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SYNTHESIS OF 1,3-BIS-(p-ALKOXYBENZOYL)-1-BIS-(2-CHLOROETHYL)AMINOMETHYLBUT-3-ENE HYDROCHLORIDES AND AN EXAMINATION OF THEIR ANTITUMOR AND ANTIBACTERIAL ACTIVITY

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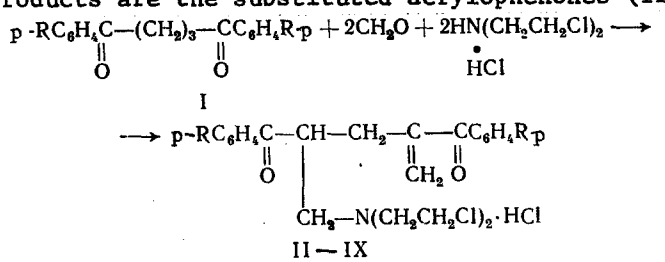
It has previously been shown [2] that the formation of aminomethylation products of 1,5-diphenyl-1,5-pentanedione is markedly affected both by the nature of the amine used, and the medium. It has been established by IR, PMR, and mass spectrometry that the reaction products can be either monoaminomethyl compounds, bisaminomethyl compounds, substituted acrylophenones, or mixtures thereof.

We here describe the aminomethylation of 1,5-bis-(p-alkoxyphenyl)-1,5-pentanediones (I) with bis-(2-chloroethyl)amine hydrochloride and paraformaldehyde in dioxane solution. It is shown that the reaction products are the substituted acrylophenones (II-IX).



R=H (II), CH_3O (III), C_2H_5O (IV), C_3H_7O (V), C_4H_9O (VI), iso-C_4H_9O (VII), $C_5H_{11}O$ (VIII), iso-$C_5H_{11}O$ (IX)

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TABLE 1. Mass Numbers and Relative Intensities (%) of the Principal Fragments of 1,3-Bis-(p-alkoxyphenyl)-1-bis-(2-chloroethyl)aminomethylbut-3-enes*

Compound	Fragment													
	M^+	a	b	c	d	e	f	g	h	i	j	k	l	m
II	417 (4)	382 (1)	368 (6)	353 (0,5)	154 (100)	312 (12)	272 (14)	105 (45)	276 (2)	—	248 (5)	171 (5)	—	—
III	477 (6,25)	442 (1,25)	428 (35)	413 (7,5)	154 (100)	342 (20)	302 (21)	125 (62,5)	336 (16)	—	278 (47)	201 (20)	189 (6,25)	121 (20)
IV	505 (6,25)	470 (1,5)	456 (1,9)	441 (6,25)	154 (100)	356 (25)	316 (45)	149 (6,25)	364 (37,5)	407 (12)	292 (50)	215 (53)	203 (10)	121 (50)
V	533 (9)	498 (15)	484 (3)	469 (3)	154 (85)	370 (25)	330 (23)	163 (92)	392 (45)	435 (14)	306 (21)	229 (78)	217 (35)	121 (100)
VII	561 (2)	526 (1)	512 (1,5)	497 (3)	154 (20)	384 (5)	344 (4)	177 (30)	420 (8)	463 (2)	320 (2)	243 (20)	231 (18)	121 (100)
VIII	589 (6)	554 (1,5)	540 (2)	525 (1)	154 (100)	398 (25)	358 (20)	191 (55)	448 (15)	491 (8)	334 (14)	257 (28)	245 (20)	121 (80)

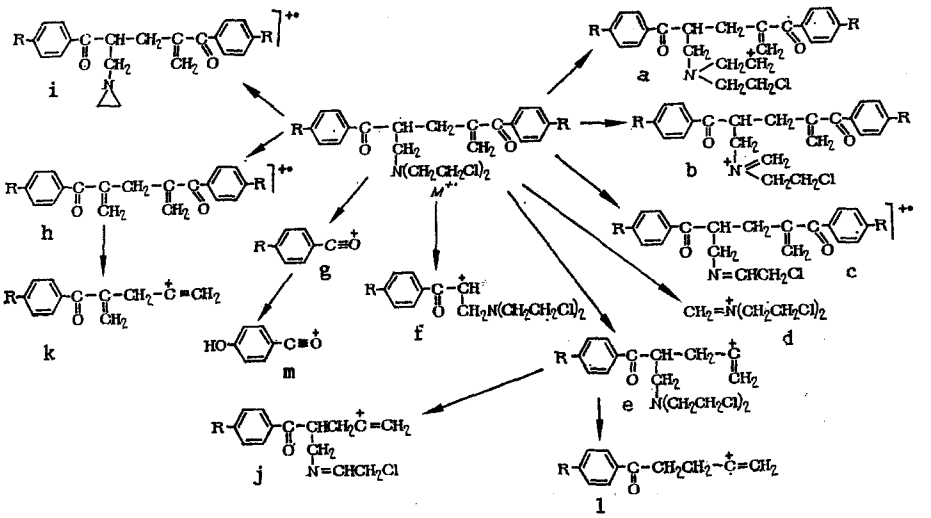
*For fragments containing chlorine, results are given only for ions containing the ^{35}Cl isotope.

TABLE 2. Toxicities and Antitumor Activity of 1,3-Bis-(p-alkoxylbenzoyl)-1-bis-(2-chloroethyl)aminomethylbut-3-ene Hydrochlorides (II-IX)

Compound	Toxicity to mice, mg/kg		% Inhibition of tumor growth					
	100	MTD	dose, mg/kg × number of doses	sarcoma 45	Walker's carcinoma	dose, mg/kg × number of doses	sarcoma 45 180	sarcoma 37
II	400	250	20±8	71 (α>0,99)	82 (α>0,98)	25×6	66,5 (α>0,98)	55,5 (α>0,95)
III	1500	1000	100×8	37,5 (α<0,95)	97,5 (α>0,99)	150×6	40 (α>0,95)	55,5 (α>0,95)
IV	1000	800	45×8	29 (α<0,95)	41 (α<0,95)		61 (α>0,95)	44 (α>0,95)
V	400	300	20×8	67 (α>0,95)	93 (α>0,99)	35×6	33 (α>0,95)	28 (α<0,95)
VI	150	75	7,5×8	56 (α>0,95)	0	15×6	33 (α>0,95)	
VII	150	80	7,5×8	43,5 (α<0,95)	51,5 (α<0,95)	15×6	66,5 (α>0,98)	61 (α>0,95)
VIII	1100	800	50×8	0	50 (α<0,95)	100×6	0	
IX	1100	800	55×8	0	23 (α<0,95)	100×6	42 (α>0,98)	

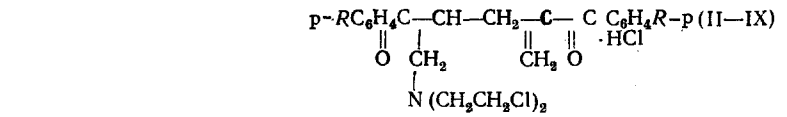
Note. α is the free term in the regression equation.

Compounds (II-IX) are colorless, crystalline solids with sharp melting points. Their IR spectra show absorption for the C=O group at 1680-1670 cm^{-1} and for $C=CH_2$ at 1640 cm^{-1}. The fragmentation diagrams of the compounds (II-IX), obtained by mass spectrometry show that all the fragments formed under electron impact are consistent with the formulae given (Table 1). The antitumor and antibacterial activities of the compounds have been studied. The results showed that their toxicities vary widely (Table 2). The LD_{100} for (II) is 400 mg/kg, and its propoxy-derivative (V) is of similar toxicity. Replacement of a hydrogen atom in the benzene ring of (II) by methoxy, ethoxy, or isopentyl reduces the toxicity (cf. (III), (IV), (VIII), and (IX) with (II)), whereas when these compounds contain butoxy or isobutoxy substituents the toxicity is considerably increased (cf. (VI) and (VII) with (II)).



It has been found that most of the test compounds possess high antitumor activity. Compounds (II) and (V) inhibit the growth of sarcoma 45 by 67-71%, and the other compounds are either weakly active against this strain (III, IV, VII) or are completely inactive. The growth of the Walker carcinoma is strongly inhibited by (II), (III), and (V), their activity against this strain reaching 82-97.5% inhibition without observable toxic effects on the body. Activity against sarcoma 180 was displayed only by (II), (IV), and (VII), which inhibited the growth of this tumor by 61-66.5% and also showed no toxic effects in the experimental animals. Against sarcoma 37, the test compounds for the most part showed low activity,

TABLE 3. Properties of



Compound	Yield, %	mp, °C	R_f	Found, %			
				C	H	N	Cl
II	46,3	206—8	0,82	61,35	5,30	3,22	22,90
III	62,1	236—7	0,77	58,01	6,36	2,86	21,35
IV	48,8	238—40	0,79	58,82	6,45	2,76	20,38
V	46,3	217—18	0,91	61,81	6,21	3,28	20,00
VI	53,5	193—5	0,93	61,78	6,80	2,84	18,00
VII	30,1	213—15	0,92	61,40	7,40	2,92	17,70
VIII	20,5	209—10	0,92	62,14	7,50	2,50	17,60
IX	22,0	220—21	0,93	62,92	7,20	2,76	17,00

Compound	Empirical formula	Calc., %				IR spectrum, cm^{-1}
		C	H	N	Cl	
II	$C_{23}H_{26}NO_2Cl_3$	60,82	5,76	3,08	23,40	1670 1630
III	$C_{25}H_{30}NO_4Cl_3$	58,74	5,82	2,72	20,67	1670 1640
IV	$C_{27}H_{34}NO_4Cl_3$	59,50	6,31	2,58	19,64	1670 1640
V	$C_{29}H_{38}NO_4Cl_3$	61,02	6,71	2,46	19,88	1680 1630
VI	$C_{31}H_{42}NO_4Cl_3$	62,20	7,05	2,34	17,70	1675 1640
VII	$C_{31}H_{42}NO_4Cl_3$	62,20	7,05	2,34	17,70	1670 1630
VIII	$C_{31}H_{42}NO_4Cl_3$	63,10	7,41	2,24	17,00	1670 1635
IX	$C_{33}H_{46}NO_4Cl_3$	63,0	7,41	2,24	17,00	1670 1630

except for (VII), which contains an isobutoxy-group (T% = 61). None of these acrylophenones showed any antitumor activity against Ehrlich's ascitic carcinoma.

In summary, it is concluded that of the substituted acrylophenone hydrochlorides examined, the most active is the compound (II) (1,3-bisbenzoyl-1-bis-(2-chloroethyl)aminomethyl-but-3-ene hydrochloride), which is unsubstituted in the benzene ring.

Examination of the antibacterial activity showed that following administration of the test compounds (II) and (V-IX), the animals died at the same time as the controls (untreated). Compounds (III) and (IV) extended the lifespan in comparison with the untreated animals by 10-15%, whereas norsulfazol increased it by 50-70%, i.e., none of the test compounds were active under these conditions.

The observation of antitumor activity in this series of novel acrylophenone derivatives encourages further study of this type of compound as potential antitumor drugs.

EXPERIMENTAL (BIOLOGY)

The antiblastic activity of compounds (II-IX) was assessed by standard methods [1].

The toxicities of the compounds were determined in mongrel white mice of both sexes and body weight 18-21 g, by a single intraperitoneal administration. Antitumor activity was determined in mongrel white rats with sarcoma 45, and Walker's carcinoma (dose 1/20 of the LD_{100}, eight daily doses) and in mice with sarcomas 180 and 37, and Ehrlich's ascitic carcinoma (dose 1/10 of the LD_{100}, six daily doses).

The therapeutic effect was assessed from the extension of the lifespan of mice with ascitic tumors, and the percentage inhibition of the growth of solid tumors, calculated the day following termination of treatment.

The compounds were insoluble in water, and for this reason they were administered intraperitoneally to the animals as suspensions in 0.5% carboxymethylcellulose solution.

The antibacterial effects of (II-IX) were examined in comparison with norsulfazol on model generalized staphylococcal infection in white mice [1]. Infection was carried out by intraperitoneal administration of a single lethal dose of a staphlococcal culture (400 million microbial cells) admixed with nutrient agar. The staphylococcal culture (400 Smith and 4-0 strains. The compounds were administered internally in a single dose in half the maximum tolerated dose, simultaneously with infection.

The experiments were carried out with 195 rats and 320 mice, and the results were evaluated statistically by the Student-Fisher method.

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a UR-20 spectrometer (West Germany), in vaseline oil, and mass spectra on an MX-1320 with direct introduction of the sample into the ionization zone, ionizing ion energy 30 eV, at its melting point.

TLC was carried out on bound layers of silica gel and gypsum, with the mobile phase n-butanol—ethyl acetate—acetic acid—water (2:5:1:3). Developer, iodine vapor.

The starting diketones (I) were obtained by the Friedel-Crafts condensation of glutaroyl chloride with alkoxybenzenes in the presence of $AlCl_3$ in CCl_4 solution [3].

1,3-Bis-(p-alkoxybenzoyl)-1-Bis(2-chloroethyl)aminomethylbut-3-ene Hydrochlorides (II-IX). A mixture of 0.1 mole of the diketone (I), 1.9 g (0.3 mole) of paraformaldehyde, 37.5 g (0.21 mole) of bis-(2-chloroethyl)amine hydrochloride, and 2 ml of concentrated hydrochloric acid in 100 ml of dioxane was heated to 85-95°C. All the components dissolved, and the products (II-IX) separated. Heating was continued for 1 h, and the mixture was then cooled to room temperature, and the solid was filtered off and recrystallized first from acetone, then from ethanol. The constants are given in Table 3.

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