SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3,4-DISUBSTITUTED 2-AMINOPYRIDINES AND 2-PYRIDONES

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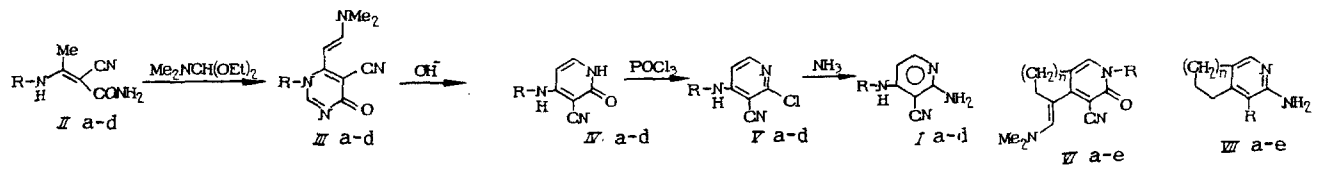
In our earlier investigation [7] of 2,3,4-trisubstituted pyridines with the amino and amidino groups at the 2- and 4-positions, we discovered compounds having analgetic activity. In continuation of this work, using the previously developed scheme [1], we have now carried out the synthesis of a new group of pyridine derivatives (Ia-d). The starting enaminoamides (II) were obtained by the reaction of cyanoacetamide with N,N-dimethylacetamide diethylacetal, followed by transamination of the enamines obtained with aromatic amines [2].;

We also studied the biological activity of pyridine (IVa,c) and isoquinoline (VIIa-g) derivatives containing a 2-amino- or 2-oxopyridine fragment, which we had previously synthesized [3, 4, 6].

It should be noted that the bicyclic carbamides (VIIc, f) were obtained from nitriles (VIId,g) not as described for VIIf in the literature [6], but by the hydrolysis of the cyano group with concentrated H_2SO_4, whereby the yield of compound VIIf was substantially increased. The method of preparation of aminopyridine VIIa unsubstituted at the 3-position was also improved: the compound was obtained by heating nitrile IVd in 75% H_2SO_4



II a-d III a-d IV a-d V a-d VI a-d VII a-e VIII a-e

p=1 (VIa, VIc, VIIa-d), 2(VIb, VIIe-g); R=H(VIa, d, VIIa), Et (VIe), COOH(VIIb, e), $CONH_2$ (VIIc, f), CN (VIId, g) C_6H_4Cl-p (Ia-Va), C_6H_4OMe-p (Ib-Vb), C_6H_4Me-m (Ic-Vc), C_6H_4Me-p (Id-Vd).

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	mp, °C (solvent)	Empirical formula
Ia	76	256—8 iso-PrOH	$C_{12}H_9ClN_4$
Ib	75	211—3 iso-PrOH	$C_{13}H_{12}N_4O$
Ic	75	151—3 iso-PrOH	$C_{13}H_{12}N_4$
Id	82	195—7 iso-PrOH	$C_{13}H_{12}N_4$
II d	70	207—8 DMF	$C_{12}H_{13}N_3O$
IIId	64	264—6 ethanol	$C_{16}H_{16}N_4O$
IVd	87	320—1 DMF-H_2O)	$C_{13}H_{11}N_3O$
Vd	95	162—4 heptane	$C_{13}H_{10}N_3Cl$
VII f	78	219—20 ethanol-H_2O)	$C_{10}H_{13}N_3O$

TABLE 2. Analgesic Activity and Acute Toxicity of Compounds I, VI, VII in Mice*

Compound	Latent period of pain reaction at thermal irritation, % with respect to control		Suppression of AcOH-induced contractions	LD_{50}, mg/kg (peroral)
	Hot plate	Tail flick		
Ia	120**	105	0	1000
Ib	137**	130**	0	1000
Ic	117	100	0	250
Id	123**	119	0	250
VIa	90	116	0	1000
VIb	88	97	0	500
VIc	105	123	0	1000
VIIa	108	117	0	500
VIIb	100	112	17	500
VIIc	127**	133**	37**	500
VIId	101	115	10	1000
VIIe	82	107	0	750
VIIf	149**	140**	0	700
VIIg	121**	133**	13	500
Analgin (50 mg/kg)	150**	140**	40**	3000

*During peroral administration in a dose of 10% of LD_{50}.

**Difference from control significant at $p < 0.05$.

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EXPERIMENTAL (CHEMICAL)

Compounds I-VII were synthesized according to [1, 3, 4, 6]. The data on the new compounds are given in Table 1. The PMR spectra were run on an XL-200 spectrometer, using TMS as internal standard, and the IR spectra on a "Perkin-Elmer 457" spectrophotometer (USA) in mineral oil. The results of the elemental analyses corresponded to the calculated values.

3-Amino-4-carbamido-6,7,8,9-tetrahydroisoquinoline (VIIf). A 50 ml portion of 95% H_2SO_4 was added to 5 g of VIIg, and the mixture was stirred at 100°C for 40-45 min. It was then cooled, made alkaline to pH 9-10 with 20% NaOH, and 4.3 g of VIIf was filtered off. Yield 78%. IR spectrum, ν_{max}, cm^{-1}: 1650 (C=O), 3200, 3300, 3450, 3550 (NH_2), absence of the C=N band. PMR spectrum, CF_3COOD, δ, ppm: 1.3-1.68 (4H, s, 6.7-CH_2) 2.2-2.8 (4H, d 5.8-CH_2), 7.3 (1H, s, 1-CH).

3-Amino-5,6-dihydro-7H-pyridine-2 (VIIa). A 450 ml portion of 75% H_2SO_4 was added to 30 g of VIId and the mixture was boiled for 1 h. It was then cooled, made alkaline with 40% NaOH to pH 9-10, and extracted with $CHCl_3$. The combined chloroform layers were dried over $MgSO_4$, evaporated, and the residue was crystallized from heptane. Yield 44%.

β-(4^1-Methylphenylamino)-α-cyanocrotonamide (IId). A 3 g portion of p-toluidine and 10 ml of glacial AcOH were added to 2 g of β-dimethylamino-α-cyanocrotonamide. The mixture was boiled for 4 h, was then cooled and 2.2 g of IId was filtered off.

1-(p-Tolyl)-5-cyano-6-(β-dimethylaminovinyl)-1,4-dihydropyrimidin-4-one (IIId). A mixture of 1 g of IId, 3 ml of a 70% dimethylformamide acetal and 5 ml of absolute ethanol was boiled for 3 h. The mixture was cooled and 0.9 g of IIId was filtered off.

2-Cyano-4-(p-tolyl)pyridin-2-one (IVd). A 10 ml portion of 1 N NaOH was added to 1 g of IIId, and the mixture was boiled for 1 h. It was then cooled and neutralized with 10% HCl to pH 6-7, and 0.7 g of IVd was filtered off.

2-Chloro-3-cyano-4-(p-tolyl)pyridine (Vd). A mixture of 25.4 g of IVd, 250 ml of $POCl_3$ and 2 ml of dimethylaniline was boiled for 2 h. Phosphorus oxychloride was distilled off under vacuum, and 350 ml of H_2O was added to the residue, and the mixture was boiled for 30 min. It was then cooled, made alkaline with 10% of NaOH to pH 7-8, an 26 g of compound Vd was filtered off.

4-Arylamino-2-amino-3-cyanopyridines (Ia-d). A 15 ml portion of a 13% solution of NH_3 in ethanol was added to 1 g of chloropyridine Va-d and the mixture was heated in an autoclave at 200-210°C for 10 h. The mixture was cooled, and the precipitate that separated out was filtered off.

EXPERIMENTAL (PHARMACOLOGICAL)

The analgetic activity of compounds I, VI, VII was studied on models of thermal [13, 11] and chemical [10] pain irritation in mice, each weighing 18-20 g. The compounds were administered perorally in a dose consisting of 10% of LD_{50}. The influence of the compounds was also studied on the arterial pressure (AP) in rats with a model of a renovascular hypertension [8] (RVH) with an indirect method of recording the AP [9]. The acute toxicity of the compounds was studied on mice by peroral administration and determination of the LD_{50} value according to a method described in [12].

The statistical treatment of the experimental results was carried out with the determination of the mean values and the standard error; in the comparison of the mean values the Student's criterion t was used.

The results of the investigation of the analgetic activity and the acute toxicity of the compounds during peroral administration are shown in Table 2, which shows that the compounds studied are in the class of slightly toxic compounds, according to the K. K. Sidorov classification [5], except for compounds Ic and Id, which are moderately toxic (LD_{50} 250 mg/kg).

Compounds VIIa, VIIc, VIIf, Ia, Ib and Id had an analgetic effect on a "hot plate" model of pain irritation. Using the thermal irritation of the tail (tail flick), an analgetic action was found in compounds VIIg, VIIc, VIIf and Ib. The remaining compounds were not active for these pain models. On using the model of a chemical pain stimulation, the compounds studied were slightly active except for compound VIIc, which in a dose of 10% of LD_{50} decreased the number of contractions caused by an intraperitoneal administration of AcOH by 40%.

TABLE 3. Influence of Compounds I, VI, VII on the AP in Rats with a Model of a Renovascular Hypertension during Oral Administration in a Dose of 10 mg/kg (indirect recording, number of animals in a group – 6)

Compound	Change in AP after the administration of the compounds, mm Hg	
	after 1 h	after 2 h
Ia	0	0
Ib	0	0
Ic	–12	–10
Id	0	0
VIa	–23*	0
VIb	–10	–10
VIc	–20*	0
VIIa	+20*	0
VIIb	–15	–10
VIIc	–10	0
VIId	–12	0
VIIe	0	0
VIIf	–25*	–30*
VIIg	0	0

*Difference from the initial AP level is significant at $p < 0.05$.

With respect to the degree of manifestation of the analgetic effect, compound VIIc and other compounds studied are inferior to the reference preparation analgin.

The data obtained in the investigation of the influence of compounds I, VI, VII and on the AP in hypertensive rats are presented in Table 3.

Table 3 shows that compounds VIa-c and VIIc,f during a single administration in a dose of 10 mg/kg to rats with RVH, caused a significant lowering of AP compared with the initial level, this property being most pronounced in compound VIIf. However, the effect of this compound was not lasting and toward the 3rd hour the AP returned to its initial level.

On the contrary, compound VIIa caused a short-term rise in the AP (by 20 mm Hg) relative to the initial level.

In the structure–activity analysis in this series, no patterns were revealed in the change in the analgetic properties of the compounds according to the change in the molecular structure. However, the presence of substituents (CN, $CONH_2$, COOH) at the 3-position of the pyridine ring resulted in the display of antihypertensive properties in the compounds; it is interesting to note that compound VIIa, which does not contain substituents in this position, caused a hypertensive reaction.

Thus, the data obtained indicate that further search for antihypertensive and analgetic preparations among the 2,4-disubstituted pyridine derivatives should be of promise.

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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SUBSTITUTED TETRAHYDROPYRAN AMIDES AND AMINES

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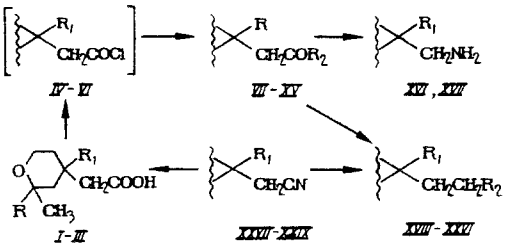
In continuation of studies on 4-substituted tetrahydropyrans, it was of interest to obtain substituted amides and amines in the series and to examine their biological activity, since some aminoalcohols of this type display biological activity [2].

Reaction of 2,2-dialkyl-4-benzyl(or phenyl)-substituted tetrahydropyran-4-ylacetic acids (I-III) [1] with thionyl chloride affords the acid chlorides (IV-VI). The latter were used in subsequent reactions without further purification, since they decompose on distillation. On reaction with amines and ammonia, they gave the amides (VII-XV). Reduction of these, and of the nitriles (XXVII-XXIX) [1] with lithium aluminohydride (LAH) gave the amines (XVIII-XXIII) and (XXIV-XXVI) respectively. Hoffman decarbonylation of the amides by treatment with sodium hypobromite in alkaline solution gave the amines (XVI, XVII), containing one carbon atom less than the starting amides.



R=CH_3 (I, II, IV, V, VII, VIII, X—XIII, XVI—XXI, XXIV, XXV, XXVII, XXVIII); Et (III, VI, IX, XIV, XV, XXII, XXIII, XXVI, XXIX); R^1=Ph (I, III, IV, VI, VII, IX—XII, XIV—XVI, XVIII, XX—XXIV, XXVI, XXVII, XXIX); CH_2Ph (II, V, VIII, XIII, XVII, XIX, XXV, XXVIII); R^2=NH_2 (VII—IX, XXIV—XXVI); N-pyrrolidyl (XII, XVIII); N-piperidyl (XI, XIII, XIV, XIX, XX, XXII); N-morphylyl (X, XXI, XXIII).

The structures of the products were proved by their PMR, IR, and mass spectra.

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a UR-20 (East Germany) in Vaseline grease, and mass spectra on an MX-1320. PMR spectra were obtained on a Varian T-60 (USA) with TMS as internal standard. TLC was carried on Silufol UV-254 plates (Czech SSR), developer iodine vapor. The elemental analyses were in agreement with the calculated values.

2,2-Dialkyl-4-benzyl(or phenyl)tetrahydropyran-4-ylcarbonyl Chlorides (IV-VI). To a mixture of 0.12 mole of one of the acids (I-III) [1] and 0.15 mole of formamide in 100 ml of dry benzene was added dropwise with stirring 0.15 mole of thionyl chloride. The mixture was then

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