c,d] (6-H)
IId	—		3,03—3,90 m			2,90 s	—	7,12—7,51 m (3,4,5-H) 8,03 d.d[c,d] (6-H)
IIe	1,38 t[b] 1,47 t[b]	—		3,15—3,63 m		2,93 s	3,98 q[b] 4,10 q[b]	6,95 s (3-H) 7,03 s (6-H)
IIf	1,35 t[b] 1,41 t[b]		2,60—3,60 m			2,95 s	4,00 q[b] 4,09 q[b]	6,75 s (3-H) 7,38 s (6-H)
IIIc	1,35 t[b]		—	—	—	—	3,79— —4,25 m	6,25 d[e] (COCH=) 6,58—7,20m (AzH) 7,45 d[e] (AzCH=)
IIId	1,28 t[b]	—	2,39—2,60 m	2,66—2,90 m	—	—	3,91 q[b] 3,95 q[b]	6,63—6,83 m (AzH)
IIIe	1,30 t[b]	—	2,63 t[b] 3,18 t[b]	—	—	—	4,05 q[b] 4,10 q[b]	6,93 d[c] (5-H) 7,45 d[d] (2-H) 7,58 d.d[c, d] (6-H)
IIIf[a]	1,30 t[b]	1,55—2,01 m	2,08—2,30 m	2,38—2,68 m	—	—	3,90 q[b] 3,95 q[b]	6,48 s (AzH)

a) In a CCl_4 solution. b) I = 6-7 Hz. c) I = 9 Hz. d) I = 2 Hz. e) I = 15 Hz.

EXPERIMENTAL (PHARMACOLOGICAL)

Hydrochlorides IIa-f and IVa, b were administered subcutaneously in the form of an 1% aqueous solution. Nonpedigree white mice, each weighing 18-25 g and white rats, each weighing 150-230 g of both sexes were used.

The acute toxicity for mice was determined according to the modified Litchfield and Wilcoxon method [1]. The AA was studied using the models of carraghenin [12] and bentonite [9] induced edemas of a rat paw. Table 3 shows the mean arithmetic values of the percent

TABLE 3. Acute Toxicity and Anti-Inflammatory Activity (AA) of Compounds IIa-f and IVa, b with Subcutaneous Method of Administration

Compound	LD_{50}, mg/kg	Mean percent of inhibition of inflammation (compared with control)*	
		carrag-henin	bentonite
IIa	320 (262—390)	66,2	49,0
IIb	322 (293—354)	54,8	50,6
IIc	500 (439—570)	17,4	0
IId	352 (322—395)	58,4	52,9
IIe	129 (114—146)	65,0	71,7
IIf	105 (95—117)	64,4	75,6
IVa	223 (192—307)	19,5	10,5
IVb	255 (211—309)	44,2	42,0
Lysine acetylsalicylate	1000 (890—1130)	37,4**	9,8**

Notes. One asterisk – the dose of compounds 50 mg/kg, two asterisks – dose 150 mg/k. The variation limits at $p \leq 0.05$ are given in brackets.

of decrease in the edema (compared with control), measured 1, 2, 3 and 5 h after the administration of the compound studied.

It was found that the β-aminoketones with cyclic structure IIa, b, d exhibit a higher AA and are less toxic than the acyclic analogs IVa, b. The introduction of strong electron donor substituents (ethoxy groups) into the aromatic ring of compounds IIa, b leads to compounds IIe, f exhibiting a higher AA, which corresponds to the data in [3]. The low AA of compound IIc, can probably be explained by the exclusion of the carbonyl group from conjugation with the aromatic ring due to its rotation around the C_{Ar}-CO bond [3], since the UV absorption bands of compound IIc are less intense and shifted to a lesser degree in the long-wave side than the bands of compounds IIa, b, d (see Table 1). The molecules of unsubstituted 1-indanone and 1-tetralone are of a planar, and those of ketones Ic, d are of a non-planar structure [5], but in view of the higher conformational mobility of the eight-membered ring compared with the seven-membered one, it is clearly easier for the carbonyl group of compound IId to enter into conjugation with the aromatic ring, than for the carbonyl group in compound IIc.

Our investigations have thus shown good prospects for the search for new anti-inflammatory agents among the cyclic β-aminoketones of the type under the consideration in this article.

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