BIS(β-AMINOKETONES)

II. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1,8-BIS(ARYL)-2,7-BIS[MORPHOLINO(PIPERIDINO)METHYL]-1,8-OCTANEDIONE DIHYDROCHLORIDES

A. G. Agababyan, G. A. Gevorgyan
G. M. Simonyan, L. K. Durgaryan,
É. V. Vlasenko, A. A. Chachoyan,
and B. T. Gardibdzhanyan

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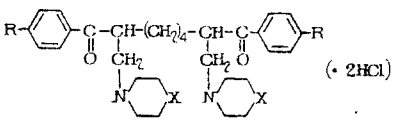
As a continuation of our search for new biologically active compounds among "coupled" aminoketones [1, 7] we synthesized 1,8-bis(aryl)-2,7-bis[morpholino(piperidino)methyl]-1-8-octanediones (I-XII) and the biological properties of their dihydrochlorides (XIII-XXIV) were examined.



I - XXIV

R=H (I, VII, XIII, XIX), OCH_3 (II, VIII, XIV, XX), OC_2H_5 (III, IX, XV, XXI), OC_3H_7 (IV, X, XVI, XXII), OC_4H_9 (V, XI, XVII, XXIII), OC_5H_{11} (VI, XII, XVIII, XXIV); X=O (I—VI, XIII—XVIII), CH_2 (VII—XII, XIX—XXIV)

The bis(β-aminoketone)I-XII derivatives of cyclic amines were synthesized in the same manner as well the corresponding dialkylamino derivatives [1], i.e., by the aminomethylation of 1,8-bis(aryl)-1,8-octandediones (XXV) in dioxane in an acid medium. Moreover, an 11-12 h period of boiling was required for the morpholine derivatives. A 6-7 h period was sufficient for most of the piperidine analogs.

The synthesized 1,8-bis(aryl)-2,7-bis[morpholine (or piperidino)methyl]-1,8-octanediones I-XII constitute crystalline substances (I-VII) or oils (VIII-XII) (Tables 1, 2).

The bases I-XII were converted to the corresponding dihydrochlorides XII-XXIV which were crystalline substances soluble in water. The latter were purified by recrystallization or reprecipitation.

The structure of the synthesized compounds was confirmed by IR-, PMR, and mass-spectrum data. The IR-spectra exhibited an intensive carbonyl group absorption band in the 1680-1670 cm^{-1} region.

The PMR spectra of compounds XII-XXIV ($CDCl_3$) have proton signals for the $(CH_2)_4$ methylene chain (1.4-1.9 ppm), for the $-\underset{|}{CH}-$ protons (4.0-4.1 ppm), for the methylene groups on the nitrogen atom $N(CH_2)_3$ (2.2-3.7 ppm) as well as for the aromatic protons (6.9-8.2 ppm). The protons of the CH_3O and $-CH_2O$ groups yield signals in the 3.8-4.2 ppm region. In addition, the compounds of the XII-XVIII morpholine series exhibit signals of the $-CH_2-O-CH_2-$ (3.4-4.0 ppm). Signals of three CH_2 groups of the piperidine ring in the 1.4-1.9 ppm region were observed in compounds XIX-XXIV.

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TABLE 1. Physicochemical Constants of 1,8-Bis(aryl)-1,8-bis(morpholinomethyl)-1,8-octanediones I-VI and Their Dihydrochlorides XIII-XVIII

Compound	Yield, %	mp, °C	Empirical formula	R_f eluent A	R_f eluent B
I	54,6	92—94	$C_{30}H_{40}N_2O_4$	—	0,14
XIII		119—121	$C_{30}N_{42}Cl_2N_2O_4$*	0,36	—
II	56,2	122—126	$C_{32}N_{44}N_2O_6$	—	0,12
XIV		192—194	$C_{32}H_{46}Cl_2N_2O_4$*	0,30	—
III	73,4	98—98,5	$C_{34}H_{48}N_2O_6$	—	0,19
XV		200—203	$C_{34}H_{50}Cl_2N_2O_6$	0,45	—
IV	52,6	94—96	$C_{36}H_{52}N_2O_6$	—	0,22
XVI		175—179	$C_{36}H_{54}Cl_2N_2O_6$	0,36	—
V	75,0	120—122	$C_{38}H_{56}N_2O_6$	—	0,17
XVII		188—190	$C_{38}H_{58}Cl_2N_2O_6$	0,27	—
VI	34,2	80—82	$C_{40}H_{60}N_2O_6$	—	0,25
XVIII		160—161	$C_{40}H_{62}Cl_2N_2O_6$	0,29	

*Calculated and mass-spectrometrically found: M^+ 492 (XIII); M^+ 552 (XIV).

TABLE 2. Physicochenmical Constants for 1,8-Bis(aryl)-1,8-bis(piperidinomethyl)-1,8-octanediones VII-XII and Their Dihydrochlorides XIX-XXIV

Compound	Yield, %	mp, °C	Empirical formula	R_f eluent B
VII	34,0	100—104	$C_{32}H_{44}N_2O_2$	—
XIX		190—192	$C_{32}H_{46}Cl_2N_2O_2$*	0,18
VIII	77,0		$C_{34}H_{48}N_2O_4$	—
XX		210—212	$C_{34}H_{50}Cl_2N_2O_4$	0,17
IX	44,0		$C_{36}H_{52}N_2O_4$	—
XXI		212—214	$C_{36}H_{54}Cl_2N_2O_4$	0,20
X	63,4		$C_{38}H_{56}N_2O_4$	—
XXII		192—196	$C_{38}H_{58}Cl_2N_2O_4$	0,22
XI	50,0**		$C_{40}H_{60}N_2O_4$	—
XXIII		182—186	$C_{40}H_{62}Cl_2N_2O_4$	0,25
XII	38,5		$C_{42}H_{64}N_2O_4$	—
XXIV		194—198	$C_{42}H_{66}Cl_2N_2O_4$	0,26

*Calculated and mass-spectrometrically found: M^+ 488.
**At 14 h of boiling.

EXPERIMENTAL (CHEMICAL)

IR-spectra were recorded on a UR-20 spectrophotometer (FRG) in the form of a paste in petroleum jelly. PMR-spectra were recorded on a Varian T-60 instrument (USA). TMS was the internal standard. Mass spectra were recorded on a MKh-1320 instrument (USSR) with a direct specimen input into the ionization region at an ionizing electron energy of 70 eV. Melting points were measured on a Boëtius type heating stand (FRG). Eluent A: n-butanol—ethanol—acetic acid—water, 8:2:1:3; eluent B: n-butyl alcohol—ethanol—acetic acid—water—ammonia, 8:2:1:3:0.5; development by iodine vapor. Element analysis data satisfied the calculated values.

The starting 1,8-bis(aryl)-1,8-octanediones XXV were obtained by method [8].

1,8-Bis(aryl)-2,7-bis(morpholinomethyl)-1,8-octanediones (I-VI) and Their Dihydrochlorides (XII-XVIII). A mixture of 0.905 mole of diketone (XXV), 4.5 g (0.15 mole) of paraformaldehyde and 12.3 g (0.1 mole) of morpholine HCl in 200 ml of dioxane acidified with 4-5 drops of HCl was heated with stirring at 90-95° for 11-12 h. The reaction mixture was treated by method A or B. Method A (for I, IV, VI): After the solvent is removed 50 ml

TABLE 3. Effect of Tested Compounds on Duration of Ethanol-Induced Lateral Position

Compound	Dose, mg/kg (v/b)	Duration of lateral position upon the simultaneous administration of alcohol and the test compound, min	p
Ethanol	3,5 g/kg	93,8±7,6	
XVI	20	60,6±5,9	<0,05
	30	54,4±3,8	<0,05
	50	69,4±6.5	<0,05
XXII	20	64,9±3,5	<0,05
	30	67,9±4,3	<0,05
Teturam	10	73,2±5,09	<0,05
	20	84,0±5,3	>0,05

of water is added to the residue. The starting ketone is filtered off and the aq. solution is extracted with ether. Then the aq. layer is made alkaline with a 40% solution of NaOH and is extracted with ether. After drying, the solvent is removed from the ether extract, and the morpholine excess is then extracted under reduced pressure. The crystalline base is purified by trituration in ether and then recrystallized from ethanol. For conversion to the hydrochloride the base is preliminarily dissolved in a 1:3 abs. ethanol - abs. ether mixture. The dihydrochlorides XIII, XVI, XVIII were recrystallized from a 1:1 ethylacetate–acetone mixture. Method B (for II, III, V): In the course of the reaction crystalline dihydrochlorides of XIV, XV, and XVII precipitate. The hydrochlorides are filtered off, washed with ether, and recrystallized from a 1:1 abs. ethanol–acetone mixture. The dioxane solution is then treated as indicated above. The base of II, III, and V was obtained from the dihydrochloride. Constants are given in Table 1.

1,8-Bis(aryl)-2,7-bis(piperidinomethyl)-1,8-octanediones (VII-XII) and their hydrochlorides (XIX-XXIV) were obtained by a manner similar to that of the above-described compounds by method A (VII, VIII, X-XII) or by method B (IX). Constants are given in Table 2.

EXPERIMENTAL (BIOLOGIAL)

The dihydrochlorides of bis(β-aminoketones) XIII-XXIV represent interesting potential local and general anesthetics as well as antimorphine and chemotherapeutic agents.

Local anesthetic activity in conduction anesthesia was examined at a concentration of 0.25% on isolated frog nerves [4]. Novocaine was used as the control.

Surface-anesthetic activity of the compounds in the form of a 1% solution was tested on rabbit cornea by the Renier method [5]. The test results were compared to dicaine.

Central anesthetic action of the compounds was tested on a "hot plate" model at a dose of 30 mg/kg ip [10]. Morphine was the control.

Morphine antagonist activity (5 mg/kg, ED_{99}) was tested on a rat tail mechanical irritation model at a dose of 10 mg/kg upon subcutaneous administration [9]. Naloxon was used as the control.

The antialcohol action of the substances was tested on models of acute and chronic alcohol intoxication [2, 3].

The chemotherapeutic experiments were conducted by the recognized method [6] on white non-pedigree rats (weighing 90-120 g) and mice (weighing 18-21 g) of both sexes.

The absolute lethal dose L_{100} was measured upon a single ip administration. This also defined the therapeutic dose of the compounds. Antitumor activity was tested on rats with sarcoma 45, Walker's carcinosarcoma, and Pliss's lymphosarcoma, and on mice with sarcoma 37 and Ehrlich's ascitic carcinoma.

Compounds XIII, XV-XXIV were administered ip to the rats (8 times) and to the mice (6 times) once a day (dose $^1/_{20}$ and $^1/_{10}$ of the LD_{100} respectively) in the form of a suspension prepared in a 0.5% solution of CM-cellulose. The therapeutic effect of each compound was evaluated by the percent at which solid tumor growth was inhibited (T%) or by the prolonged longevity of mice (PL, %) in comparison to the control

TABLE 4. Dynamics of 10% Alcohol and Water Consumption by Alcoholized Animals (in ml; M ± m)

Experimental conditions	Water consumption				Ethanol consumption			
	before administration of compound		after administration of compound		before administration of compound		after administration of compound	
	1st week	4th week*	1st week	2nd week	1st week	4th week	1st week	2nd week
Ethanol	37,9±0,79	15,7±0,7	17,3±1,4	21,1±1,6	9,2±0,98	24,6±4,4	23,4±4,03	22,9±4,7
Teturam	32,1±1,5	14,7±0,85	13,9±1,7*	7,2±3,04*	10,01±0,68	21,5±2,4	13,8±0,6*	2,5±0,3*
Compound XVI	28,1±1,6	15,2±1,2	16,4±1,2	15,4±1,5	6,6±0,92	20,2±2,2	18,3±1,7	14,4±1,2*

*Difference significant at $p < 0.05$.

The resultant data were statistically processed by the Student-Fisher method.

The test results on surface anesthetic and central anesthetic activity demonstrated that the tested compounds do not possess these properties.

The local anesthetic activity tests showed that compounds XIII, XIX, and XX were the most effective on conduction anesthesia. Their activity was 62, 30, and 29% respectively whereas that of novocaine was 92%.

Compounds XVI, XXII, and XXIV exhibited the greatest antagonism to opioids. Their activity was equal to 46.6, 46.9, and 36.7% respectively. Naloxon at a dose of 3 mg/kg exhibited an activity of 95%.

The results for antialcohol activity in the acute series of experiments are given in Table 3 and demonstrate that a simultaneous administration of ethanol and compounds XVI and XXII reliably reduces the duration of the animals' lateral position by 42.6 and 31.5% respectively. In the chronic series of experiments, addiction was considered complete in the 4th week where, under conditions of free choice of water and 10% alcohol, after 10 days of ip administration of a 25% solution of alcohol, the rats consistently preferred alcohol (Table 4). Following the administration of compound XVI alcohol consumption decreased by 28.8% in the 2nd week. Water consumption remained at the same level, although there was some reduction in comparison in the control group.

Thus, compounds XVI and XXII reduce the lateral position duration by 42.6 and 31.5% and compound XVI in the chronic experiment suppresses addiction to alcohol by 28.8%.

The acute toxicity test results for morpholine-containing dihydrochlorides of bis-β-aminoketones XIII, XV-XVIII showed that among those compounds the unsubstituted XIII compound and the butoxy derivative XVII turned out to be toxic (LD_{100} 200-250 mg/kg). The absolute lethal dose of the remaining compounds was 100 mg/kg regardless of the nature of the radical.

The antitumor activity tests for compounds XIII, XV-XVIII showed that all of them are ineffective at therapeutic doses against Walker's carcinosarcoma and Ehrlich's ascitic carcinoma. Some of them exhibited slight activity (T% = 33-45) in the tests on sarcoma 37 and Pliss's lymphosarcoma. In the sarcoma 45 test compounds with ethyoxy- and butoxy radicals (XV, XVI) exhibited a pronounced therapeutic action and suppressed tumor growth by 68%. In contrast to the morpholine-containing compounds, the piperidin-containing dihydrochlorides of bis(β-aminoketones)XIX-XXIV proved to be highly toxic (LD_{100} 40-300 mg/kg). They were inactive against Ehrlich's ascitic carcinoma. The dihydrochlorides with methoxy, butoxy or amyloxy (XX, XXIII, XXIV) radicals manifested only slight antitumors activity against sarcoma 45 whose tumor growth was suppressed by 30-50%. Compounds with ethoxy and butoxy radicals (XXI, XXIII) exhibited reliable anittumor activity against sarcoma 37 and Walker's carcinosarcoma. Tumor growth in these cases was suppressed by 61%.

Thus, our experimental data point to the promising nature of synthesizing dihydrochlorides of bis(β-aminoketone) that exhibit conduction anesthesia, antagonist activity to opiates, antialcohol activity as well as antitumor properties among the aminoketones.

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SYNTHESIS OF 1-(β-AMINOETHYL)- AND 1-(γ-AMINOPROPYL)-4-(CYANOETHOXYCARBONYL)METHYLENEPYRIMIDINE DERIVATIVES AS POTENTIAL ANTIHISTAMINICS

L. V. Ershov and V. G. Granik

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Recently we worked out a new approach to the synthesis of 1-substituted 4-methylenepyrimidines which is based upon condensation of dimethylformamide diethylacetal with the primary amino and β-methyl groups of α-ethoxycarbonyl-β-amino-β-methyl-acrylonitrile and cyclization of amidinodienediamine (I) obtained with strongly basic primary amines [1].

On the basis of the fact that for the development of antihistaminic activity the structure of the compounds under investigation frequently has to contain an aromatic or heterocylic ring substituted with an ω-aminoalkyl group [11] and as heterocycle a pyrimidine moeity [4, 9, 12, 13], we have attempted to synthesize substituted 4-methylenepyrimidines of that type with the purpose of studying their antihistaminic activity.

Dieneaminoamidine I was reacted with aminoethanol and N-acetylethylenediamine, as a result of which 1-β-hydroxyethyl-(IIa) and 1-β-acetaminoethyl- (IIb) -4-(cyanoethoxycarbonyl)-methylenepyrimidines were obtained. β-Hydroxyethyl derivative IIa was converted with $SOCl_2$ to corresponding β-chloro derivative (IIc). By alkylation of IIc with piperidine, morpholine, and 4-benzhydrylpiperazine corresponding β-aminoethyl derivatives (IId-f) were prepared.

Compounds containing a γ-aminoporpyl side-chain at position 1 of the pyrimidine ring (IIg-i) were synthesized by reaction of I with γ-(4-benhydrylpiperazino)-, γ-piperidino-, and γ-morpholinopropylamines [5, 6], which were prepared by alkylation of the corresponding secondary amines with acrylonitrile and subsequent reduction of the intermediate β-aminonitriles with Raney nickel and $NaBH_4$ according to [8].

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