Thus, N-phenyl-substituted salts (compounds VIII, IX, and XII) have greater antimicrobial activity than N-methyl and N-ethyl-substituted salts (compounds I, II, V).

Increasing the chain length in 2-alkyl-substituted N-phenyl salts (compounds XI, XII) increases the antimicrobial activity by more than three-fold.

Substituting alkyl radicals in position 2 of the quinoline ring by benzyl radicals, both in N-alkyl- and N-phenyl-substituted quaternary salts, increases the antimicrobial activity twofold.

The nature of the substituent in position 3 of the quinoline ring (compounds XIV, XV), as can be seen from Table 1, has no influence on the activity of the preparations.

Comparison of preparations having different anions shows that the antimicrobial action of preparations containing the anion I^- significantly exceeds that of preparations with the anion ClO_4^-.

Preparations with the anion BF_4^- are also more active than those with ClO_4^- anion.

The establishment of a dependence of antimicrobial activity on chemical structure opens up the possibility of conducting a directed synthesis of quaternary quinolinium salts for the purpose of obtaining preparations active in antimicrobial respects. In our opinion, the synthesis of these compounds should be conducted along the line of obtaining quaternary salts with long radicals in 2-alkyl-substituted N-phenyl salts, with substitution of alkyl radicals in position 2 of the quinoline ring with benzyl radicals in N-alkyl- and N-phenyl-substituted quaternary quinolinium salts.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF PYRROLO[1,2,3-de]-QUINOXALINE DERIVATIVES

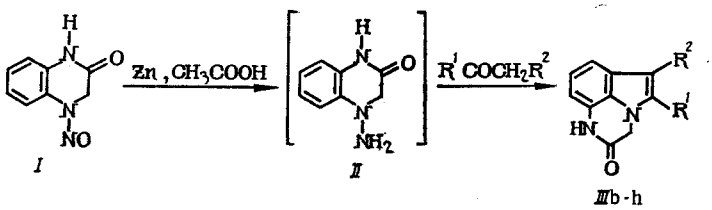
A. N. Grinev, Yu. I. Trofimkin, E. V. Lomanova, N. I. Andreeva, and M. D. Mashkovskii

UDC 615.214:547.863.7

Among the derivatives of pyrazino[1,2-a]indole, substances were discovered having high psychotropic activity. These substances include the novel antidepressant pyrazidole, which has been authorized for use in medical practice [1]. In connection with this, pyrrolo[1,2,3-de]quinoxalines, similar in structure to pyrazidole, were synthesized and studied with respect to pharmacological activity, in particular, psychotropic activity.

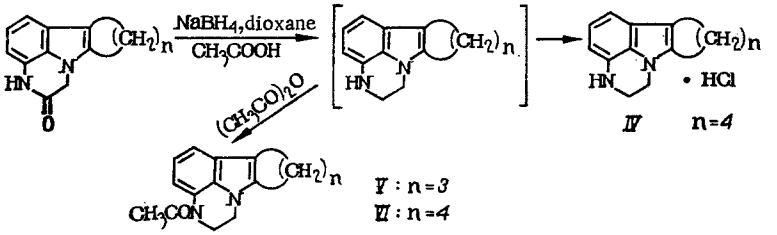
The first representative of this series, 1,2-tetramethylene-5-ketopyrrolo[1,2,3-de]quinoxaline (IIIa), has been prepared earlier [2]. We obtained a series of 5-ketopyrrolo[1,2,3-de]quinoxaline derivatives via Fischer condensation of various ketones with 1-amino-3-keto-1,2,3,4-tetrahydroquinoxaline (II). In the Fischer reaction, the ketone was added to a solution obtained by reduction of the nitro derivative (I) with zinc in acetic acid and containing II, giving the 5-ketopyrrolo[1,2,3-de]quinoxalines (IIIa-h).

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 12, No. 7, pp. 80-84, July, 1978. Original article submitted January 18, 1978.

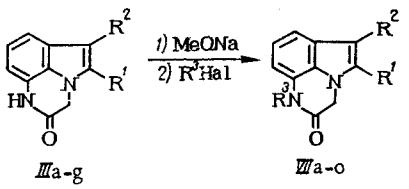


It is interesting to note that acetoacetate and benzoylacetate esters enter into Fischer reaction with formation of IIIg, h only on adding equimolar amounts of hydrochloric acid to the reaction solution. Condensation of methyl benzyl ketone with II leads to IIId also in the presence of hydrochloric acid.

We have studied several reactions of 5-ketopyrrolo[1,2,3-de]quinoxalines IIIa-g. On reduction of IIIa and IIIb with sodium borohydride in acetic acid according to a recently described method [3], pyrrolo[1,2,2-de]-quinoxalines were obtained and isolated as the derivatives IV-VI.



On alkylation of the sodium derivatives of IIIa-g with various alkylating agents (methyl iodide, chloroacetonitrile, bromoacetate ester, dialkylaminoalkyl chlorides), various N-alkyl derivatives (VIIa-o) were obtained.



The IR spectra for IIIa-g show an absorption band for an amide NH group at 3160-3200 cm^{-1}, absent in the spectra for N-substituted derivatives, and absorption bands for a carbonyl group (1680 cm^{-1}). In the spectra for VIIa-o, the absorption band for the carbonyl group is shifted to a lower frequency (1660 cm^{-1}). The UV spectra of the pyrrolo[1,2,3-de]quinoxaline derivatives are characterized by the presence of two maxima at 262 and 312 nm (log ε 3.15 and 3.11) and a minimum at 280 nm (log ε 3.04).

EXPERIMENTAL PHARMACOLOGICAL PART

Because of the structural similarity of the newly synthesized compounds to pyrazidole, they were studied with respect to a series of properties characterizing their psychotropic activity. Compounds VIIi, j, k, *l*, and m were administered internally as aqueous solutions, and IIIa, IIIb, and IV as an aqueous suspension with Tween 80.

All of the studied compounds show low toxicity. The LD_{50} for VII in white mice was 470 mg/kg for internal administration; for the remainder of the compounds, the LD_{50} was over 500 mg/kg. In view of the low toxicity of the compounds, they were used in relatively high doses (50-250 mg/kg) internally 60 min before the introduction of psychotropic preparations (reserpine, tetrabenazine, phenamine, etc.). Each dose of the preparation was administered to six animals (mice or rats).

In contrast to pyrazidole, no antidepressive activity was observed in the investigated compounds. In doses of 50-250 mg/kg, the preparations either have no influence on the depressant action of tetrabenazine (hypothermia and ptosis) and reserpine in mice or they somewhat increase the action (IV, VIIi, VIIj). Thus, 1 h after intraperitoneal administration of tetrabenazine (40 mg/kg) in mice, the body temperature of the animals, measured rectally, decreased to 33.8°C, whereas during preliminary administration of VIIi and VIIj in doses of 100 mg/kg, the temperature decreased to 31.5 and 31.6°C, respectively, and the ptosis increased from 2.1 units in control mice to 3.6-3.8. In doses of 50-200 mg/kg, all of the studied compounds have practically no influence on the effect of phenamine (group toxicity and hyperthermia; phenamine dose 5 and 7.5 mg/kg, subcutaneously) and do not significantly change the hypothermal action of L-dopa (200 mg/kg,

TABLE 1. 5-Ketopyrrolo[1,2,3-de]quinoxalines

Compound	R^1	R^2	Yield, %	mp, °C	Found, % C	Found, % H	Found, % N	Formula	Calc., % C	Calc., % H	Calc., % N
IIIa	—$(CH_2)_4$—		56	285*	—	—	—	$C_{14}H_{14}N_2O$	—	—	—
IIIb	—$(CH_2)_3$—		40	253—5	74,0	5,29	13,27	$C_{13}H_{12}N_2O$	73,56	5,69	13,19
IIIc	—$(CH_2)_5$—		34	259—61	74,88	6,70	11,57	$C_{15}H_{16}N_2O$	74,97	6,71	11,69
IIId	CH_3	C_6H_5	22	279—80	77,87	4,99	10,52	$C_{17}H_{14}N_2O$	77,84	5,38	10,68
IIIe	C_6H_5	C_6H_5	42	268—70	81,45	5,03	8,34	$C_{22}H_{16}N_2O$	81,46	4,97	8,64
IIIf	CH_3	CH_3	38	259—61	71,82	5,88	13,89	$C_{12}H_{12}N_2O$	71,98	6,04	13,99
IIIg	CH_3	$COOC_2H_5$	34	268—9	65,44	5,08	10,85	$C_{14}H_{14}N_2O_3$	65,10	5,46	10,85
IIIh	C_6H_5	$COOC_2H_5$	22	234—5	70,94	4,77	8,64	$C_{19}H_{16}N_2O_3$	71,24	5,03	8,75

*Data from [2].

TABLE 2. N-Substituted Pyrrolo[1,2,3-de]quinoxalines

Compound	R^1	R^2	R^3	Yield, %	mp, °C	Found, % C	Found, % H	Found, % N	Formula	Calc., % C	Calc., % H	Calc., % N
VIIa	—$(CH_2)_3$—		CH_3	60	157—9	74,56	6,15	12,15	$C_{14}H_{14}N_2O$	74,31	6,24	12,38
VIIb	—$(CH_2)_4$—		CH_3	70	131—3	74,73	6,44	11,60	$C_{15}H_{16}N_2O$	74,97	6,71	11,66
VIIc	—$(CH_2)_5$—		CH_3	40	113—5	75,07	6,80	10,84	$C_{16}H_{18}N_2O$	75,56	7,13	11,02
VIId	—$(CH_2)_3$—		CH_2COOCH_3	43	153—4	67,32	5,69	9,67	$C_{16}H_{16}N_2O_3$	67,59	5,67	9,85
VIIe	—$(CH_2)_4$—		CH_2COOCH_3	52	195—7	68,52	6,05	9,11	$C_{17}H_{18}N_2O_3$	68,44	6,08	9,39
VIIf	—$(CH_2)_4$—		CH_2CN	46	227—9	72,33	5,70	15,63	$C_{16}H_{15}N_3O$	72,43	5,70	15,84
VIIg	$CH_3C_6H_5$		CH_3	28	218—9	78,75	5,97	10,24	$C_{18}H_{16}N_2O$	78,34	5,84	10,14
VIIh (Tartrate)	—$(CH_2)_3$—		$CH_2CH_2N(C_2H_5)_2$	60	143—5	63,54	6,91	10,37	$C_{21}H_{28}N_3O_4 \cdot H_2O$	63,77	7,40	10,63
VIIi	—$(CH_2)_4$—		$CH_2CH_2N(C_2H_5)_2$	85	81—2	73,75	8,36	12,67	$C_{20}H_{27}N_3O$	73,81	8,36	12,91
VIIi (Tartrate)	—$(CH_2)_4$—		$CH_2CH_2N(C_2H_5)_2$		158—9	66,06	7,50	10,42	$C_{22}H_{30}N_3O_4 \cdot H_2O$	65,98	7,55	10,49
VIIj	—$(CH_2)_5$—		$CH_2CH_2N(C_2H_5)_2$	92	95—7	74,57	8,73	11,91	$C_{21}H_{29}N_3O$	74,29	8,61	12,38
VIIj (Tartrate)	—$(CH_2)_5$—		$CH_2CH_2N(C_2H_5)_2$		137—9	66,64	7,94	10,16	$C_{23}H_{32}N_3O_4$	66,64	7,78	10,14
VIIk	—$(CH_2)_4$—		$CH_2CH_2CH_2N(CH_3)_2$	84	137—9	73,39	8,57	13,28	$C_{19}H_{25}N_3O$	73,28	8,09	13,49
VIIl (Tartrate)	CH_3	CH_3	$CH_2CH_2N(C_2H_5)_2$	64	163—5	64,30	7,60	10,88	$C_{20}H_{28}N_3O_4$	64,14	7,54	11,22
VIIm (Tartrate)	CH_3	$COOC_2H_5$	$CH_2CH_2N(C_2H_5)_2$	47	202—4	57,04	6,68	7,92	$C_{24}H_{33}N_3O_9$	56,79	6,55	8,28
VIIn	CH_3	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	65	115—6	76,50	7,67	11,67	$C_{23}H_{27}N_3O$	76,42	7,53	11,63
VIIn (Tartrate)	CH_3	C_6H_5	$CH_2CH_2N(C_2H_5)_2$		188—9	68,79	6,99	9,38	$C_{25}H_{30}N_3O_4$	68,76	6,96	9,62
VIIo	C_6H_5	C_6H_5	$CH_2CH_2N(C_2H_5)_2$	90	155—6	79,82	6,84	10,12	$C_{28}H_{29}N_3O$	79,40	6,90	9,92
VIIo (Tartrate)	C_6H_5	C_6H_5	$CH_2CH_2N(C_2H_5)_2$		190—1	71,82	6,74	8,23	$C_{30}H_{32}N_3O_4$	72,27	6,47	8,42

intraperitoneally) in mice. Compound IV in a dose of 200 mg/kg somewhat increases the duration of the soporific effect of hexanal (50 mg/kg intravenously) in mice. Thus, in a control, the duration of narcotic sleep was 7 (4.8-9.2) min, in comparison to 18 (10-26) min on preliminary introduction of IV. The rest of the studied compounds did not change the activity of hexanal. In doses of 100 mg/kg they also did not change the hypothermal action of apomorphine (10 mg/kg, subcutaneously). None of the preparations in doses of 200 mg/ kg changed the toxicity of Corazole (124 mg/kg, subcutaneously) nor exhibited cholinolytic activity.

Thus, study of antidepressant and neurolytic activity shows that the synthesized compounds are weakly active.

EXPERIMENTAL CHEMICAL PART

The IR spectra of the obtained substances were taken in Vaseline oil on a UP-10 spectrophotometer, and the UV spectra, on a EPS-3 spectrophotometer.

5-Ketopyrrolo[1,2,3-de]quinoxalines (IIIb-h)*. Zinc dust (6.5 g, 0.1 mole) was added in small portions of 0.02 mole 1-nitroso-3-keto-1,2,3,4,-tetrahydroquinoxaline in 35 ml glacial acetic acid under cooling in ice and stirring at temperatures not exceeding 25°C. The residue was filtered off and washed on the filter with 5-10 ml acetic acid. A carbonyl compound was added to the combined filtrates and the product was stirred at 80-90°C for 1.5 h, cooled in ice, the precipitating crystals were filtered off, washed on the filter with water; and recrystallized from dioxane. The properties of the obtained compounds are given in Table 1.

1,2-Tetramethylenepyrrolo[1,2,3-de]quinoxaline Hydrochloride (IV). Glacial acetic acid (2.5 ml, 0.034 mole) was added dropwise to a suspension of 0.017 mole IIIa and 3.1 g (0.085 mole) sodium borohydride in 30 ml dioxane at 10-11°C with vigorous stirring. After this, the solvent was distilled off in vacuo, the residue separated with water, extracted three times with 15-ml-portions of chloroform, dried with magnesium sulfate, treated with an ether solution of HCl, and IV separated in 41% yield, mp 231-233°C (from 2:1 ether–methanol mixture). Found, %: C 67.76, H 7.15, N 11.44, Cl 14.07. $C_{14}H_{16}N_2 \cdot HCl$. Calculated, %: C 67.60, H 6.89, N 11.26, Cl 14.25.

1,2-Trimethylene-2-acetylpyrrolo[1,2,3-de]quinoxaline (V). The reaction was conducted analogously to the synthesis of IV. For the reaction, 0.017 mole IIIb, 3.1 g sodium borohydride, 5.1 ml glacial acetic acid, and 20 ml dioxane were used. The residue obtained after separation of the reaction mixture with water was extracted three times with 15-ml portions of benzene and the benzene solution was dried with magnesium sulfate. Acetic anhydride (2.5 ml, 0.034 mole) was added to the dry benzene solution, which was then heated at boiling for 3 h. The solvent was vacuum distilled off to dryness in a water bath. The residue was dissolved in 20 ml methanol, heated at boiling with carbon, filtered, the filtrate cooled with ice, and IV separated. Yield 3 g (60%), mp 147-148°C from acetone. Found, %: C 75.00, H 6.63, N 11.47. $C_{15}H_{16}N_2O$. Calculated, %: C 74.97, H 6.71, N 11.66.

1,2-Tetramethylene-6-acetylpyrrolo[1,2,3-de]quinoxaline (VI). This compound was obtained analogously to V from 0.017 mole IIIa. Yield 2.5 g (51%), mp 109-110°C from hexane. Found, %: C 75.95, H 7.08, N 10.88. $C_{16}H_{18}N_2O$. Calculated, %: C 75.56, H 7.13, N 11.01.

N-Substituted pyrrolo[1,2,3-de]quinoxalines (VIIa-o). To a solution of 0.01 mole IIIa-g in 25 ml dry dimethylformamide was added 4.3 ml of a sodium methylate solution obtained from 92 g sodium and 920 ml methanol. The reaction mixture was evaporated in vacuo to half of the initial volume, then cooled. An alkylating agent (0.02 mole) in 15 ml dry dimethylformamide was added to the obtained solution of the sodium derivative and the reaction solution was boiled for 3 h. It was then decanted into water with ice and VIIa-o filtered off. Compounds VIIa-g were recrystallized from a mixture of methanol and dioxane. The tartrates of compounds VIIh-j, m-o were recrystallized from alcohol or aqueous alcohol. Data on VIIa-o are given in Table 2.

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*For IIId the reaction was conducted on addition of hydrochloric acid to the reaction solution over 7-10 min. For IIIg, h the reaction was conducted over 1.5 h on addition of hydrochloric acid.