SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-(β-ARYLETHYL)AMIDINES AND N,N'-BIS(β-ARYLETHYL)AMIDINES

N. B. Marchenko, V. G. Granik, R. G. Glushkov, L. I. Budanova, V. A. Kuzovkin, V. A. Parshin, and R. A. Al'tshuler

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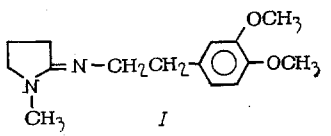
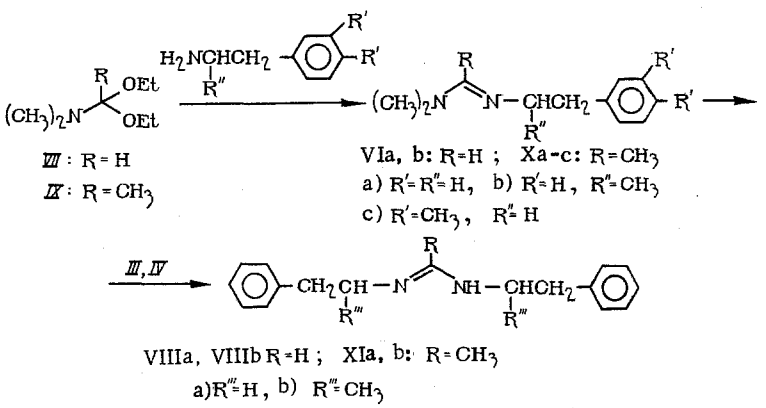
The present work is devoted to the development of methods for synthesizing amidines having β-arylethyl groupings attached to their N atoms, and to the study of their biological activity. It should be noted that amidines of this kind include a number of substances with biological activity [1, 2], including the coronary dilator mixidine, i.e., 1-methyl-2-[β-(3,4-dimethoxyphenyl)ethyl]iminopyrrolidine (I) [3, 4]



I

In view of this, we have attempted to develop a general method for synthesizing noncyclic analogs of I from dimethylformamide (DMF) and dimethylacetamide (DMA). Bearing in mind the ability of adducts of DMF with phosphorus oxychloride to react with amines to form amidines [5], we reacted the complex of DMF with phosphorus oxychloride (II) with β-phenylethylamine (III), β-phenylisopropylamine (IV) and homoveratrylamine (V), thus obtaining N,N-dimethyl-N'-(β-arylethyl)formamidines (VIa-VIc) in yields of 51, 52, and 35%, respectively. We also examined the possibility of preparing VIb and VIc from the diethyl acetal of DMF (VII). It should be noted that the reactions of VII with aromatic amines have been investigated in great detail [6], but that there is direct evidence [6] that amide acetals do not react with highly basic amines. In contrast to this, we have found that VII reacts smoothly with amines IV and V in various solvents to form amidines VIb and VIc in yields of 80 and 67%, respectively. Amidines VIa and VIb are starting materials for the preparation of N,N'-bis(β-arylethyl)formamidines (VIIIa and VIIIb). The latter were prepared by reamination of amidines VIa and VIb with the corresponding amines. Analogously, N-(β-arylethyl)-acetamidines (Xa-Xc) and N,N'-bis(β-arylethyl)acetamidines (XIa and XIb) were synthesized from the diethyl acetal of DMA (IX).



VIIIa, VIIIb R = H; XIa, b: R = CH_3
a) R''' = H, b) R''' = CH_3

It should be noted that attempts to prepare amidine Xb from the adduct of DMA with phosphorus oxychloride (XII) did not meet with success. We used gas–liquid chromatography to

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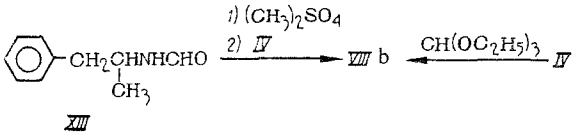
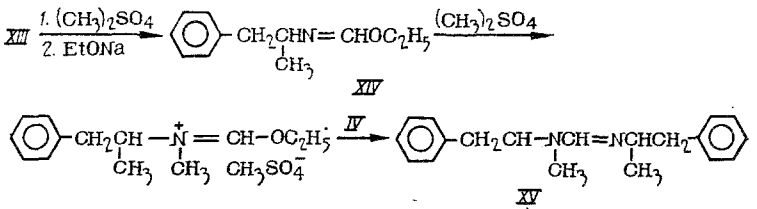
make a more detailed study of the reaction of adducts II and XII with amines. After carrying out the reaction, we alkalized the reaction mixture, extracted it with chloroform, and analyzed the extract by gas–liquid chromatography. We found that the reaction products of II and IV are DMF, amine IV and amidine VIb in a ratio of 1.36:1:6.7. The bis product VIIb was not detected in the reaction mixture. On the other hand, analysis of the mixture obtained by reacting adduct XII with amine IV showed that it contained DMA, amine IV, amidine Xb and the bis derivative XIb in a ratio of 24.4:20.7:1:6.4. In other words, amidine formation takes place to a much smaller extent in the latter case, and mainly the starting DMA and amine IV are detected in the mixture. We can hypothesize that in the case of adduct XII, the reaction with the amine proceeds mainly by removal of a proton from the CH_3 group to form an α-chloro enamine, which is converted back into DMA when treated with alkali. The possibility of proton elimination in this way has been considered in detail in the case of the DMA acetal (IX) [6]. Compound VIIIb was also synthesized by two alternate methods, viz., from N-formyl-β-phenylisopropylamine (XIII) via a methyl sulfate complex and by reaction of amine IV with ethyl orthoformate.



For the biological study, we also prepared an amidine with completely substituted nitrogen atoms, viz., N,N'-bis(β-phenylisopropyl)-N'-methylacetamidine (XV). This was synthesized from XIII via the imino ether (XIV) according to the following scheme:



The pharmacological properties of the above compounds were tested on male mice weighing 18-20 g, male rats weighing 100-140 g, and cats, on the basis of indices characteristic of phenylethylamine derivatives.

The action of the compounds on the central nervous system was investigated on the basis of the following indices: a) their effect on the behavior of mice and rats, including a qualitative record of the motor activity of the animals on an Animex instrument; b) their effect on the body (rectal) temperature of mice; c) their interaction with amphetamine (3-5 mg/kg, i.p.) according to hyperactivity and hyperthermia tests on mice; d) their interaction with reserpine (2 mg/kg, i.p.) according to ptosis, hypodynamic and hypothermic tests on mice; and e) their effect on the spasmogenic action of tryptamine (5 mg/kg, i.v., rat) and 5-hydroxytryptophane (50 mg/kg, i.p., mouse).

The action of the compounds on the peripheral adrenoreactive system was studied on the basis of the following indices: a) their effect on arterial pressure, respiration and third-eyelid tonus in experiments on narcotized cats and rats; b) their effect on arterial pressure in experiments on rats with destroyed spinal marrow; and c) their interaction with adrenaline and the adrenolytic tropaphene in the experiments indicated above.

The acute toxicity of the compounds was tested on mice. The test preparations were administered intraperitoneally in all experiments.

The toxicity of the compounds varies considerably (the LD_{50} is 220, 160, and 300 mg/kg, respectively for VIa-VIc and 40-60 mg/kg for Xa-Xc, VIIIa, VIIIb, XIb, and XV), but the general picture of the acute intoxication induced by these compounds was similar. The leading symptoms were dyspnea followed by depression of respiration, and death was preceded by clonic-tonic spasms.

In studying the effect of the compounds on the central nervous system, we administered VIa-VIc to mice in doses of 12.5-50 mg/kg and to rats in doses of 10-25 mg/kg, and VIIIa, VIIIc, XIb and XV to mice in doses of 5-25 mg/kg and to rats in doses of 5-10 mg/kg. It was found that VIa-VIc slightly enhance the reflex reaction of the animals to audiotactile stimuli at the above doses. A short-lived moderate increase in motor activity was noted in a

TABLE 1. N,N-Dimethyl-N'-(β-arylethyl)amidines

Compound	Yield (%)	Melting point (deg) or boiling point (deg/mm)	Found (%)				Empirical formula	Calculated (%)			
			C	H	N	P		C	H	N	P
VIa phosphate	51	171—3*	48,45	6,91	10,30	11,23	$C_{11}H_{16}N_2 \cdot H_3PO_4$	48,18	6,93	10,22	11,31
VIb phosphate	90	190—1*	50,11	7,29	9,57	10,97	$C_{12}H_{18}N_2 \cdot H_3PO_4$	50,00	7,29	9,72	10,76
VIc phosphate	67	201—2*	46,65	7,01	8,48	9,5	$C_{13}H_{20}N_2O_2 \cdot H_2PO_4$	46,71	6,89	8,38	9,28
Xa	92	101—6/1	75,61	9,27	—	—	$C_{12}H_{18}N_2$	75,79	9,47	—	—
Xb	83	90—4/1	76,65	9,90	—	—	$C_{13}H_{20}N_2$	76,47	9,80	—	—
Xc	32	159—162/1	67,56	8,78	10,59	—	$C_{14}H_{22}N_2O_2$	67,2	8,2	11,2	—

*The phosphates of VIb and VIc were crystallized from methanol; the phosphate of VIa was crystallized from ethanol.

number of experiments. These compounds were inactive in the other tests. The remaining compounds had no marked effect on the central nervous system.

The pheripheral action of VIa-VIc, VIIIa, VIIIb, XIb and XV when administered intravenously to cats and rats in doses of 1-5 mg/kg is characterized by a short-lived moderate hypotensive effect. In contrast to these compounds, Xa-Xc at the same doses constantly increased the arterial pressure of rats by 20-40 mm Hg. This effect is not long-lasting, it is prevented and neutralized by administration of the adrenolytic tropaphene. The pressor action of Xa-Xc on cats was not constant (the preparations displayed a hypotensive action in some experiments), but a moderate increase in third-eyelid tonus is observed constantly. Compounds Xa-Xc have no significant influence on the effects of adrenaline.

Thus, the above pharmacological investigations indicate that compounds VIa-VIc have the elements of a central stimulant action, while compounds Xa-Xc have the elements of a peripheral sympathomimetic action. Compounds VIIIa, VIIIb, Xb and XV are inactive in both senses.

EXPERIMENTAL SECTION

N,N-Dimethyl-N'-(β-phenylisopropyl)formamidine (VIb). A. A cooled solution of 6 g (0.082 mole) of DMF in 10 ml anhydrous benzene was treated dropwise with a solution of 6 g (0.038 mole) of phosphorus oxychloride in 10 ml anhydrous benzene and a solution of 5 g (0.038 mole) of amine IV in 10 ml anhydrous benzene. The reaction mixture was taken up in water, alkalized to pH 10.0, and extracted with benzene. The benzene extract was dried with sodium sulfate, evaporated, and the residue distilled to give 3.75 g of amidine VIb. Amidines VIa and VIc were prepared analogously.

B. A mixture of 6.7 g (0.046 mole) of acetal VII and 5.5 g (0.046 mole) of amine IV was heated at 80° for 2 h, and then distilled to give 7.2 g of amidine VIb. Amidines VIa, VIc and Xa-Xc were prepared analogously.

The yields, physical characteristics and elementary analysis data of these compounds are given in Table 1.

N,N'-Bis(β-phenylisopropyl)formamidine (XIII). A. A mixture of 1.4 g (0.0074 mole) of amidine VIb, 1 g (0.0074 mole) of amine IV and 10 ml DMF was boiled in the presence of p-toluenesulfonic acid for 5 h. The DMF was evaporated off and the residue distilled to give amidine XIIb in a yield of 79%. Amidines VIIIa, XIa and XIb were synthesized analogously. The phosphate of amidine XIa was prepared by adding a solution of phosphoric acid in acetone

TABLE 2. N,N'-Bis(β-arylethyl)amidines

Compound	Yield (%)	Melting point (deg) or boiling point (deg/mm)	Found (%)			Empirical formula	Calculated (%)		
			C	H	N		C	H	N
VIIIa	60	134—150/1	75,05	7,7	10,07	$C_{17}H_{20}N_2 \cdot H_2O$	75,55	8,14	10,37
VIIIb	79	146—7/1	81,00	9,00	9,54	$C_{19}H_{24}N_2$	81,43	8,57	10,00
XIa*	81	216—7†	59,82	7,03	—	$C_{18}H_{22}N_2 \cdot H_3PO_4$	59,34	6,87	—
XIb	66,3	148—150/1	81,26	9,11	9,47	$C_{20}H_{26}N_2$	81,63	8,84	9,53

*Found: P 8.10%; calculated: P 8.5%.
†Compound XI was crystallized from methanol.

to a solution of amidine XIa in acetone. The yields, physical characteristics and elementary analysis data of these compounds are given in Table 2.

B. A mixture of 20.2 g (0.15 mole) of amine IV and 100 ml of ethyl orthoformate was boiled for 4 h. The orthoformate was distilled off and the residue distilled to give a 42% yield of amidine VIIIb.

C. A mixture of 5 g (0.03 mole) of formylamine XIII and 3.8 g (0.03 mole) of dimethyl sulfate was heated at 60° for 2 h. The resulting complex was washed with anhydrous ether and treated dropwise with a solution of 4.05 g (0.03 mole) of amine IV in 5 ml anhydrous benzene. The reaction mixture was left for 1 h, treated with water, adjusted to pH 10.0 with 50% potash solution, and extracted with benzene. The benzene extract was dried with sodium sulfate, the benzene evaporated off, and the residue distilled to give a 70% yield of amidine VIIIb.

N-Ethoxymethylene-β-phenylisopropylamine (XIV). A mixture of 10 g (0.0615 mole) of formylamine XIII and 7.75 g (0.0615 mole) of dimethyl sulfate was heated at 60° for 3 h. The reaction mixture was made alkaline with a solution of sodium ethoxide, evaporated, and the residue extracted with benzene. The benzene was evaporated off and the residue distilled to give 5.25 g (45%(of imino ether XIV, bp 66-67°/1-2 mm. Found, %: C 75.20; H 8.6; N 7.80. $C_{12}H_{17}NO$. Calculated, %: C 75.39; H 8.90; N 7.32.

N,N'-Bis(β-phenylisopropyl)-N'-methylacetamidine (XV). Dimethyl sulfate (2.9 g, 0.023 mole) was added to 4.4 g (0.023 mole) of N-ethoxymethylene-β-phenylisopropylamine (XIV) at 20-25°. The resulting complex was washed twice with anhydrous ether and treated with 3.1 g (0.023 mole) of amine IV in 10 ml anhydrous benzene at 20-25°. The reaction mixture was left for 1 h, taken up in water, alkalized to pH 10.0, extracted with benzene, and the extract dried with sodium sulfate. The benzene was evaporated off and the residue distilled to give 3.5 g (52%) of amidine XV, bp 164-165°/1-2 mm. Found, %: C 81.90; H 8.86; N 9.31. $C_{20}H_{26}N_2$. Calculated, %: C 81.63; H 8.84; N 9.53.

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