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AZACYCLOALKANES.

XXX. PYRROLO [1,2-a] PYRAZINES WITH VARIABLE DEGREES OF PYRAZINE RING SATURATION AND THEIR HYPOTENSIVE ACTIVITY

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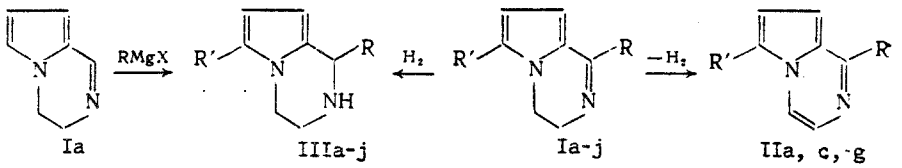
UDC 615.225.2:547.863].07

In connection with current literature data on the hypotensive activity of 1,2-substituted pyrroles [8], we synthesized several structurally related derivatives of pyrrolo [1,2-a] pyrazine for the purpose of pharmacological studies. We have previously described [2, 3] how we obtained various 3,4-dihydropyrrolo[11,2-a]pyrazines (I). In the present study we describe the synthesis of pyrrolo[1,2-a]pyrazines (II) and 1,2,3,4-tetrahydropyrrolo[1,2-a]-pyrazines (III) and present some of the reuslts from our study of their hypotensive activity.

Compounds II and III were obtained from the corresponding 3,4-dihydropyrrolo[1,2-a]-pyrazines according to the following pattern:



Ia IIIa-j Ia-j IIa, c,-g

R′ = H (a, c-j), CH_3 (b); R = H (a, b), Me (c) *r*-Pr (d), cyclohexyl (e), CH_2Ph (f), Ph (g), *n*-$MeOC_6H_4$ (h), *n*-FC_6H_4 (i), *n*-ClC_6H_4 (j)

In order to obtain pyrrolo[1,2-a]pyrazines of II in the form of the bicyclic compound Ia, we examined various versions of dehydrogenation. When Ia is heated in xylene with phenanthrenequinone, chloranyl or 2,3-dichloro-5-dicyanobenzo-1,4-quinone, intensive resinification takes place which prevents the separation of the reaction products. Dehydrogenation of Ia in the presence of Pd/C resulted in a IIa yield of 63% [5]. In accordance with GLC data when Ia is heated in xylene in the presence of a Raney nickel catalyst, the result is a 4:1 mixture of IIa and 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine IIIA from which IIa can be separated at a 37% yield. Consequently, when Ia is dehydrogenated it is simultaneously hydrogenated because of the hydrogen formed during the reaction or the hydrogen adsorbed on the catalyst [7]. Special experiments have shown that the tetrahydrobicyclic compound of IIIa can be dehydrogenated in pyrrolo[1,2-a]pyrazine (IIa), although the process does not go to completion. At the same time, when 1-methyl and 1-phenyl-3,4-dihydropyrrolo[1,2-a]-pyrazine (Ic, g) are dehydrogenated over a nickel catalyst under analogous conditions, only the corresponding pyrrolo[1,2-a]pyrazines of IIc, g are generated, although according to GLC data a parallel formation of the partial IIIc, g dehydrogenation products takes place during the process. The absence of these substances in the reaction mixture after the completion of the process is probably related to the fact that the dehydrogenation of the

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 9, pp. 1054-1059, September, 1987. Original article submitted June 4, 1986.

TABLE 1. 1,2,3,4-Tetrahydropyrrolo[1,2-a]pyrazines and Their Acid Maleates

Compound	Yield, %	bp/mm Hg (mp, °C)	n_D^{20}	Found, %			Empirical formula	Calculated, %			Acid maleates		
				C	H	N		C	H	N	bp/mm Hg	found N, %	calculated N, %
IIIa	95	100—1/7	1,5530	68,49	8,13	—	$C_7H_{10}N_2$	68,82	8,29	—	151—2	11,91	11,76
IIIb	77,3	122—3/8	1,5547	69,76	8,75	20,56	$C_8H_{12}N_2$	70,55	8,88	20,57	162—3	11,32	11,10
IIIc	94	105—7/12	1,5465	70,27	8,81	20,63	$C_8H_{12}N_2$	70,55	8,88	20,57	143—4	11,15	11,10
IIId	86	118—20/7	1,5302	73,18	9,77	17,01	$C_{10}H_{14}N_2$	73,12	9,82	17,06	131—2	10,25	9,99
IIIe	82	120—1/1	1,5573	76,28	9,93	13,80	$C_{13}H_{20}N_2$	76,42	9,87	13,71	156—7	9,02	8,74
IIIf	85	153—5/2	1,5927	79,11	7,53	13,31	$C_{14}H_{16}N_2$	79,21	7,60	13,19	169—70	8,67	8,53
IIIg	91	138—40/3 (73—4)	—	78,90	7,17	14,10	$C_{13}H_{14}N_2$	78,75	7,12	14,13	140—1	8,92	8,91
IIIh	82,4	148—50/2 (72—3)	—	73,86	7,11	12,37	$C_{14}H_{16}N_2O$	73,65	7,06	12,27	181—2	8,01	8,13
IIIi	89	137—9/2 (104—6)	—	—	—	12,96	$C_{13}H_{13}FN_2$	—	—	12,95	158—9	8,70	8,43
IIIj	87	144—6/2	—	66,82	5,72	12,38	$C_{13}H_{13}ClN_2$	67,09	5,63	12,04	168—9	7,91	8,03

*Corresponding 3,4-dihydropyrrolo[1,2-a]pyrazines were obtained by dehydrogenation.

1-substituted bicyclic comounds of III takes place more easily than it does in the case of the unsubstituted IIIa.

The presence of a reactive azomethine group in the structure of 3,4-dihydropyrrolo-[1,2-a]pyrazines (I) made it possible to use them to synthesize the 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines (III).

We were able to obtain a measurable yield of 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (IIIa) by reducing the bicyclic compound Ia with $NaBH_4$, $LiAlH_4$ or by dehydrogenation over Pt or Pd catalysts [1]. These methods were also used to reduce other bicyclic compounds of I. The presence of alkyl substituents in the pyrrole or pyrazine rings did not interfere with the reduction process. At the same time, we could not reduce 1-aryl-3,4-dihydropyrrolo-[1,2-a]pyrazines with $NaBH_4$, so we had to use $LiAlH_4$ or hydrogenation over Pt or Pd catalysts.

The second method we used to obtain 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines (III) was based on the addition of Grignard reagnets (RMgX) (where R is an alkyl, arylalkyl, or aryl) on the azomethine bond of the bicyclic Ia compound. The end products of III are obtained at a high yield (70 to 80%) when the molar ratio of the bicyclic Ia compound to the Grignard reagent is 1:2.2 (when that ratio was 1:1.2 the reaction did not go to completion and the yield of the 1-substituted bicyclic compounds did not exceed 50%).

The examined method supplements the above-mentioned method of obtaining 1-substituted 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines of III and makes it possible to synthesize them from the available 3,4-dihydropyrrolo[1,2-a]pyrazine (Ia).

We were not successful in employing the Grignard reaction with 1-substituted-3,4-dihydropyrrolo[1,2-a]pyrazines for the purpose of obtaining 1,1-substituted derivatives.

The non-substituted IIIa compound and the 1-alkylsubstituted bicyclic compounds of IIIb-f were mobile, transparent fluids. The 1-arylsubstituted IIIg-j compounds were slightly colored crystalline substances with low melting points that can be vacuum-distilled without decomposition (Table 1). The hydrochlorides of the bicyclic III compounds darken upon standing, and are relatively more stable than the acid maleates (see Table 1).

The structure of the synthesized 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines was confirmed by spectral data. For example, the PMR spectrum of IIIg has a proton singlet (δ 1.8 ppm) of the NH-group, 2 proton multiplets (δ 3.0-3.3 and 3.8-4.0 ppm) on the C_3 and C_4 atoms, a proton singlet on the C_1 atom (δ 4.9 ppm), 3 multiplets in the 5.4-6.5 ppm interval of the pyrrole ring protons, and a centered multiplet (δ 7.3 ppm) of the benzene ring protons. The UV spectrum of the IIg bicyclic compound has pyrrole ring absorption bands at λ_{max} 225 nm ($\log \sigma\varepsilon$ 4.42) and characteristic benzene ring absorption bands at λ_{max} 274 nm ($\log \varepsilon$ 3.28) and 280 nm ($\log \varepsilon$ 3.32).

A pharmacological study of the pyrrolo[1,2-a]pyrazine salts on anesthetized rats showed that they exhibit hypotensive activity (Table 2). The hypotensive effect of the compounds depended on the dose of the preparation. Thus, a doubling of the dose in most of the compounds resulted in a reduction of hypotensive activity, although in the case of the IIIb compounds such an increase resulted in hypertension. As is illustrated by the 1-phenyl derivatives of pyrrolo[1,2-a]pyrazines, one can see that the hypotensive activity depends on the degree to which the pyrazine ring is saturated (Ig > IIIg > IIg). The most active compounds were the bicyclic Ig and IIIe compounds, which contained phenyl and cyclohexyl radicals, respectively. The introduction of substituents into the phenyl radical resulted in diminished activity. Our pharmacological study showed that the examined compounds induce a pronounced but short-term drop in arterial pressure. The hypotensive effect of the preparations was combined with the onset of pronounced bradycardia. In the control experiments the bradycardia was removed by the action of an atropine M-choline receptor blocking agent at a dose of 0.5 mg/kg. The data we obtained allow us to associate the hypotensive action of the compounds under examination and their ability to shorten pulse rate with their activation of the cardiovascular system's M-choline receptors.

EXPERIMENTAL CHEMICAL

UV spectra were recorded on a Perkin-Elmer 402 instrument in alcohol. PMR spectra were read on a Varian T-60 spectrometer. The solvent was CCl_4, the internal standard was TMS, and scale was δ, ppm. GLC was performed on a LKhM-8MD chromatograph with a glass capillary column (30 m, diameter 0.25 mm), phase SE-30, and vaporizer temperature of 300°C. Experimental conditions: thermostat temperature 95°C, carrier gas (nitrogen) intake pressure

TABLE 2. Arterial Pressure Change in Anesthetized Rats as Affected by Certain Derivatives of Pyrrolo-[1,2-a]pyrazine*

Compound	Change in arterial pressure, mm Hg	
	dose of preparation, mmole	
	0.05	0.1
Ia	—26	—33
Ig	—79	—66
Ih	—58	—25
Ii	—35	—75
Ij	—30	—13
IIg	—40	—32
IIIa	—37	—17
IIIg	—53	—61
IIIh	—24	—48
IIIi	—12	+23
IIIb	—4	+4
IIId	—60	—55

*Each compound was tested in three experiments.

0.13 kg/cm^2. TLC was performed on Kiselgel 60 F 254 plates (Merck Co.) in a benzene—alcohol—25% aq. ammonia 95:15:1 system with spot detection in UV light or iodine vapor. Melting point was determined on a Boëtius microheater.

1. Synthesis of Pyrrolo[1,2-a]pyrazines

Pyrrolo[1,2-a]pyrazine (IIa). A. Dehydrogenation in the Presence of Pd/C. A solution of 3 g of Ia in 50 ml of xylene in the presence of 2.5 g of 10% Pd/C was boiled for 15 h. The reaction mixture was filtered, the filtrate was evaporated, and the residue was distilled. Yield of IIa was 1.86 g (63%), bp 111-112°C (15 mm); n_D^{21} 1.6215; R_f 0.47; τ_{sp} 8 min. Literature data [6]: bp 71°C (2 mm); n_D^{20} 1.6176. Hydrochloride — mp 159-160°C. Literature data [4]: mp 160-161°C.

b. Dehydrogenation in the Presence of a Raney Nickel Catalyst. A solution of 2 g of Ia in 60 ml of xylene was heated for 8 h in the presence of 10 g of Raney nickel with intense stirring. GLC data indicated that the specimen of the reaction mixture taken after 4 h contained three substances: Ia, IIa, and IIIa. The hot reaction mixture was filtered and another portion of Raney Ni was added (10 g) after which the mixture was boiled until GLC data indicate the disappearance of product Ia (about 8 h). The catalyst was filtered off, the filtrate evaporated, and the remaining mxiture of IIa and IIIa was treated with 2 ml of diethyloxalate (during which the IIIa was converted to oxalates) and kept for 8 h. The reaction mass was then treated with 30 ml of 10% HCl followed by ether extraction. The aqueous layer was made alkaline with 20% NaOH and extracted with benzene. The benzene was then evaporated and the residue was distilled. The yield of IIa was 1.1 g (37%), bp 122-124°C (20 mm); n_D^{22} 1.6203.

C. Dehydrogenation of 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine in the Presence of Raney Nickel. Dehydrogenation of 3.05 g of IIIa was accomplished in a similar manner as that of Ia in the presence of a Raney nickel catalyst. However, in this case the process was not taken to completion in which case GLC data indicated the formation of a 1:5:4 mixture of the bicyclic compounds Ia, IIa, and IIIa, respectively.

1-Methylpyrrolo[1,2-a]pyrazine (IIb). A solution of 2.68 g of Ib in 50 ml of xylene was boiled for 8 h in the presence of 10 g of Raney nickel with intense stirring. The hot reaction mixture was filtered and a new portion of Raney nickel (10 g) was added. The mixture was then boiled for 8 h until the GLC data indicated the disappearance of the starting product. The catalyst was filtered off, the filtrate evaporated, and the residue was distilled. The yield of IIb was 1.5 g (57%), bp 119-120 (16 mm); n_D^{17} 1.6135; R_f 0.51; τ_{sp} 9 min. Literature data [5]: bp 110-112°C (10 mm). Hydrochloride — mp 208-209°C. Found %: Cl 21.03. $C_8H_{16}N_2 \cdot HCl$. Calculated %: C 21.02.

1-Phenylpyrrolo[1,2-a]pyrazine (IIg) was obtained in a similar manner from 3.92 g of Ig in 60 ml of xylene. The yield of IIg was 2.7 g (69.5%), bp 145-146°C (1 mm); mp 73-74°C (from ethanol); n_D^{22} 1.6730; R_f 0.57. Hydrochloride – mp 184-186°C. Literature data [4]: mp 185-187°C (with decomposition).

2. Synthesis of 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines by the Reduction of 3,4-Dihydropyrrolo[1,2-a]pyrazines

1,2,3,4-Tetrahydropyrrolo[1,2-a]pyrazine (IIIa). A. Reduction by $NaBH_4$. A mixture of 3.8 g (0.01 mole) of $NaBH_4$ and 20 ml of 70% aq. ethanol was added to a solution of 6 g (0.05 mole) of Ia in 30 ml of ethanol. The reaction mixture was kept at room temperature for 2 h, heated for 2 h, and the precipitate was filtered and washed with alcohol. The filtrate was concentrated by evaporation and the residue was extracted with benzene. The benzene was vaporized and the residue was distilled. The yield of IIIa was 5.1 g (84%); R_f 0.31; τ_{sp} 9.5 min.

B. Reduction by $LiAlH_4$. A 3.6-g (0.03-mole) portion of $LiAlH_4$ in 50 ml of abs. ether was added dropwise to a suspension of 2.28 g (0.06 mole) of Ia in 50 ml of abs. ether. The reaction mixture was boiled for 2 h, treated with 10 ml of water, and heated for 15 min. The ether layer was then separated, evaporated with benzene, and the residue was distilled. The yield of IIIa was 3.2 g (87%).

C. Catalytic Hydrogenation. A solution of 12 g of Ia in 80 ml of ethanol was hydrogenated over 0.4 g of PtO_2 at room temperature and atmospheric pressure until the theoretical quantity of H_2 was absorbed (about 3 h). The catalyst was filtered off, the filtrate was boiled down, and the residue was distilled. The yield of IIIa was 11.2 g (92%).

Compound IIIa was hydrogenated in a similar manner in the presence of 10% $PdO/BaSO_4$. This resulted in a 95% yield of IIIa. In the course of our attempt to hydrogenate an alcohol solution of 1.2 g of Ia in the presence of 10 g of Raney nickel under the conditions described above, the process practically came to a halt after the absorption of 60 ml of hydrogen (the theoretical volume was 224 ml).

In a similar manner, the tetrahydropyrrolo[1,2-a]pyrazines IIIb-j were obtained by reduction. The yields, element analysis data, and physicochemical constants of these compounds and their salts are given in Table 1.

3. Synthesis of 1-Substituted 1,2,3,4-Tetrahydropyrrolo[1,2-a]pyrazines by Reacting 3,4-Dihydropyrrolo[1,2-a]pyrazine with Grignard Reagents*

1-Cyclohexyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (IIIa). A solution of 3 g (0.025 mole) of Ia in 10 ml of abs. ether was added to a solution of cyclohexyl magnesium chloride obtained from 1.37 g (0.055 mole) of magnesium, 6.52 g (0.055 mole) of chlorohexane, and 40 ml of abs. ether. The reaction mixture was boiled for 3 h, treated with 10 ml of water, and acidified with 20% H_2SO_4 after which the ether layer was separated. The aqueous layer was made alkaline with a saturated KOH and extracted with ether. The benzene was then evaporated and the residue was distilled. The yield of IIIe was 4 g (80%), bp 120-122°C (1 mm); n_D^{22} 1.5563; R_f 0.47.

1-Benzyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (IIIf) was obtained in a similar manner from 1.37 g (0.055 mole) of magnesium, 6.95 g (0.055 mole) of benzyl chloride, and 3 g (0.025 mole) of Ia. The yield of IIIf was 4.35 g (82%), bp 145-147°C (1 mm); n_D^{20} 1.5950.

1-Phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (IIIg) was obtained in a similar manner from 1.37 g (0.055 g-atom) of magnesium, 8.65 g (0.055 mole) of bromobenzene, and 3 g (0.025 mole) of Ia. The yield of IIIg was 3.6 g (72.6%), bp 130-132°C) (1 mm); R_f 0.45.

When the mole ratio of Ia to Grignard reagent was 1:1.2 the yield of compounds IIIe, f, and g was decreased by 30 to 40%.

*The constants of compounds IIIe, f, and g which were obtained by this method, correspond to the substances formed upon the reduction of the corresponding 1-substituted 3,4-dihydropyrrolo[1,2-a]pyrazines Ie, f, and g (see Table 1).

EXPERIMENTAL PHARMACOLOGICAL

The compounds under examination were investigated for the purpose of ascertaining their effect on the cardiovascular system. The experiments were conducted on mongrel white rats weighing 200 to 350 g and anesthetized with Nembutal (45 mg/kg ip). Arterial pressure was meausred in the carotid artery with an EMT-34 type electromanometer made by the Elema-Shonander Company (Sweden) and was continuously recorded on a N-338 automatic recorder. Heartbeat frequency was determined by a digital cardiotachometer which was actuated by arterial pressure pulse waves. The average arterial pressure and heartbeat frequency index were measured by digital instruments and printed out on a F-5003 type digital printer.

All of the test preparations were dissolved in physiological solution and administered iv at doses which did not exceed 0.1 ml per 100 g of body weight.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF O-AMINOALKYL DERIVATIVES OF OXIMES OF PYRIDYLPHENYLMETHANONES

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UDC 615.214.32.012.1

For the purpose of pharmacological investigations we have synthesized aminoethyl (Ia-h) and 3-amino-2-hydroxypropyl (IIa-h) ethers of pyridylphenylmethanone oximes. The choice of the compounds to be investigated was determined by the fact that in the last years medical practice has seen the coming into use of a group of antidepressants that differ in chemical structure from classical antidepressants by the absence of condensed rings in their molecules, for example zimelidine – N,N-dimethyl-3-(4-bromophenyl)-3-(pyrid-3-yl)allylamine [3]. It is also known that antidepressant and also β-adrenergic blocking activity is shown by some aminoethyl and 3-amino-2-hydroxypropyl ethers of various diketones, respectively (for example noxiptilin, mariptilin, IPS-339, and falintolol [3, 6-8]). The latter group of compounds can thereby be considered to be aza vinylogs of 1-aryloxy-3-aminopropan-2-ols (AAP), among which many preparations having β-adrenergic blocking properties are found (see [4, 9]). It can be seen that structure I contains the pyridylphenylmethanone moiety of zimelidine and the aminoethyloximino fragment present in a series of other antidepressants, and the structures of ethers II unit fragments of zimelidine and of β-adrenergic blockers – derivatives of 3-aminopropane-1,2-diol. It should be added that among AAP compounds having antidepressant activity are found, for example 1-(4-propionylphenoxy)-3-(4-phenylpiperazino) propanol-2 (centpropazine) [10].

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 9, pp. 1059-1063, September, 1987. Original article submitted May 6, 1986.

0091/150X/87/2109-0624$12.50