SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF QUATERNARY AMMONIUM SALTS OF CERTAIN BISINDOLES AND PYRROLOINDOLES OF DIFFERENT STRUCTURES

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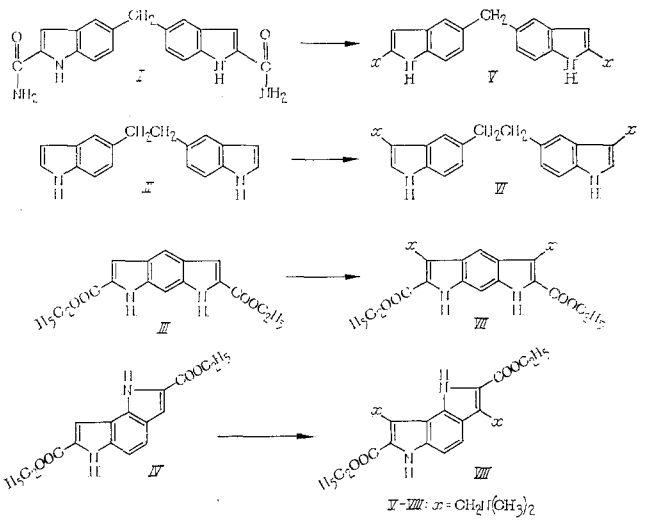
UDC 615.216.5:547.759.1].012.1

In the preceding papers [1, 2], it has already been reported that certain pyrroloindole and bisindole quaternary ammonium salts exhibit curarelike properties. In continuation of these investigations, we prepared bisgramines V-VIII by the Mannich reaction from the previously synthesized by us bisindoles I, II [3, 4] and pyrrolindoles III, IV [5, 6], and the bisgramines were then converted into the corresponding bisquaternary trimethylammonium salts IX-XII.



V-VIII: x = $CH_2N(CH_3)_2$

We have already reported [1] the synthesis and curarelike properties of bisgramine based on bis(5-indolyl)methane with dimethylaminomethyl groups at the 3-position of the indole ring. To obtain isogramine V based on bis(5-indolyl)methane with dimethylaminoethyl groups at the 2-position, we carried out an aminolysis of a diacid chloride of 2,2'-dihydrocarbonyl-bis(5-indolyl)methane [7] by an aqueous solution of dimethylamine, followed by lithium aluminum hydride reduction of amide I formed. Since amide I is slightly soluble in THF, the reduction is carried out in a Soxhlet extractor. Amide I, placed in the extraction tube gradually dissolves in a hot THF and is reduced to amine V in a quantitative yield.

The structure of compounds synthesized was confirmed by IR, UV, and PMR spectral data. The molecular weights were determined mass-spectrometrically.

To study the pharmacological properties, bigramines V, VII, and VIII were converted into water-soluble quaternary salts, dimethylsulfates IX, XI, and XII by the action of dimethyl sulfate, and bisgramine VI into diiodomethylate X. For comparison, we also studied the known 3,8-di(trimethylammoniummethyl)-1H,6H-indolo[7,6-g]indole dimethylsulfate (XIII) [8].

The S. Ordzhonikidze Scientific-Research Chemical-Pharmaceutical Institute, Tbilisi University, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 1, pp. 29-31, January, 1984. Original article submitted June 23, 1983.

 0091-150X/84/1801-0014$08.50

The course of the reaction and the purity of the compounds were controlled and the R_f was determined by the TLC method on Silufol UV-254. The IR spectra were run on the UR-20 spectrophotometer (GDR) in mineral oil, the UV spectra on the Specord spectrophotometer in ethanol, and the PMR spectra on the CFT-20 Varian spectrometer (USA), using TMS as internal standard.

The mass spectra were run on the MX-1303 apparatus with a modified system of sample introduction (direct introduction into the ion source) at an energy of ionizing electrons of 50 eV.

2,2'-Di(dimethylaminocarbonyl)-bis(5-indolyl)methane (I). A solution of 1.48 g (4 mmoles) of the diacid chloride of 2,2'-dihydroxycarbonyl-bis(5-indolyl)methane in 20 ml of dioxane is added slowly, with stirring, to 30 ml of cold aqueous solution of dimethylamine. Stirring is continued for 2 h. The white precipitate that separates is filtered, washed with water to pH 7.0, and dried over KOH. Yield, 1.3 g of (I) (84%), mp 315-317°C. R_f 0.37 (benzene—acetone, 1:1). IR spectrum, ν, cm^{-1}: 3310 (NH of indole), 1650 (shoulder), 1620 (C=O). Found, %: C 71.5; H 6.1; N 14.4. $C_{23}H_{24}N_4O_2$. Calculated, %: C 71.1; H 6.2; N 14.4.

2,2'-Bis(dimethylaminomethyl)-bis(5-indolyl)methane (V). The synthesis is carried out in a Soxhlet extractor. A 0.55-g portion (1.7 mmoles) of amide is placed in the extraction tube and 0.38 g (10 mmoles) of lithium aluminum hydride and 250 ml of THF are placed in a flask. The mixture is boiled for 20 h. When cool, 3 ml of water are added, and the mixture is left to stand overnight. It is then filtered and the precipitate washed with THF. The filtrate and THF washings are combined and evaporated to 10 ml. The solution obtained is added, with stirring, to a dilute solution of hydrochloric acid, and the mixture is filtered. The filtrate is then poured into a dilute solution of alkali. The precipitate is filtered and washed to pH 7.0, and dried over NaOH. Yield, 0.48 g (94%) of V, mp 101-102°C. IR spectrum, ν, cm^{-1}: 3420 (NH of indole), 1440, 1460 (aliphatic CH). PMR spectrum, δ, pm (in acetone-d_6): 9.9 (1-H); 6.16 (3-H, dd); 7.28 (4-H, d); 6.9 (6-H, dd); 7.21 (7-H, d); 4.04 (CH_2, s); 3.50 (CH_2-N, d); 2.18 (CH_3-N, s); $J_{1,3}$ = 1.8 Hz, J_{3,CH_2} = 0.5 Hz, $J_{4,6}$ = 1.5 Hz, $J_{6,7}$ = 8.2 Hz. Found, %: C 76.3; H 8.0; N 15.4. M^+ 360. $C_{23}H_{28}N_4$. Calculated, %: C 76.6; H 7.8; N 15.5. M 360.

3',3-Di(dimethylaminomethyl)-1,2-(5',5-diindolyl)ethane (VI). A 4.7-g portion (50 mmoles) of N,N-dimethyl-methyleneimmonium chloride is added to a solution of 2.60 g (10 mmoles) of II in 50 ml of dry dimethylformamide, and the mixture is stirred for 2-3 h at 20°C. The mixture is diluted with cold water and made alkaline to pH 10.0. The precipitate is filtered, washed with water to pH 7.0, and dried *in vacuo* over KOH. Yield, 3.7 g (97%) of VI, mp 358-359°C (dec). IR spectrum, ν, cm^{-1}: 3430 (NH). UV spectrum, λ_{max}, nm: 227; 277; 289.8; 298.5. PMR spectrum, δ, ppm (in d-DMSO): 10.5 (1H, br s); 7.36 (2H, d); 3.47 (N-CH_2, s); 2.12 (N-CH_3, s); 7.05 (4H, d); 6.91 (6H, dd); 7.19 (7H, d); 2.95 (CH_2, s); $J_{4,6}$ = 1.5 Hz; $J_{4,7}$ = 0.3 Hz; $J_{6,7}$ = 8.2 Hz. Found, %: C 77.1; H 8.0; N 14.8. M^+ 374. $C_{24}H_{30}N_4$. Calculated, %: C 77.0; H 8.0; N 14.9. M 374.

3,5-Di(dimethylaminomethyl)-2,6-diethoxycarbonyl-1H,7H-pyrrolo[3.2-f]-indole (VII). A solution of 0.6 g (2 mmoles) of III in 35 ml of dry acetonitrile is added dropwise to a suspension of 0.56 g (6 mmoles) of N,N-dimethyl-methyleneimmonium chloride, $[CH_2{=}N^+(CH_3)_2]Cl^-$, in 30 ml of dry acetonitrile. The mixture is stirred for 3 h at room temperature, the solvent is decanted, and the precipitate is dissolved in 100 ml of water. The solution is made alkaline to pH 11.0-12.0 by a 10% solution of NaOH, and extracted with ether. The ether extract is dried over Na_2SO_4 and evaporated. Yield, 0.68 g (82%) of VII. Colorless crystals, mp 184-185°C, R_f 0.53 (acetone—33% aqueous solution of ammonia, 300:1). IR spectrum, ν, cm^{-1}: 3330 (NH), 1690 (CO). UV spectrum, λ_{max}, nm (log ε): 232 (4.31); 303 (4.30); 337 (4.03) shoulder; 350 (4.20). PMR spectrum, δ, ppm (in DMSO-d_6): 10.66 (1H, 7H, br s); 7.32 (4H, s); 8.10 (8H, s); 4.94 (CH_2N, s); 2.21 (CH_3N, s); 1.37 (CH_3Et, t); 3.33 (CH_3Et, q), $J_{CH_2CH_3}$ = 7 Hz. Found, %: C 64.5; H 7.4; N 13.6. M^+ 414. $C_{22}H_{30}N_4O_4$. Calculated, %: C 63.8; H 7.2; N 13.5. M 414.

3,8-Di(dimethylaminomethyl)-2,7-diethoxycarbonyl-1H,6H-pyrrolo[2,3-e]indole (VIII) is obtained by the procedure described in [9], mp 167-168°C, which corresponds to the literature data.

2,2'-Di(trimethylammoniummethyl)-bis(5-indolyl)methane Dimethyl Sulfate (IX). A 1-ml portion of freshly distilled dimethyl sulfate is added to a solution of 0.72 g (2 mmoles) of amine V in 50 ml of THF, and the mixture is stirred for 1 h and then diluted with 50 ml of ether. The precipitate is filtered and dried in vacuo. Yield, 1.2 g (97%) of IX, mp 196-198°C. Found, %: C 52.7; H 6.7; N 9.3; S 10.1. $C_{27}H_{40}N_4O_8S_2$. Calculated, %: C 52.9; H 6.6; N 9.2; S 10.4.

3,3'-Di(trimethylammoniummethyl)-1,2-(5,5'-diindolyl)ethane Diiodide (X). A 1-ml portion of freshly distilled methyl iodide is added dropwise to a solution of 0.37 g (1 mmole) of VI in 0.1 liter of ethanol. The mixture is stirred for another 1 h, and diluted with 0.2 liter of dry ether. The precipitate is filtered, washed with dry ether, and dried *in vacuo*. Yield, 0.6 g (90%) of X, decomp. temp. 230-232°C. IR spectrum, ν, cm^{-1}: 3410-3435 (NH); 1715 (C=O). UV spectrum, λ_{max}, nm: 223; 289.8; 310. Found, %: C 47.5; H 5.5; N 8.5; I 38.5. $C_{26}H_{36}N_4I_2$. Calculated, %: C 47.4; H 5.5; N 8.5; I 38.6.

3,5-Di(trimethylammoniummethyl)-2,6-diethoxycarbonyl-1H,7H-pyrrolo[3,2-f]indole Dimethyl Sulfate (XI). A 0.4-g portion (1 mmole) of compound VII is dissolved in 40 ml of absolute ethanol and 0.32 g (2.5 mmoles) of dry diethyl sulfate are added. The mixture is stirred for 3 h and diluted with 0.5 liter of dry ether. The precipitate is filtered, washed with dry ether, and dried. Yield, 0.58 g (91%) of XI, decomp. temp. 170°C. Found, %: C 46.6; H 6.5; N 8.5; S 9.2. $C_{26}H_{42}N_4O_{12}S_2$. Calculated, %: C 46.9; H 6.3; N 8.4; S 9.6.

3,8-Di(trimethylammoniummethyl)-1H,6H-pyrrolo[2,3-e]indole Dimethyl Sulfate (XII). This is obtained in the same way as compound XI from 2.07 g (5 mmoles) of VIII, 220 ml of absolute ethanol, and 1.39 g (11 mmoles) of dry dimethyl sulfate. Yield, 1.73 g (52%) of XII, decomp. temp. 57°C. Found, %: C 46.9; H 6.1; N 8.8; S 9.5. $C_{26}H_{42}N_4O_{12}S_2$. Calculated, %: C 46.9; H 6.3; N 8.4; S 9.6.

3,8-Di(trimethylammoniummethyl)-1H,6H-indolo[7.6-g]indole Dimethyl Sulfate (XIII). This is obtained by the method described in [9], decomp. temp. 165°C, which corresponds to the literature data.

EXPERIMENTAL PHARMACOLOGY

In experiments on cats narcotized intraperitoneally with urethane (0.6-0.7 g/kg) and chloralose (30-40 mg/kg), we studied the curarelike properties of the compounds by the method already described in [1]. We also studied the influence of the compounds on arterial pressure and respiration. The toxicity was determined on mice and LD_{50} was calculated [10]. The compounds were administered intravenously.

EXPERIMENTAL RESULTS

Compounds IX-XII block the neuromuscular transmission in narcotized cats in doses shown in Table 1. In these doses they cause a gradual depression, and eventual standstill of res-

TABLE 1. Curarelike Activity and Toxicity of Bisquaternary Indole Derivatives

Compound	Narcotized cats	Mice
	dose causing block neuromuscular transmission and respiration standstill, mg/kg	LD_{50}, mg/kg
IX	10	11,4
X	7	8,5
XI	20	17,9
XII	5	2,9
XIII	1—2*	9,1

*Causes heart standstill [9].

piration. Compound XIII does not influence the neuromuscular transmission; 3-5 min after its introduction in doses of 1-2 mg/kg, the heart stops and the animal dies.

Compounds IX-XI, in small doses equal to 1-2 mg/kg, cause a short-term increase of 40-80 mm Hg in the arterial pressure and excitation of respiration. These effects are prevented by ganglio-blocking preparation hexonium (0.3-0.5 mg/kg) or temequine (0.2 mg/kg). Hence, the arterial hypertension and intensification of respiration are caused by excitation of ganglia and formations related to them, i.e., nicotinelike properties of the compounds. In contrast, compound XII decreases the arterial pressure and after its administration, the nicotinelike preparation, cytisine (15 μg/kg), does not lead to increase in pressure and respiration excitation. Hence, compound XII exhibits ganglio-blocking action.

The results of our investigation presented in the present article and in earlier papers [1, 2] show that among the bisquaternary ammonium derivatives of indole there are compounds with moderately pronounced curarelike, ganglio-blocking, and nicotinelike properties.

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SYNTHESIS, STRUCTURE, AND BIOLOGICAL ACTIVITY OF α-ACYL DERIVATIVES OF β-N-R-OXAMOYLPHENYLHYDRAZINES

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UDC 615.276:547.556.8].012.1

In a search for biologically active compounds, we synthesized a series of new α-acyl-β-N-R-oxamoyl derivatives of phenylhydrazine [1].

The synthesis was carried out by acylation of β-N-R-oxamolyphenylhydrazines [1] by carboxylic acid chlorides in dry chloroform in the presence of triethylamine:

II, a: R = CH_3, R^1 = butyryl; b: R = C_3H_7, R^1 = butyryl; c: R = iso-C_3H_7, R^1 = butyryl; d: R = C_4H_9, R^1 = butyryl; e: R = iso-C_4H_9, R^1 = butyryl; f: R = cyclohexyl, R^1 = butyryl; g: R = CH_3, R^1 = valeryl; h: R = iso-C_3H_7, R^1 = valeryl; i: R = C_4H_9, R^1 = valeryl; j: R = iso-C_4H_9, R^1 = valeryl; k: R = $C_6H_5CH_2$, R^1 = valeryl; *l*: R = cyclohexyl, R^1 = valeryl; m = R = CH_3, R^1 = cinnamoyl; n: R = C_3H_7, R^1 = cinnamoyl; o: R = iso-C_3H_7, R^1 = cinnamoyl; p: R = C_4H_9, R^1 = cinnamoyl; q: R = iso-C_4H_9, R^1 = cinnamoyl; r: R = cyclohexyl, R^1 = cinnamoyl.

The Kharkov Pharmaceutical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 1, pp. 32-34, January, 1984. Original article submitted March 4, 1983.