DERIVATIVES OF PYRAZINO- AND PIPERAZINO[1,2-a]INDOLE

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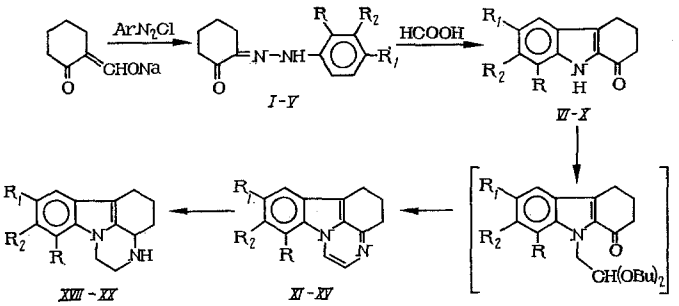
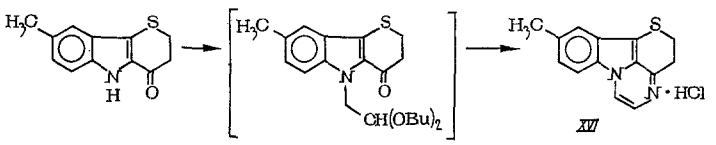
UDC 615.31:[547.861.3+547.751].012.1

With the objective of searching for biologically active substances in the pyrazino[1,2-a]indole series which we had previously discovered, we have carried out the synthesis of some new representatives of this heterocyclic system by the following scheme:

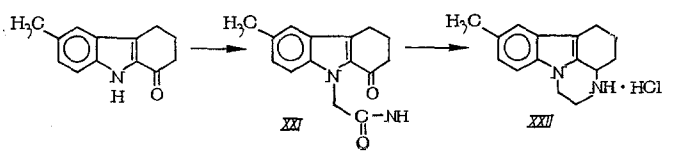


Similarly, from 2,3-dihydro-4-keto-8-methylthiopyrano[3,2-b]indole we have prepared 2,3-dihydro-10-methylpyrazino[1,2-a]thiopyrano[3,2-b]indole (XVI), which was isolated in the form of its hydrochloride.



The piperazino[1,2-a]indole derivatives (XVII-XIX) were obtained on reduction of XII, XIII, and XV with sodium in boiling alcohol. Additionally, XVII and XVIII could be prepared by hydrogenating the pyrazino[1,2-a]indole derivatives over Raney nickel catalyst at a pressure of 60-70 atm and a temperature of 50°. An attempt to carry out the catalytic hydrogenation of the pyrazine ring at elevated pressure in compounds which contained a chlorine atom in the molecule (XII, XIV) led to the formation of piperazino[1,2-a]-indole (XX), which does not contain substituents in the benzene ring of the molecule; that is, hydrogenolysis of the chlorine atom takes place in this reaction along with reduction of the pyrazine ring.

We also found that the piperazino[1,2-a]indoles could be prepared by reductive cyclization of the N-acetamide derivatives of 1-keto-1,2,3,4-tetrahydrocarbazole with sodium in boiling alcohol.



Pharmacological studies showed that 1,10-trimethylenepiperazino[1,2-a]indole derivatives have a number of properties which are characteristic of both substances with an antidepressive action (imizin and the like) and also of compounds with neuroleptic action (aminazin, etc.). For example, XVII intensifies the central effect of phenamine and weakens the effect of reserpine. A similarity with antidepressive preparations

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TABLE 1. Properties and Analytical Data for Compounds Prepared

Compound	R	R_1	R_2	Yield (%)	Mp (in deg)	Found (%)			Empirical formula	Calculated (%)		
						C	H	N		C	H	N
I	CH_3	H	H	86	95—6 [3]	—	—	—	—	—	—	—
II	CH_3	CH_3	H	75	72—3 [4]	—	—	—	—	—	—	—
III	H	H	Cl	90	152—3	60,53	5,48	11,90	$C_{12}H_{13}ClN_2O$	60,88	5,53	11,83
IV	Cl	Cl	H	70	192—3	53,43	4,52	10,54	$C_{12}H_{12}Cl_2N_2O$	53,15	4,46	10,36
V	H	OCH_3	H	72	233—4	67,08	6,89	12,18	$C_{13}H_{16}N_2O_2$	67,21	6,94	12,06
VI	H	H	CH_3	71	165—6 [4]	—	—	—	—	—	—	—
VII	CH_3	CH_3	H	78	224—5 [4]	—	—	—	—	—	—	—
VIII	H	H	Cl	73	223—4	65,76	4,80	6,10	$C_{12}H_{10}ClNO$	65,60	4,59	6,37
IX	Cl	Cl	H	66	194—5	56,77	3,55	5,59	$C_{12}H_9Cl_2NO$	56,71	3,57	5,51
X	H	OCH_3	H	42	181—2 [5]	—	—	—	—	—	—	—
XI	CH_3	H	H	74	139—40	81,09	6,42	12,48	$C_{15}H_{14}N_2$	81,04	6,34	12,60
XII·HCl	CH_3	CH_3	H	68	244—6(dec.)	70,12	6,35	10,38	$C_{16}H_{16}N_2 \cdot HCl$	70,44	6,28	10,27
XIII	H	H	Cl	54	158—9	68,89	4,55	11,68	$C_{14}H_{11}ClN_2$	69,28	4,56	11,55
XIV	Cl	Cl	H	61	134—5	60,28	3,77	10,00	$C_{14}H_{10}Cl_2N_2$	60,66	3,63	10,11
XV·HCl	H	OCH_3	H	61	250—2(dec.)	65,47	5,52	9,85	$C_{15}H_{14}N_2O \cdot HCl$	65,57	5,50	10,19
XVII·HCl	OCH_3	OCH_3	H	62	260—2(dec.)	64,77	6,70	9,90	$C_{15}H_{18}N_2O \cdot HCl$	64,85	6,53	10,08
XVIII	CH_3	CH_3	H	93	114—5	79,72	8,32	12,00	$C_{16}H_{20}N_2$	79,95	8,39	11,65
XIX·HCl	H	H	Cl	74	234—6	59,00	5,30	10,13	$C_{14}H_{15}ClN_2 \cdot HCl$	59,37	5,69	9,89
XX·HCl	H	H	H	80	220—2(dec.)	67,50	6,91	11,12	$C_{14}H_{16}N_2 \cdot HCl$	67,59	6,85	11,26
XXII·HCl	H	CH_3	H	52	241—2(dec.)	68,48	7,27	10,89	$C_{15}H_{18}N_2 \cdot HCl$	68,56	7,29	10,66

of the imipramin type is very characteristic of the 1,10-trimethylenepiperazino[1,2-a]indole derivatives studied. The most active compounds in the tested series are XVII and XX. The corresponding pyrazino[1,2-a]indole derivatives are inferior to the piperazino[1,2-a]indole derivatives in activity. The compounds studied have a comparatively low toxicity. For example, the LD_{50} of compound XVII is 150 mg/kg.

EXPERIMENTAL

Cyclohexane-1,2-dione Monoarylhydrazones (I-V). To a mixture of 0.1 mole of cyclohexanone and 0.15 mole of ethyl formate, cooled to 5°, was added, with stirring, an alcoholic sodium methoxide solution prepared from 0.1 gram-atom of sodium and 23 ml of methanol. The sodium derivative of formylcyclohexanone which precipitated was allowed to stand for 5 or 6 h, and then the precipitate was dissolved by adding 50 ml of cold water. The solution so obtained, cooled to 0-5°, was added to an aqueous solution of the aryldiazonium chloride prepared by the usual method from 0.1 mole of arylamine, 30 ml of concentrated hydrochloric acid, and 0.1 mole of sodium nitrite, and the mixture was brought to pH 5.0-6.0 with sodium acetate. The crystals which separated were filtered off, washed with cold water, and dried. Data on the compounds obtained (I-V) are given in Table 1.

1-Keto-1,2,3,4-tetrahydrocarbazoles (VI-X). A mixture of 0.1 mole of the cyclohexane 1,2-dione monoarylhydrazone, 50 ml of 85% formic acid, and 10 ml of dimethylformamide was boiled for 30 min. After cooling, the deposited crystals were filtered off, washed with water, and dried. Data on compounds (VI-X) are given in Table 1.

1,10-Trimethylenepyrazino-[1,2-a]indole Derivatives (XI-XV). Synthesis of these was performed by the method previously described [1].

1,10-Trimethylenepiperazino[1,2-a]indole Hydrochlorides (XVII-XX). a) Reaction with sodium in alcohol was carried out by the method which we have previously described [1]. b) In an autoclave was placed 0.05 mole of the 1,10-trimethylenepyrazino[1,2-a]indole, 220 ml of ethanol, and 10 g of Raney nickel paste. Hydrogenation was carried out at a pressure of 60 atm and a temperature of 50° until the absorption of hydrogen ceased. The catalyst was separated, the alcohol was evaporated, the thick oil remaining was dissolved in ether, and the hydrochloride was precipitated from the ice-cooled ether solution by an ether solution of hydrogen chloride. Data on compounds XVII-XX are given in Table 1.

1-Keto-1,2,3,4-tetrahydro-6-methylcarbazolyl-9-acetamide (XXI). To a suspension of 4 g of 1-keto-1,2,3,4-tetrahydro-6-methylcarbazole in 20 ml of dry dioxane was added an alcoholic solution of sodium ethoxide, prepared from 0.46 g of sodium. The solvent was distilled off from the solution formed at 120°, and remaining solvent was removed at the same temperature under vacuum. To the solid N-sodium derivative was added a solution of 2 g of chloro-

acetamide in 40 ml of dry dimethylformamide, and the reaction mixture was boiled for 30 min; then it was poured into water. The crystals which separated were filtered off and dried. The yield of XXI was 5 g (96%), mp 213-214°. Found, %: C 70.28; H 6.10; N 10.94. $C_{15}H_{16}N_2O_2$. Calculated, %: C 70.29; H 6.29; N 10.93.

2,3-Dihydro-10-methylpyrazino[1,2-a]thiopyrano[3,2-b]indole Hydrochloride (XVI). This compound was prepared, like (XI-XV), from 2,3-dihydro-4-keto-8-methylthiopyrano[3,2-b]indole. The yield was 41%, mp > 220° (dec). Found, %: N 9.80; S 11.48. $C_{14}H_{12}N_2S \cdot HCl$. Calculated, %: N 10.12; S 11.59.

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