the flow as compared to the initial rate by 80 ± 11.2% within 1.5 to 2 h. The most active was compound III, which in doses of 0.2 mg/kg increases the rate volume of coronary blood flow by 50 ± 9.2%, while in doses of 0.5 mg/kg increases it by 100 ± 8.6% and maintains it at that level to the end of the experiment (4 to 5 h and longer – average values of 12 experiments). In this fashion an increased dose of this preparation increases the intensity of its coronary dilating activity. Compound III, in the doses used, shows no appreciable activity on the systemic arterial pressure. The minimum effective doses are 5(I), 0.5(II) and 0.2 (III) mg/kg.

The acute toxicity of the hydrochloride of 2,2-dimethyl-3-oxy-8-ethyl-azaspiro[5,5]undecane was studied on white mice weighing 18 to 20 g. Within 24 h after intraperitoneal administration of the substance investigated, we calculated the dose causing mortality of 50% of the animals. LD_{50} for mice with intraperitoneal administration of compound III, calculated according to Berens, is 310 mg/kg.

An analysis of the data obtained with respect to the dependence of the compound's activity on its structure, easily leads to the conclusion that minor changes in the radical R in a series of compounds leads to an appreciable change in the coronary dilating activity of the compounds investigated. These results allow us to suggest that further changes in the structure of the R radical may lead to the development of molecules with new configurations with optimal coronary dilating activity.

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ARYLALKYLAMINE DERIVATIVES.

XIII. SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-ARYLALKENYL DERIVATIVES OF SUBSTITUTED β-PHENYLETHYLAMINES

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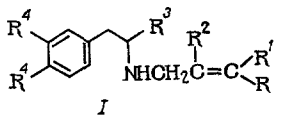
In earlier work we attempted to prepare N-arylalkenyl derivatives of substituted β-phenylethylamines I by the reduction of N-substituted amides of α,β-unsaturated carboxylic acids with lithium aluminum hydride (LAH) [1]. A complex mixture of products was obtained from which compound I could not be isolated.



I

In the present work two alternative methods of synthesizing I (methods A and B) have been investigated and the adrenergic activity of the compounds has been studied. The amides IV were chosen as starting compounds and these were obtained by the condensation of β-phenylethylamines IIII with the acid chlorides of substituted α,β-unsaturated carboxylic acids II.

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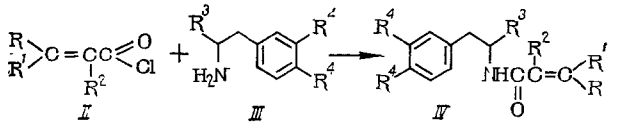
TABLE 1. Sympatholytic and Adrenolytic Action of the Hydrochlorides of the N-Arylalkenyl Derivatives of Substituted β-Phenylethylamines (I)

Compound	R	R^1	R^2	R^3	R^4	Sympatholytic action		Adrenolytic action	
						after 10 min	after 60 min	after 10 min	after 60 min
1	trans-C_6H_5	H	H	CH_3	H	90 (73–107)	58 (13,8–102,2)	93 (79–107)	41 (9–79)
2	cis-C_6H_5	H	H	CH_3	H	88 (78,2–97,8)	56 (51–61)	86 (60,6–111,4)	1
3	$(CH_3O)_2C_6H_3$	H	H	CH_3	H	84 (67,8–100,2)	21 (–4,4–46,4)	52 (–4–108)	+198 (–6,1–402,1)
4	C_6H_5	CH_3	H	CH_3	H	88 (75,3–100,7)	60 (36,8–83,2)	63 (–5–131)	+106 (–68,6–280,6)
5	C_6H_5	H	CH_3	CH_3	H	94	61 (34–88)	45 (–40,8–130,8)	+196 (–55,5–447,5)
6	C_6H_5	CH_3	H	H	CH_3O	95 (90,5–100,5)	69 (38–100)	96 (84–108)	+88 (–10–186)
7	C_6H_5	H	CH_3	H	CH_3O	80 (59,2–100,8)	24 (16,4–31,6)	79 (66,6–91,4)	+136 (–39,8–311,8)
8	C_6H_5	CH_3	CH_3	H	CH_3O	99	65 (47,2–82,2)	82 (55,3–108,7)	+160 (121–199)
9	Octatensine					57 (50,7–63,3)	84 (75,7–92,3)	+185 (34,6–335,4)	+134 (107,2–160,8)
10	Piperoxan					28 (20,6–35,4)	16 (5,7–26,3)	81 (66,7–95,3)	38 (15,9–60,1)
11	Segontin					85 (81–89)	96 (90,6–101,4)	70 (53,5–86,5)	90 (74,7–105,3)

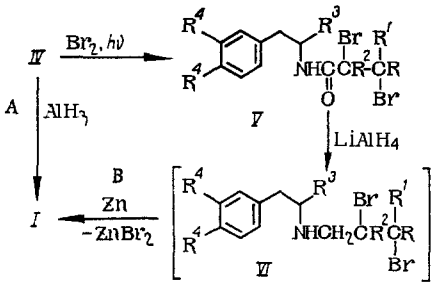
Note. Limits are indicated in parentheses. Plus signs denote an increase in the contraction of the vas deferens.



The IR spectra of the amides IV contained widely different absorption bands for the C=C bond, the amide carbonyl, and the aromatic ring.

The dibromides V were obtained by bromination of IV, but attempts to selectively reduce V failed since in addition to reduction of the carbonyl group, partial removal of the halogen atom took place (thin-layer chromatography and elemental analysis).

The mixture was debrominated with zinc and the product recrystallized to give the pure hydrochloride of I.



Good results were obtained when the unsubstituted amides IV were reduced with aluminum hydride [2]. Tests showed that the reduction occurred selectively and in high yield. The IR spectra of I show absorption bands corresponding to the associated N=H group (3200-3350 cm^{-1}), the C=C bond (1640-1660 cm^{-1}), and the aromatic ring (1600-1605 and 1590 cm^{-1}). In the PMR spectra of I the protons of the double bond gave signals associated with the substituents R, R^1, and R^2. For the β-carbon atom δ=3.2-5.8 ppm, and for the γ-carbon δ=6.3-6.5 ppm. The methyl groups at the double bond gave a multiplet ($\delta \approx$ 0.9-1.4 ppm) [3] and the tertiary carbon atom, a doublet ($\delta \approx$ 1.0 ppm).

The compounds I (R=C_6H_5, R^1=R^2=H, R=CH_3, R^4=H) synthesized by the two methods (A and B) gave hydrochlorides with different melting points corresponding to the cis- and trans-isomers. For example, a compound obtained by method A with mp 205-206°C apparently corresponds to the cis-isomer [4]; this is confirmed by signals in the PMR spectrum corresponding to protons of a cis-configuration double bond with δ=3.5 and 6.9 ppm [5]. The compound obtained by method B (melting point of the hydrochloride 220-221°C), doubtless corresponds to the trans-isomer since it was prepared from trans-cinnamic acid.

EXPERIMENTAL

Pharmacological

The sympatholytic and adrenoblocking action of the substituted β-phenylethylamine N-arylalkenyl derivatives I was studied in tests on the isolated vas deferens of the rat [6]. The sympatholytic action was judged by the decrease in the contraction of the organ caused by $1 \cdot 10^{-6}$ g/ml of epinephrine. The test was carried out four times with a final concentration of 0.05 μmole/ml. The control compounds were: the sympatholytic octatensine, the adrenoblocking agent piperoxan and the "weighted" arylalkylamine segontin.

The results of the tests were treated statistically (arithmetic means with degrees of confidence) and are given in Table 1. As can be seen from Table 1, after 10 min the compounds showed considerable blocking effect on the postganglionic sympathetic nerves and the adrenoreceptors; in this respect they surpass octatensine and piperoxan and equal segontin. However, after 60 min there was a considerable decrease in the sympatholytic action, and even an inversion of the adrenoblocking action. The inversion of the action of epinephrine, produced by octatensine, is explained by reaction to the denervation of the organs [7]. A similar effect is caused by compounds I only when the sympatholytic action is lowered and therefore is not dependent on it.

A comparison of the adrenoblocking action of the cis- and trans-isomers of N-(β-phenylisopropyl)-3-phenyl-2-propenylamine (see Table 1; compounds 1 and 2) shows that they possess the same initial activity, but that for the cis-isomer this activity has completely disappeared after 60 min.

TABLE 2. N-Arylalkyl Substituted Amides of α,β-Unsaturated Acids IV $R(R^1)C=CR^2CONHCHR^3-CH_2-C_6H_3(R^4)_2$

R	R^1	R^2	R^3	R^4	Yield, %	Melting point, °C	Found, %			Empirical formula	Calculated, %			R_f
							C	H	N		C	H	N	
C_6H_5	H	CH_3	CH_3	H	80,0	89—90	81,48	7,36	4,58	$C_{19}H_{21}NO$	81,68	7,57	5,0[illegible]	0,81
C_6H_5	CH_3	H	CH_3	H	80,6	109—10	81,72	8,01	5,00	$C_{19}H_{21}NO$	81,68	7,57	5,0[illegible]	0,81
C_6H_5	CH_3	CH_3	CH_3	H	61,5	Oil*	81,90	7,61	4,81	$C_{20}H_{23}NO$	81,87	7,90	4,[illegible]	0,84
C_6H_5	H	CH_3	H	CH_3O	77,0	99—100	—	—	4,29	$C_{20}H_{23}NO$	—	—	4,[illegible]	0,71
C_6H_5	CH_3	H	H	CH_3O	55,5	90—1	73,58	7,31	4,60	$C_{20}H_{23}NO$	74,00	6,91	4,[illegible]	0,61
C_6H_5	CH_3	CH_3	H	CH_3O	70,5	Oil†	—	—	4,40	$C_{21}H_{25}NO$	—	—	4,[illegible]	0,89
C_6H_5	C_6H_5	H	H	CH_3O	65,5	104—6	78,63	6,92	4,26	$C_{21}H_{25}NO$	78,20	6,55	3,[illegible]	0,66

*bp 210–215°C (4 mm mercury).
†bp 220–230°C (1 mm mercury).

TABLE 3. Hydrochlorides of N-arylalkenyl Derivatives of Substituted β-Phenylethylamines I $R(R^1)C=CR^2-CH_2NHCHR^3CH_2C_6H_3(R^4)_2 \cdot HCl$

R	R^1	R^2	R^3	R^4	Yield, %	Melting point, °C	Found, %		Empirical formula	Calculated, %		R_f
							N	Cl^-		N	Cl^-	
C_6H_5	H	H	CH_3	H	75,2	220—1	4,60	12,07	$C_{18}H_{21}N \cdot HCl$	4,94	12,38	0,[illegible]
$C_6H_3(OCH_3)_2$	H	H	CH_3	H	61,7	133—4	4,02	9,83	$C_{20}H_{25}NO_2 \cdot HCl$	4,05	10,29	0,1
C_6H_5	H	CH_3	CH_3	H	61,3	143—4	5,03	11,56	$C_{19}H_{23}N \cdot HCl$	4,60	11,80	0,
C_6H_5	CH_3	H	CH_3	H	75,5	145—6	4,59	11,40	$C_{19}H_{23}N \cdot HCl$	4,60	11,80	0,6
C_6H_5*	CH_3	CH_3	CH_3	H	47,3	—	5,01	11,06	$C_{20}H_{23}N \cdot HCl$	4,44	11,28	0,8
C_6H_5	H	CH_3	H	CH_3O	69,2	164—5	4,07	10,10	$C_{20}H_{25}NO_2 \cdot HCl$	4,07	10,30	0,
C_6H_5	CH_3	H	H	CH_3O	65,5	190—1	4,01	10,05	$C_{20}H_{25}NO_2 \cdot HCl$	7,07	10,20	0,
C_6H_5	CH_3	CH_3	H	CH_3O	70,4	159—60	4,30	9,82	$C_{21}H_{27}NO_2 \cdot HCl$	3,89	9,84	0,

*Hygroscopic.

Thus, although these N-arylalkenyl derivatives of substituted β-phenylethylamines I possess sympatholytic and adrenoblocking activity, because of their short-term action they are of no practical use.

Chemical

IR spectra were taken on a UR-20 spectrometer using mineral oil, PMR spectra on a Varian T-60 using carbon tetrachloride with tetramethylsilane as internal standard. Thin-layer chromatography was carried out on aluminum oxide (grade II activity), mobile phase – benzene–acetone (4:1), developer – iodine vapor.

The α,β-substituted cinnamic acids were prepared by the Reformatsky reaction [8].

N-(β-Phenylisopropyl)amide of β-Methylcinnamic Acid (IV; $R=C_6H_5$, $R^1=CH_3$, $R^2=H$, $R^3=CH_3$, $R^4=H$). To 0.1 mole of the acid chloride of II in 150 ml of benzene was added dropwise with stirring a mixture of 0.1 mole of the amine III ($R^3=CH_3$, $R^4=H$) and 0.1 mole of pyridine in 200 ml of benzene. The mixture was refluxed for 6 h and dilute hydrochloric acid (1 : 10) added to bring the solution to pH 2.0-3.0. The benzene layer was separated and washed with a 10% solution of sodium carbonate. After evaporation of the benzene, the amide was recrystallized from petroleum ether and then recrystallized from a benzene–petroleum ether mixture (1 : 2). The remaining amides were obtained in the same way (see Table 2).

N-[β-(3,4-Dimethoxyphenyl)ethyl]amide of 2,3-Dibromo-3-phenylpropionic Acid (V; $R=C_6H_5$, $R^1=R^2=R^3=H$, $R^4=CH_3O$). This was obtained by the action of bromine on the corresponding amide IV [9]. Yield 76.4%, mp 160-161°C, R_f 0.81. Found, %: Br 33.96; N 3.16. $C_{19}H_{21}Br_2NO_3$. Calculated, %: Br 33.90; N 2.97.

The same method was used to prepare V [$R=(CH_3O)_2C_6H_3$, $R_f=R^2=R^3=H$, $R=CH_3O$]. Yield 62%, mp 65-66°C, R = 0.73. Found, %: Br 29.82; N 3.13. $C_{21}H_{25}Br_2NO_5$. Calculated, %: Br 30.08; N 2.64.

IR spectrum, ν cm^{-1}: 3250-3350 (N=H), 1670 (amide C=O).

N-(β-Phenylisopropyl)-3-phenyl-2-propenylamine (I; $R=C_6H_5$, $R^1=R^2=H$, $R^3=CH_3$, $R_4=H$). Method A. Lithium aluminum hydride (1.17 g, 0.03 mole) was added portionwise to 8.5 g (0.02 mole) of V ($R=C_6H_5$, $R^1=R^2=H$, $R^3=CH_3$, $R^4=H$) [9] in a mixture of 100 ml of absolute ether and 150 ml of absolute tetrahydrofuran, and the reaction mixture stirred at room temperature for 18 h. After cooling, the complex and the excess LAH were decomposed with a 5% solution of sodium carbonate, the precipitate filtered off, washed on the filter with benzene, and the solvent evaporated. The residue was dissolved in benzene, washed with dilute hydrochloric acid (1:10), the aqueous layer made alkaline with a 5% solution of sodium carbonate, the amine extracted with benzene and the solvent evaporated. Thin-layer chromatography showed two spots (R_f 0.43 and R_f 0.64 which could not be separated. The residue containing the amines was dissolved in 50 ml of acetone and 25 ml of a 5% solution of hydrochloric acid, and to this was added with mixing 6 g of activated zinc powder [10] in small portions (the solution is quickly decolorized). After mixing for 6 h at room temperature, the solvent was evaporated and 100 ml of benzene was added to the residue. A 10% solution of sodium carbonate was added to the residue to give a pH of 9.0-10.0 and the amine I was extracted with ether. After removal of the solvent, the residue was dissolved in ether, the solution filtered, and the precipitated hydrochloride recrystallized from an acetone–ether mixture to give 2.5 g (50%) of I, mp 205-206°C, R_f 0.64. Found, %: Cl 12.46- N 4.72. $C_{18}H_{21}N\cdot HCl$. Calculated, %: Cl 12.38; N 4.94. IR spectrum of the base, ν cm^{-1}: 3280-3350 (associated N=H), 1660-1670 (C=C), 1600 and 1580 (aromatic C=C).

Method B. A solution of 0.015 mole of IV dissolved in 150 ml of absolute tetrahydrofuran was added dropwise to an ethereal solution of 0.035 mole of aluminum hydride [2], and the reaction mixture mixed for 4 h at 0-2°C and then left to stand overnight. The complex and the excess aluminum hydride were decomposed with a 100 ml of ether and a 5% sodium hydroxide solution, the precipitate filtered off, washed on the filter with 100 ml benzene, and the solvent evaporated. The residue was dissolved in absolute ether, the solution filtered, and the precipitated hydrochloride recrystallized from an acetone – ether mixture (Table 3). IR spectrum of base, ν cm^{-1}: 3290-3380 (associated N = H), 1650 (C=C), 1600 and 1580 (aromatic C=C), 1005 (trans- ).

The remaining N-arylalkenyl derivatives of substituted β-phenylethylamines I were obtained by method B. Physicochemical constants are given in Table 3.

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SYNTHESIS OF 5-SUBSTITUTED 2-CHLORO-7-METHYLIMIDAZO[1,2-a]PYRIMIDINE AND THEIR BACTERIAL AND FUNGICIDAL ACTIVITY

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UDC 615.281/.282:547.859'781

The compounds 2-alkyl (aryl-, heteryl-) substituted and 2,5-disubstituted imidazo[1,2-a]pyrimidines display antibacterial, antiprotozoal, antipyretic [1], diuretic [2], hypotensive [3], and antistrychnine [4] activity. However, the biological properties of 2,5-substituted amino-, R-amino, alkoxy-, aryloxy-imidazo [1,2-a]pyrimidine have not been studied probably because they cannot be prepared by known methods [5]. Alkylation of unsymmetric aminopyridines with halogen carbonyl reagents or condensation of aminoimidazoles with 1,3-dicarbonyl compounds [7] generally give mixtures of isomers which are difficult to separate. We have developed a method for the preparation of 2-chloro-5-H-(hydroxy-, alkoxy-, amino-)-7-methylimidazo-[1,2-a]pyrimidine from 2,5-dichloro-7-methylimidazo[1,2-a]pyrimidine which is free from these disadvantages.

The aim of the present work was to synthesize some 5-substituted 2-chloro-7-methylimidazo[1,2-a]-pyrimidines and to study their biological properties. The starting compound 2,5-dichloro-7-methylimidazo-[1,2-a]pyrimidine (III) was synthesized by reacting 2,3,5,8(1)-tetrahydro-7-methylimidazo [1,2-a]pyrimidine-2,5-dione (I) or 2-amino-4-methyl-6-oxo-1,6-dihydropyrimidine-1-acetic acid (II) [6] with phosphorous oxychloride in an organic solvent (e.g. dimethylaniline). The IR spectrum of compound III shows absorption bands at 725 and 760 cm^{-1} corresponding to the stretching vibrations of the CCl group, and at 1620 cm^{-1} due to the C=N bond. Selective attack by a nucleophilic agent is possible on one or both of the electrophilic centers at C_2 and C_5 which are activated by the chlorine atom in compound III. It should be noted that hydrolysis, alkoxylation, and amination of compound III leads to nucleophilic substitution of the chlorine atom at position 5 of the bicyclic ring. Reduction of III with zinc dust proceeds analogously. Nucleophilic substitution of the chlorine atom in position 5 of the imidazopyrimidine system is explained by the lower electronic population of the pyrimidine ring in comparison with the imidazole ring.

To confirm the structures of the compounds synthesized, we reacted 2-chloro-5-phenylamino-7-methylimidazo[1,2-a]pyrimidine (IX) and thiourea to give 5-phenylamino-7-methylimidazo[1,2-a]pyrimidine-2(3H)-thione (XI) which owing to the presence of active hydrogens in the methylene group at position 3 forms the ilidene derivative XII.

Zaporozh Medical Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 12, No. 10, pp. 64-67, October, 1978. Original article submitted January 16, 1978.

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