SYNTHESIS OF 1,8-DIARYL-2,7-DI(HEXAMETHYLENEIMINOMETHYL)-1,8-OCTANEDIONES AND THEIR ANAESTHETIC PROPERTIES

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Aminomethyl derivatives of substituted pentane- and hexanediones with weakly expressed sympatholytic, antitumorigenic and antibacterial activity have previously been synthesized in [4, 5].

A newly revealed property of "binary" molecules of β-amino ketones, their antinarcotic effect [6], opens new prospects in the search for potential biologically active compounds in the series of β-diamino diketones.

For this purpose, we synthesized in the present work, 1,8-diaryl-2,7-di(hexamethyleneiminomethyl)-1,8-octanediones (I-VII), and studied the biological properties of their dihydrochlorides (VIII-XIV).

$$[p\text{-}RC_6H_4COCH(CH_2N(CH_2)_6)CH_2CH_2—]_2$$

I—VII

R = H (I, VIII), OMe (II, IX), OEt (III, X), OPr (IV, XI), OBu (V, XII), OAm (VI, XIII), F (VII, XIV).

Compounds I-VII were synthesized by aminomethylation of 1,8-diaryl-1,8-octanediones (XV-XXI), using paraformaldehyde and hexamethyleneimine hydrochloride in a dioxane medium.

Compounds I-IV, VI, VII are white crystalline substances with an unpleasant odor, and are insoluble in water. Compound V is a thick oil, which decomposes during distillation. Compounds I-VII were converted into the corresponding dihydrochlorides VIII-XIV by the action of an ether solution of HCl.

Compound VII was reduced by $LiAlH_4$ in an absolute ether—THF medium to 1,8-di(p-fluorophenyl)-2,7-di(hexamethyleneiminomethyl)-1,8-octanediol (XXII), which was converted into the corresponding dihydrochloride (XXIII).

Compounds VIII-XIV, XXIII are white crystalline substances, which are soluble in water. In the IR spectra of compounds I-XIV there is an absorption band of the carbonyl group in the 1685-1670 cm^{-1} region, while in the IR spectrum of compound XXIII, the absorption band of the CO group is absent and an absorption band is observed in the 3400-3200 cm^{-1}, characteristic of the OH group.

The molecular weight of compound I was determined mass-spectrometrically (M^+ 516).

Generalizing the results of biological tests, it should be noted that the compounds VIII-XIV have antimorphinic action, with the exception of II; in contrast with the analogous monostructural β-amino ketones, which show high activity in infiltration anaesthesia [2], they do not have a local anaesthetic effect. Diamino diketones XIII-XIV are slightly toxic compounds, having a local irritant effect in high concentrations.

The previously discovered [6] new property of diamino diketones, their antinarcotic effect, is also characteristic of the dihydrochlorides VIII-XIV.

EXPERIMENTAL (CHEMICAL)

The IR spectra were run on a UR-20 spectrophotometer (GDR) in mineral oil, the mass spectra on a MX-1320 mass spectrometer with direct introduction of the samples into the ionization zone, at an energy of 60 eV of the ionizing electrons and at their melting points.

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TABLE 1. 1,8-Diaryl-2,7-di(hexamethyleneiminomethyl)-1,8-octanediones I-VII and Their Dihydrochlorides VIII-XIV

Compound	Yield, %	mp, °C	R_f	Found, %				Empirical formula	Calculated, %			
				C	H	N	Cl		C	H	N	Cl
I	43,9	78—82	0,63	78,81	9,04	5,58		$C_{34}H_{48}N_2O_2$	79,01	9,34	5,52	
II	52,3	86—90	0,70	75,20	9,50	5,00		$C_{36}H_{52}N_2O_4$	74,91	9,06	4,85	
III	59,5	83—8	0,69	76,04	9,95	4,70		$C_{38}H_{56}N_2O_4$	75,52	9,32	4,63	
IV	45,6	75—8	0,71	75,53	9,99	4,72		$C_{40}H_{60}N_2O_4$	75,96	9,55	4,43	
V	63,5	oil	0,70	76,40	9,50	4,11		$C_{42}H_{64}N_2O_4$	76,21	9,75	4,24	
VI	47,2	66—7	0,72	75,98	10,07	3,40		$C_{44}H_{68}N_2O_4$	76,60	9,96	4,07	
VII	54,8	68—70	0,73	74,06	8,80	5,36		$C_{34}H_{46}F_2N_2O_2$	73,81	8,36	5,07	
VIII	92,0	160—4	0,73			4,81	11,61	$C_{34}H_{48}N_2O_2 \cdot 2HCl$			4,76	12,07
IX	94,1	176—7	0,71			4,52	10,60	$C_{36}H_{52}N_2O_4 \cdot 2HCl$			4,32	10,96
X	93,9	177—9	0,74			3,96	9,94	$C_{38}H_{56}N_2O_4 \cdot 2HCl$			4,14	10,40
XI	93,0	171—2	0,78			3,80	10,00	$C_{40}H_{60}N_2O_4 \cdot 2HCl$			3,97	10,05
XII	56,5	173—6	0,85			4,09	10,10	$C_{42}H_{64}N_2O_4 \cdot 2HCl$			3,80	9,68
XIII	93,2	166—9	0,87			3,95	8,91	$C_{44}H_{68}N_2O_4 \cdot 2HCl$			3,72	9,41
XIV	92,0	162—5	0,80			4,80	10,80	$C_{34}H_{46}F_2N_2O_2 \cdot 2HCl$			4,45	11,32

Note. Compounds I-XIV were obtained in the form of stereoisomers, which could not be separated.

TABLE 2. Pharmacological Characteristic of Dihydrochlorides of 1,8-Diaryl-2,7-di(hexamethyleneiminomethyl)-1,8-octanediones VIII-XIV

Compound	Infiltration anaesthesia EC_{50}, %	Surface anaesthesia, Reniéux units	Analgesia, mm, Hg	Antagonism to morphine in ED_{99}, %	LD_{50}, mg/kg	Local anaesthetizing action
Novocaine	0,05 (0,029—0,078)	34,5	20±0,48	0	192 (176,6—208,7)	—
Dicaine	0,11 (0,004—0,027)	1300	—	—	20 (17,7—22,6)	+++
Morphine	0,38 (0,32—0,45)	0	68,3±1,2	0	440 (408,5—483,9)	—
VIII	0	0	15,5±1,7	10	326 (271,6—391,2)	++++
IX	43 (0,26—0,64)	79	8,5±2,6	45,4	230 (193,3—273,7)	++++
X	0	81	10,8±1,5	36,9	320 (254—403,2)	++++
XI	0	0	9,4±1,2	15	235 (174,07—317,2)	++++
XII	0	0	9,8±1,2	0	252 (208,3—304,9)	+++
XIII	0	0	10,1±1,3	0	270 (225—324)	+++
XIV	0	316	16,5±1,8	24,6	312 (305,8±318,24)	++++

Note. — Absence of local-irritating action, +++ point necrosis, ++++ strong necrosis.

The TLC was carried out on a stationary layer of silica gel, gypsum, with the ether–methanol–water–hydrochloric acid system (5:3:1.5:0.4) as the mobile phase (for compound XIV) and on aluminum oxide, grade II activity with benzene–isopropanol (25:5) as the mobile phase (for compound XXIII). Iodine vapors were used to develop the chromatograms.

1,8-Diaryl-2,7-di(hexamethyleneiminomethyl)-1,8-octanediones (I-VII) and Their Dihydrochlorides (VIII-XIV). A mixture of 0.04 mole of diketone XV-XXI, 3.6 g (0.12 mole) of paraformaldehyde, 10.5 g (0.08 mole) of hexamethyleneimine hydrochloride in 100 ml of dioxane is heated at 85-95°C for 8-10 h. The solvent is removed at reduced pressure. The residue is dissolved in 75-100 ml of water, and the solution is extracted with ether (2 × 50 ml). The aqueous layer is shaken with activated carbon, filtered and the filtrate is made alkaline with 40% alkali to pH 10.0 according to universal indicator paper, and extracted with ether (3 × 75 ml). The ether extract is dried over anhydrous Na_2SO_4. Compounds I-VII are obtained from the ether solution after the evaporation of the solvent, in the form of thick oils, which solidify on prolonged standing. The compounds are purified by grinding in 30-50 ml of cold ethanol (Table 1).

Compounds I-VII are converted into the corresponding dihydrochlorides VIII-XIV by the action of an ethereal solution of HCl. These are recrystallized from an ethyl acetate–acetone, 30:5, mixture (see Table 1).

1,8-Di(p-fluorophenyl)-2,7-(hexamethyleneiminomethyl)-1,8-octanediol (XXII) and Its Dihydrochloride (XXIII). A solution of 9.7 g (0.0175 mole) of compound VII in 150 ml of THF is added dropwise, with stirring, to a suspension of 1.5 g (0.04 mole) of $LiAlH_4$ in 150 ml of absolute ether. The mixture is boiled for 3-4 h, decomposed with water, the ether layer is decanted, and the aqueous layer is extracted with ether (3 × 50 ml). The combined ether extracts are dried over anhydrous $MgSO_4$. After the distillation of the solvent, 9.5 g (97.5%) of an oily product XII are obtained. Found, %: C 73.0, H 9.20, N 5.45. $C_{34}H_{50}F_2N_2O_2$. Calculated, %: C 73.25, H 9.02, N 5.03.

The dihydrochloride (XXIII) is hygroscopic, mp 60°C (ethyl acetate–acetone). Found, %: N 5.08, Cl 10.88. $C_{34}H_{50}F_2N_2O_2 \cdot 2HCl$. Calculated, %: N 4.45, Cl 11.28, R_f 0.80.

EXPERIMENTAL (PHARMACOLOGICAL)

The pharmacological characteristics of the synthesized compounds were established from anaesthesiometry and analgesiometry tests; their antagonistic activity towards narcotic analgetics, as well as the acute toxicity and local-irritant effect were evaluated.

The investigation of their local anaesthesizing activity with respect to infiltration anaesthesia was carried out on isolated nerves of a frog [1]. The concentration of a compound was determined which blocks the potential of an effect caused by a supramaximal irritation of the nerve to the extent of 50% (EC_{50}). Novocaine was used as the control preparation. The experimental results given in Table 2 showed that only compound IX exhibited a weak local anaesthetizing activity.

The surface-anaesthetic action of the compounds in a 1% concentration was determined on a cornea of a rabbit [3]. Dicain was used as a control preparation. Activity was established only for compound XIV. However, in high concentrations, this compound exhibits a local irritant effect.

Study of the central anaesthetic action of the compounds on a model of a mechanical irritation of the tail of a rat [7] weighing 110-120 g, with subcutaneous administration in doses of 10 and 30 mg/g showed that these compounds have no analgetic properties.

The antimorphinic action of the compounds tested was studied on a model of suppression of the analgetic effect of morphine. It was found that the compounds are characterized by possession of antimorphinic activity. The antagonistic action with respect to opioides is most strongly manifested in compound IX (see Table 2), which in a dose of 10 mg/kg administered subcutaneously, suppressed the morphinic analgesia to the extent of 45.4%. Increased doses of the compound were masked by development of toxic effects. The control preparation naloxone in a dose of 3 mg/kg suppressed the analgesia on this model to the extent of 99%.

The acute toxicity of the compounds was determined on white mice by intraperitoneal method of administration. The data obtained showed that they have a lower acute toxicity than novocaine. The local irritant effect of the compounds was studied on guinea pigs [8].

The experimental results recorded 1, 3, and 24 h after administration, showed that in low concentrations (0.1-0.5%) the compounds do not exhibit a local irritant effect. In 1% concentrations a point necrosis and in 2% concentrations a strong necrosis is observed (in compounds XII, XIII – a point necrosis).

The compounds studied do not have anti-inflammatory or antibacterial activity.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-ALKYL DERIVATIVES OF 2,3,4,5-TETRAHYDRO-1H-1,5-BENZODIAZEPIN-2-ONE

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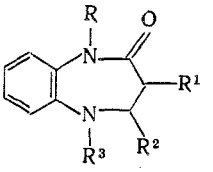
It is known that derivatives of the bicyclic system of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one are characterized by different kinds of physiological activity [9]. We have previously published [6] a study on the anti-inflammatory activity of N-acylderivatives of tetrahydrobenzodiazepinones. At the same time it was reported that 1-dialkylaminoalkyl substituted benzodiazepinones are prospective analgesics and antiphlogistics [13].

The aim of the present work was to synthesize derivatives of 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-ones (IV-XXII) containing alkyl substituents at the 1- and 1,5-positions of the heterocyclic ring, and to study their biological properties. We have developed for this purpose preparative methods for introducing the alkyl substituents into the 1-position of the benzodiazepine ring. Compounds IV-XVI were obtained by the alkylation of 5-acetyl-2,3,4,5-tetrahydro-1,5-benzodiazepin-2-ones (I-III) [6, 10, 11] under conditions of interphase catalysis.



I – XXII

R=H (I—III, XXI), CH_2Ph (IV, XV, XVI), Me (V, XIX, XX), Et (VI, XVII), Pr (VII), Pr-i (VIII), Bu (IX), Bu-i (X), Am-i (XI), $CH_2CH{=}CH_2$ (XII, XVIII), $(CH_2)_2NEt_2$ (XIII), $(CH_2)_3OPh$ (XIV), CH_2CH_2OH (XXII); R^1 = H (I—XVIII, XX—XXII), Me (XIX); R^2 = H (I, IV—XIV, XVII—XIX, XXI, XXII), Me (II, XV, XX), Ph (III, XVI); R^3 = H (XVII, XVIII), Ac (I—XVI, XXII), Me (XIX, XX), Et (XXI).

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