1,6-BISARYL-2,5-DIHEXYLIMINOMETHYL-1,6-HEXANEDIONES AND THEIR REDUCTION PRODUCTS. THE BIOLOGICAL ACTIVITY OF THEIR SALTS

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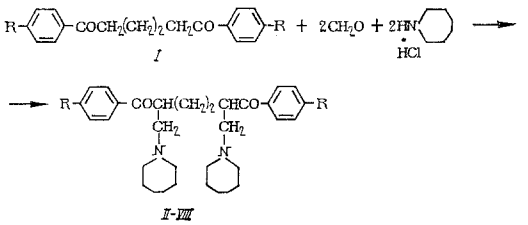
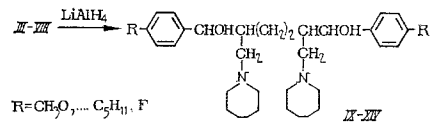
The aminomethylation of araliphatic 1,5-diketones has been reported [1], and it was shown that aminomethylation occurred at only one of the two α-CH_2 groups. However, the aminomethylation of 1,6-diketones has not been described in the literature. In extending the Mannich reaction to 1,6-diketones, we have synthesized 1,6-bisaryl-2,5-dihexamethyleneiminomethyl-1,6-hexanediones (II-VIII).



An examination of the aminomethylation of diketones (I) has shown that in ethanol, both in the presence of acid and base, hardly any reaction occurs, (I) being recovered almost quantitatively. Attempts to effect aminomethylation in dioxane in the presence of base (pH 8.0-9.0) were likewise unsuccessful, but in the presence of acid (pH 1.0-2.0), the bishexamethyleneiminomethyl derivatives (II-VIII) were obtained in good yields.

Since both aminoketones [2] and aminoalcohols [3] are biologically active, we deemed it desirable to convert the dihexamethyleneiminomethyl diketones (III-VIII) into the corresponding 1,6-bisaryl-2,5-dihexamethyleneiminomethyl-1,6-hexanediols (IX-XIV) with lithium aluminohydride in dry ether and THF.



Compounds (III-VI) and (VIII) were crystalline solids, but (II) and (VII) were viscous oils which decomposed on distillation under reduced pressure. The IR spectra showed carbonyl absorption at 1690 and 1720 cm^{-1}. Compounds (IX-XIV) were viscous oils which crystallized on prolonged keeping. The IR spectra of (IX-XIV) showed no carbonyl absorption, but absorption occurred at 3200-3400 cm^{-1}, characteristic of the CH–OH group.

In order to study their biological activity, the compounds were converted into their dihydrochlorides and dimethiodides (XV-XXXIV), which were colorless crystalline solids, the first of these being soluble in water, and the second insoluble.

EXPERIMENTAL PHARMACOLOGY

Bearing in mind that these compounds, like a number of adrenergic and antiadrenergic drugs [4], contain hydroxyphenylethanol or hydroxyphenylpropanol moieties, the effects of the compounds on α-adrenoreceptors and on the conduction of stimuli via the sympathetic nerves were examined in isolated rat vas deferens [5].

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TABLE 1. Effects of 1,6-Bisaryl-2,5-dihexamethyleneimino-methyl-1,6-hexanedione Dihydrochlorides and Dimethiodides (XV-XXXIV) (diols) in Concentrations of 0.05 mM on the Contraction of Rat Vas Deferens

Compound	Reduction in contraction of the vas deferens induced by transmural stimulation, as % of control		Reduction in contraction of the vas deferens induced by adrenaline, as % of the control	
	after 10 min	after 60 min	after 10 min	after 60 min
XV	96 (93,8—98,2)	92 (79,3—104,7)	+120 (20,5—219,5)	+200 (—14,2—414,2)
XVIII	1	21 (0,7—41,3)	21 (—1,8—43,8)	28 (—6—62)
XIX	6 (—11—23)	34 (19,1—48,9)	32 (—18,2—82,2)	38 (—1,3—77,3)
XX	67 (51,5—82,9)	76 (48,4—103,6)	+51 (—38,9—140,9)	+86 (—73—245)
XXI	11 (—4,6—26,6)	9 (1,3—16,7)	42 (—13,3—97,3)	25 (9,7—40,3)
XXII	3 (—4,3—10,3)	6 (—10—22)	34 (9,2—58,8)	18 (—18,5—54,5)
XXIII	13 (7,6—18,4)	18 (1,5—34,5)	48 (6,4—89,6)	46 (2,2—89,8)
XXIV	7 (—1,5—15,5)	11 (—6,4—28,4)	26 (—5,1—57,1)	21 (—10,8—52,8)
XXV	9 (—3—21)	38 (9,4—66,6)	39 (—10,7—88,7)	82 (39—125)
XXVI	98	86 (52—120)	+63 (—85—211)	1
XXVII	98	95 (85,5—104,5)	62 (24—100)	+33 (—41—107)
XXVIII	40 (2,8—77,2)	74 (44,5—103,5)	12 (—3,3—27,3)	39 (23,5—54,5)
XXX	96 (89,1—102,9)	96 (91—101)	18 (—34,4—70,4)	18 (—34,4—70,4)
XXXI	23 (4—42)	1	+38 (—37,3—113,3)	+ 100 (—45—245)
XXXII	13 (—16,2—42,2)	1	+100 (35,2—164,8)	1
XXXIII	21 (—20,6—62,6)	6 (—8,6—20,6)	+13 (—25,1—51,1)	1
XXXIV	64 (40,8—87,2)	71 (44,3—97,4)	+23 (—21,8—67,8)	25 (12,8—62,8)
Octadine	57 (50,7—63,3)	84 (75,7—92,3)	+185 (134,6—335,4)	+134 (107,2—160,8)

Note. (+) denotes an increase in the contraction of the vas deferens induced by adrenaline (as % of control). The range of variation is shown in brackets. The formulae of (XV-XXXIV) are given in Tables 4 and 6.

TABLE 2. Toxicities and Antitumor Activity of 1,6-Bisaryl-2,5-dihexamethyleneiminomethyl-1,6-hexanedione Dimethiodides (XXI-XXV)

Compound	Toxicity in mice, mg/kg			Inhibition of tumor growth, %						
	LD_{100}	LD_{50}	maximum tolerated dose, mg/kg	dose, mg/kg	number of doses	sarcoma 45	Walker's carcinosarcoma	dose, mg/kg	number of doses	sarcoma 180
XXI	20	13	5	1	8	26	20	2	6	36,7
XXII	40	32	20	2	8	0	0	4	6	19,0
XXIII	50	45	40	2,5	8	12	0	0,5	6	13,0
XXIV	40	30	20	2	7	36	--	4	6	36,7
XXV	70	55	40	3	8	0	0	7	6	0

The effects of the compounds were assessed by the reduction in contractions of the vas deferns induced by transmural electrical stimulation and by adrenaline in a concentration of $1 \cdot 10^{-6}$ g/ml. The compounds were tested in a final concentration of 0.05 mM.

It was found that the dihydrochlorides of hexanediols (XXVI-XXX) blocked the transmission of stimuli via the sympathetic nerves (Table 1). It is noteworthy that compounds containing methoxy or ethoxy groups, or fluorine, in the benzene ring were more active than compounds containing the butoxy group. The dimethiodides (XXXI-XXXIV) had reduced sympatholytic activity, the most active in this instance being a compound containing butoxy groups (XXXIV).

The derivatives of hexanedione (XV-XXV) were inferior to the corresponding hexanediols (XXVI-XXXIV) in their sympatholytic activity. Only (XV), which does not contain a substituent in the benzene ring, showed good blocking activity in the transmission of stimuli via the sympathetic nerves.

The test compounds had no very marked blocking effects on the α-adrenoreceptors of the vas deferens. Furthermore, (XV) and (XXXI), like octadine, strongly enhanced the reaction of the organ noradrenaline. The activity of the most active compound (XV) was also studied in narcotized cats. It was found that when administered intravenously in doses of 0.1 and 1 mg/kg, (XV) had no effect on respiration, arterial pressure, or the tonus of the nictitating membrane. It had a brief adrenomimetic effect, and did not display any blocking effects in the postgangliar cervical sympathetic nerves.

TABLE 3. Properties of 1,6-Bisaryl-2,5-dihexamethyleneimino-methyl-1,6-hexanediones (II-VIII)

Compound	Yield, %	mp, °C	R_f	Found, %			Molecular formula	Calculated, %		
				C	H	N		C	H	N
II	89,5	—	0,6	78,46	8,91	5,83	$C_{32}H_{44}N_2O_2$	78,7	9,05	5,71
III	91,5	103—8	0,49	74,84	8,61	5,60	$C_{34}H_{48}N_2O_4$	74,48	8,81	5,12
IV	88,7	98—100	0,53	74,40	9,07	5,05	$C_{36}H_{52}N_2O_4$	74,9	9,06	4,85
V	92,0	88—90	0,54	75,54	9,21	5,14	$C_{38}H_{56}N_2O_4$	75,75	9,35	4,65
VI	84,1	77—8	0,56	76,41	9,01	4,85	$C_{40}H_{60}N_2O_4$	75,96	9,55	4,43
VII	77,6	—	0,57	75,90	10,00	4,48	$C_{42}H_{64}N_2O_4$	76,2	9,75	4,24
VIII	95,0	96—8	0,5	73,5	8,30	5,72	$C_{32}H_{42}N_2O_2F_2$	73,4	8,06	5,34

TABLE 4. 1,6-Bisaryl-2,5-dihexamethyleneiminomethyl-1,6-hexanedione Dihydrochlorides and Dimethiodides (XV-XXV)

Compound	R	mp, °C	R_f	Found, %		Molecular formula	Calculated, %	
				N	Hal		N	Hal
XV	H	169—71	0,85	4,27	13,00	$C_{32}H_{46}N_2O_2Cl_2$	4,98	12,61
XVI	OCH_3	159—62	0,86	5,09	10,81	$C_{34}H_{50}N_2O_4Cl_2$	4,51	11,4
XVII	C_2H_5O	118—20	0,84	4,11	10,40	$C_{36}H_{54}N_2O_4Cl_2$	4,31	10,95
XVIII	C_3H_7O	179—81	0,88	3,99	10,86	$C_{38}H_{58}N_2O_4Cl_2$	4,15	10,46
XIX	C_4H_9O	170—73	0,89	4,15	10,44	$C_{40}H_{62}N_2O_4Cl_2$	3,97	10,05
XX	F	175	0,84	4,82	12,06	$C_{32}H_{44}N_2O_2F_2Cl_2$	4,69	11,87
XXI	CH_3O	224—26	0,64	3,54	29,6	$C_{36}H_{54}N_2O_4I_2$	3,36	30,25
XXII	C_2H_5O	187—190	0,60	3,40	29,46	$C_{38}H_{58}N_2O_4I_2$	3,25	29,4
XXIII	C_3H_7O	140—42	0,59	3,01	28,70	$C_{40}H_{62}N_2O_4I_2$	3,14	28,6
XXIV	C_4H_9O	146—50	0,6	2,94	26,90	$C_{42}H_{66}N_2O_4I_2$	3,06	27,62
XXV	F	215	0,56	3,58	31,3	$C_{34}H_{48}N_2O_2F_2I_2$	3,46	31,4

TABLE 5. Properties of 1,6-Bisaryl-2,5-hexamethyleneimino-methyl-1,6-hexanediols (IX-XIV)

Compound	Yield, %	mp, °C	R_f	Found, %			Molecular formula	Calculated, %		
				C	H	N		C	H	N
IX	99,0	61—64	0.57	74,40	9,45	5,59	$C_{34}H_{52}N_2O_4$	73,9	9,4	5.08
X	99,3	79—82	0.62	74,65	9,31	5,01	$C_{36}H_{56}N_2O_4$	74,4	9,7	4,81
XI	98,8	68—70	0.61	75.42	10,01	4,23	$C_{38}H_{60}N_2O_4$	75,2	9,93	4,6
XII	99,5	55—58	0,67	75.20	10,4	4,21	$C_{40}H_{64}N_2O_4$	75,4	10,11	4,4
XIII	99,0	88—90	0,69	75,48	9,97	4,36	$C_{42}H_{68}N_2O_4$	75,8	10,3	4,21
XIV	97,2	—	0.65	72,53	9,1	5,42	$C_{32}H_{46}N_2O_2F_2$	72,75	8,76	5,3

There is a literature report of diaminodiketones which display slight antitumor activity [6]. It was of interest to examine the toxicities and antitumor activity of the new derivatives of this type, hexanediones (XXI-XXV).

The toxicities of the compounds were determined in white mongrel mice weighing 18-20 g following a single intraperitoneal dose. Their LD_{50} values ranged from 13 to 55 mg/kg. The most toxic compound was the methoxy derivative (XXI). As the length of the alkoxy group was increased, or when it was replaced by fluorine in the benzene ring, the toxicity was reduced (Table 2).

Antitumor activity was studied in rats with sarcoma 45 and Walker's carcinosarcoma 256, and in mice with sarcoma 180. At the end of the course of treatment the percentage inhibition of the tumor was calculated. The compounds were administered intraperitoneally. As Table 2 shows, some activity was shown by the butoxy derivative (XXIV), which suppressed the growth of sarcomas 45 and 180 by 36%. The methoxy compound (XXI) showed similar activity against sarcoma 180. None of the compounds was effective against Walker's carcinosarcoma. A slight increase in activity against sarcoma 45 was noted when the length of the alkoxy group was increased, but replacement of the alkoxy group by fluorine resulted in total loss of antitumor activity against these strains.

In addition to the measurement of these biological properties, the effects of the compounds on cardiac arrhythmia induced by electrical stimulation of the right cardiac auricle in cats narcotized with hexenal (hexobarbital) were examined. They displayed no antiarrhythmic activity.

TABLE 6. 1,6-Bisaryl-2,5-dihexamethyleneiminomethyl-1,6-hexanediol Dihydrochlorides and Dimethiodides (XXVI-XXXIV)

Compound	R	mp, °C	R_f	Found, %		Molecular formula	Calculated, %	
				N	Hal		N	Hal
XXVI	CH_3O	113—15	0,81	4,71	11,4	$C_{34}H_{54}N_2O_4Cl_2$	4,46	11,35
XXVII	C_2H_5O	109—13	0,82	3,97	11,13	$C_{36}H_{58}N_2O_4Cl_2$	4,29	10,87
XXVIII	C_4H_9O	97—100	0,82	3,54	9,64	$C_{40}H_{66}N_2O_4Cl_2$	3,95	10,00
XXIX	$C_5H_{11}O$	155—60	0,83	3,93	9,20	$C_{42}H_{70}N_2O_4Cl_2$	3,8	9,61
XXX	F	195—98	0,79	4,34	11,50	$C_{32}H_{48}N_2O_2F_2Cl_2$	4,65	11,8
XXXI	CH_3O	133—35	0,65	3,61	30,52	$C_{36}H_{58}N_2O_4I_2$	3,35	30,3
XXXII	C_2H_5O	123—25	0,63	3,29	28,9	$C_{38}H_{62}N_2O_4I_2$	3,24	29,3
XXXIII	C_3H_7O	145—48	0,65	2,87	28,7	$C_{40}H_{66}N_2O_4I_2$	3,15	28,4
XXXIV	C_4H_9O	110—12	0,68	3,16	26,9	$C_{42}H_{70}N_2O_4I_2$	3,04	27,5

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a UR-20 spectrometer (East Germany), in vaseline oil. TLC was carried out on layers of silica gel bound with gypsum, with the mobile phase butanol–ethanol–benzene–acetic acid–water (8:2:1:1:3) (for (II-VIII) and (XV-XXV); on Silufol with mobile phase butanol–ethanol–acetic acid–water (8:2:1:3) (for XXI-XXV, XXXI-XXXIV), and on grade II alumina with mobile phase benzene–isopropanol (25:5) (for IX-XIV, XXVI-XXX). The developer used was iodine vapor.

The diketones (I) required for the synthesis of (II-VIII) were obtained by the Friedel-Crafts reaction, namely, by condensation of dicarboxylic acid chlorides with substituted benzenes in the presence of $AlCl_3$ in CCl_4 or ligroin, or in the case of (I) (R = H), in benzene [7].

1,6-Bisaryl-2,5-dihexamethyleneiminomethyl-1,6-hexanediones (II-VIII). A mixture of 0.04 mole of the diketone (I), 3.6 g (0.12 mole) of paraformaldehyde, and 10.5 g (0.08 mole) of hexamethyleneimine hydrochloride in 150 ml of dioxane was boiled gently for 8-10 h. After removal of the solvent, the residue was dissolved in water and extracted with ether to remove unreacted diketone. The aqueous layer was treated with a solution of caustic alkali, extracted with ether, and the ether extracts dried over sodium sulfate. After removal of the solvent, the residue [an oil in the cases of (III) and (IV)], a crystalline solid, was recrystallized from ethanol (Table 3). The dihydrochlorides (XV-XX) (recrystallized from ethyl acetate–acetone) and dimethiodides (XXI-XXV) (from ethyl acetate) were prepared (Table 4).

1,6-Bisaryl-2,5-dihexamethyleneiminomethyl-1,6-hexanediols (IX-XIV). To a suspension of 0.04 mole (1.5 g) of lithium aluminohydride in dry ether was added dropwise with stirring 0.0175 mole of (II-VIII) in 150 ml of THF. The mixture was heated for 2-3 h, decomposed with water, the upper layer separated, and the lower layer extracted with ether (3 × 50 ml). The combined extracts were dried over anhydrous magnesium sulfate, and the residue after removal of the solvent crystallized on standing (Table 5). The dihydrochlorides (recrystallized from ethyl acetate) and dimethiodides (from ethyl acetate–ethanol, 1:1) were prepared (Table 6).

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