UDC 615.782-012:547.822.3

10. Nobuo Itoh : Synthesis of 1-Substituted 4-Phenyl-4-piperidinol Derivatives as Possible Analgesic.

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1-Methyl-4-phenyl-4-piperidinepropionate is a well-known compound used therapeutically as a synthetic analgesic. Lee[1] and Beckett, *et al.*[2] first pointed out that 3-alkyl group has a favorable effect upon the physiological property of this compound. Of the two diastereoisomeric 3-methylprodines, the racemic β-isomer is twice and the levorotatory β-isomer is 4 times more active than the original compound. The influence of 1- and 4-substituents of the above-mentioned piperidinol derivatives was further discussed by Elpern, *et al.*[3] who made clear that 1-phenethyl- and 1-cinnamyl-4-phenyl-4-propionyloxypiperidine is 25 times and 240 times respectively more active than the corresponding 1-methyl derivative, whereas the activity is diminished to 1/2.5 and 1/4 respectively, when 4-propionoyloxy is replaced by acetoxyl group in the above 1-phenethyl and 1-cinnamyl derivatives.

Since it seemed worth while to examine the physiological activity of various 1,3-disubstituted 4-phenyl-4-propionoyloxypiperidines to provide some further informations on the relation between the chemical structure and physiological activity, synthesis of such compounds was undertaken.

For such a synthesis, 1,3-dialkyl-4-piperidinones appeared to be a suitable intermediate, which had been prepared by the present author in the course of synthesis regarding emetine and rotundine.[4] Thus, for the preparation of 1-phenethyl derivative, phenethylamine was condensed with formaldehyde and alkylmalonic acid, followed by decarboxylation and esterification to give 2-alkyl-3-phenethylaminopropionate (Ⅲ), which could also be prepared advantageously from the same amine and an appropriate 2-alkylacrylic ester.

3-Phenethylaminoalkylpropionate (Ⅲ) thus obtained was further condensed with acrylic ester to give 3,3′-(phenethylimino)dipropionic ester derivatives (Ⅳ). (Ⅳ) was then condensed by the Dieckmann method to the cyclic 3-ketoester which, without being isolated and characterized, was directly submitted to ketonic fission. 1-Phenethyl-3-alkyl-4-piperidinones (Ⅴ) obtained was a viscous oil, which was purified by vacuum distillation and characterized as the crystalline picrate or hydrochloride.

4-Piperidinones thus prepared did not react with phenyl Grignard reagent, but they entered into reaction smoothly with phenyllithium to yield 4-phenyl-4-piperidyloxylithium which was converted into the corresponding propionoyloxy derivative by the conventional method. The reaction process is shown in Chart 1.

1-[2-(N-Alkylanilino)ethyl]-3-methyl-4-phenyl-4-(propionyloxy)piperidine was similary prepared by substituting 2-(N-alkylanilino)ethylamine for phenethylamine in the above reaction. The synthesis proceeded according to the route shown in Chart 2.

Physiological properties of the racemic compounds thus prepared were examined by the courtesy of Prof. H. Ozawa and others in the Pharmaceutical Institute of Tohoku University and the results are tabulated briefly in Tables Ⅸ and Ⅹ.

*1 Toda-machi, Kitaadachi-gun, Saitama-ken (伊藤信夫).

1) J. Lee : Medicinal Chem., **1**, 438 (1951).
2) A. H. Beckett, J. Walker : J. Pharm. Pharmacol., **7**, 1037 (1955).
3) B. Elpern, W. Wetteran, P. Carabateas, L. Grumbach : J. Am. Chem. Soc., **80**, 4916 (1958).
4) S. Sugasawa, K. Mizukami : This Bulletin, **6**, 359 (1958).

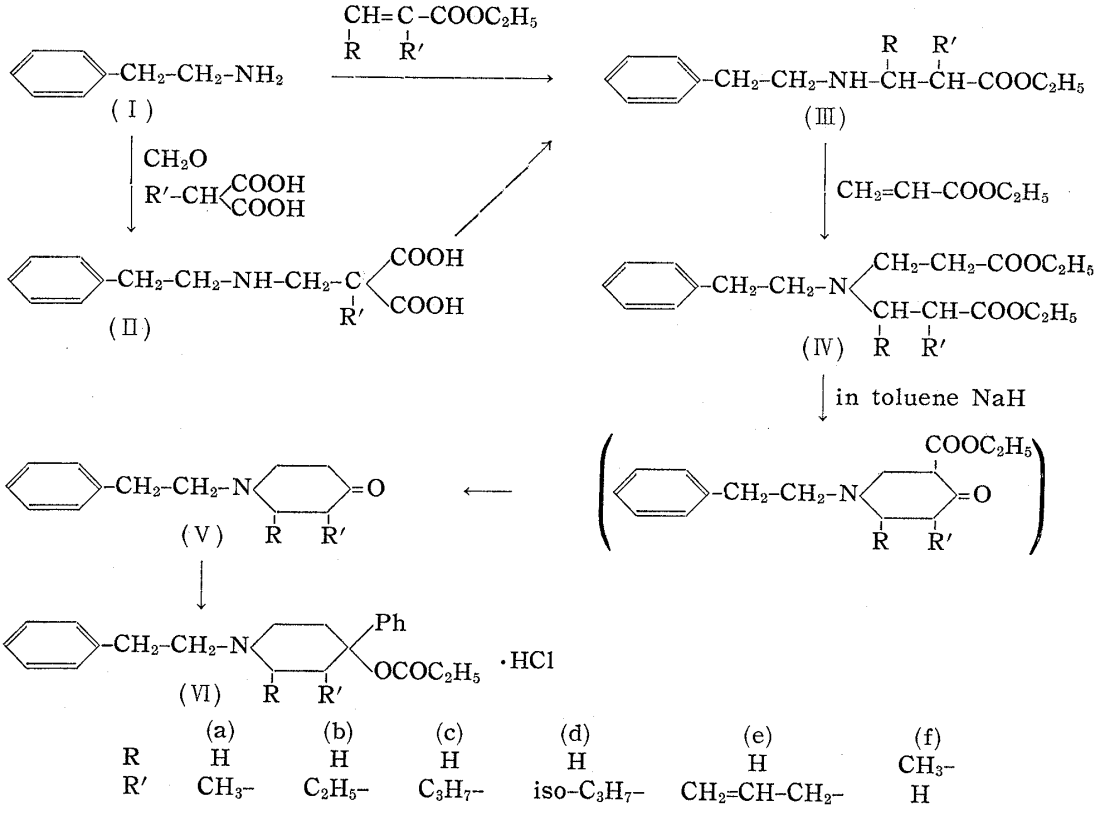


Chart 1.

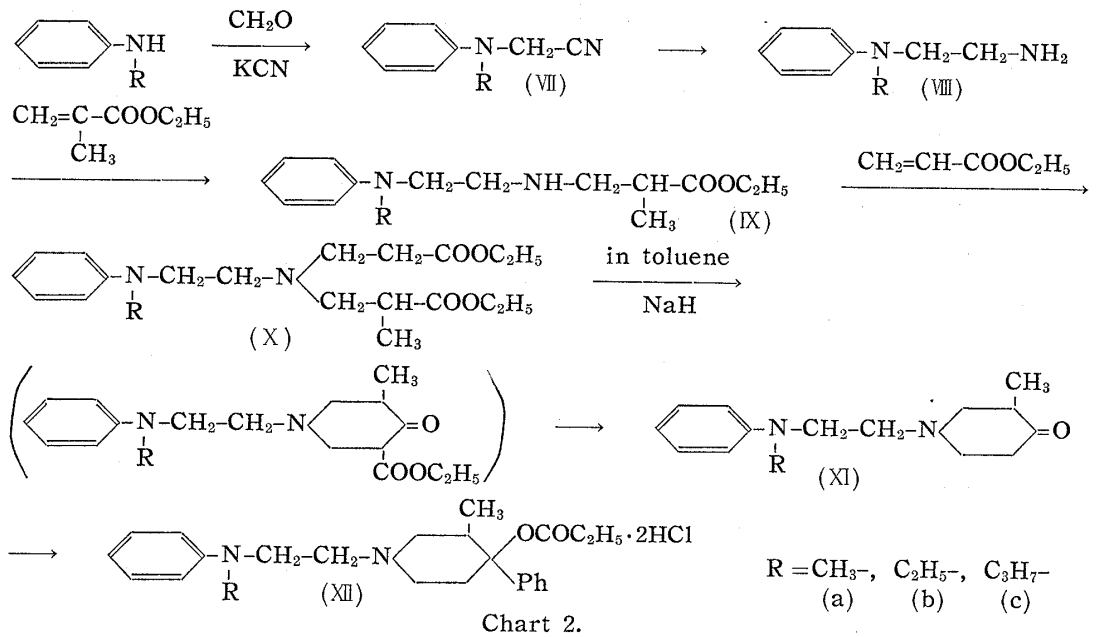


Chart 2.

The analgesic and antitussive properties of the piperidinol derivatives were also examined and the results are summarized in Tables IX and X. As is illustrative in these tables, there seems to exist a definite relationship between the size and nature of alkyl substituents at 1- and/or 3-position of piperidinol ring and physiological properties of these compounds.

1-[2-(N-Methylanilino)ethyl]-3-methyl-4-phenyl-4-(propionoyloxy)piperidine hydrochloride possesses the most significant physiological activity of all the compounds synthesized

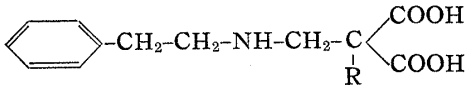
in the present work. As an analgesic it is 7.9 times and 1.25 times more active than morphine hydrochloride and petidine hydrochloride, respectively, and as an antitussive, 6.4 times and 9.6 times more active than these drugs.

During the course of the present work, Beckett[5] also published the synthesis of some of the above-mentioned compounds.

Stereochemical investigations of these compounds and their optical resolution will be the subject of a future work.

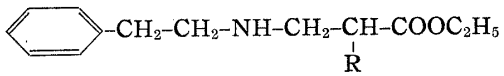
Experimental

Ethyl (phenethylaminomethyl)malonic Acid (IIb)——Ethylmalonic acid (11 g.) dissolved in a mixture of EtOH (100 cc.) and H_2O (100 cc.) was mixed with phenethylamine (10 g.) and 35% HCHO (5 g.), and the whole was allowed to stand at room temperature. After some time, the condensation product separated out, which was collected, dissolved in $NaHCO_3$ soln., and precipitated by acidification with AcOH. For analysis this procedure was repeated once more (Table I).

Table I. 

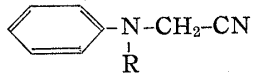
R	m.p. (°C, decomp.) (from EtOH)	Yield (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_2H_5	178	80	63.39	7.16	5.28	63.00	6.92	5.14
C_3H_7	165	62	64.51	7.57	5.01	64.69	7.77	4.88
iso-C_3H_7	153	36	64.51	7.52	5.01	64.65	7.78	5.06
CH_2=CH-CH_2	158	58	65.00	6.86	5.06	64.91	6.55	4.93

Ethyl 2-(Phenethylaminomethyl)butyrate (IIIb)——The foregoing malonic acid (IIb) (17 g.) was mixed with 60% AcOH (150 cc.) and the mixture was refluxed for 4 hr. to complete decarboxylation. The resultant clear solution was evaporated *in vacuo* to dryness. The residual acid was dissolved in dehyd. EtOH, esterified with dry HCl gas, and worked up as usual (Table II).

Table II. 

R	b.p. (°C/mm. Hg)	Yield (%)	Oxalate m.p. (°C, decomp.) (from EtOH)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_2H_5	145/3	71	220~221	60.37	7.53	4.14	60.23	7.43	4.13
C_3H_7	146/2	79	224~225	61.24	7.71	3.96	61.52	7.89	4.19
iso-C_3H_7	145~146/2	71	209~210	61.24	7.71	3.96	61.17	7.80	4.01
CH_2=CH-CH_2	145~148/2	66	213~214	61.54	7.12	3.99	61.45	7.43	4.17

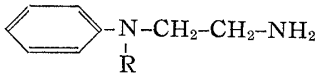
(N-Methylanilino)acetonitrile(VIIa)——A solution of N-methylaniline (25 g.) in aq. HCl (23 cc. of 35% HCl and 57 cc. of H_2O) was added to a mixture of benzene (50 cc.) and Et_2O (25 cc.). To this mixture, 33% HCHO (21.2 cc.) was added with a solution of KCN (18 g.) in H_2O (78 cc.) during 40 min. with cooling and stirring. Cooling and stirring were continued for an additional 6 hr. and then the reaction solution was extracted with benzene. The extract was dried, the solvent was removed, and the residue was purified by distillation *in vacuo* (Table III).

Table III. 

R	b.p. (°C/mm. Hg)	Yield (%)	IR ν_{CN} (cm^{-1})
CH_3	105~110/2	90	2240
C_2H_5	105~110/0.5	90	2240
C_3H_7	127~128/2	90	2240

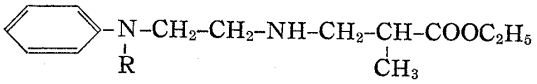
5) A. H. Beckett, A. F. Casy, G. Kirk: J. Med. Pharm. Chem., **1**, 37 (1959).

N-Methyl-N-phenylethylenediamine (VIIIa)——The foregoing nitrile (VIIa) was reduced catalytically at 100 atm. and 60° over Raney Ni catalyst. The product was distilled *in vacuo* (Table IV).

TABLE IV. 

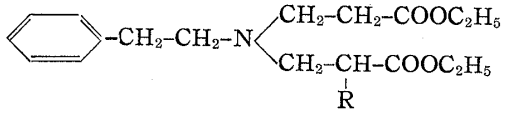
R	b.p. (°C/mm. Hg)	Derivatives	m.p. (°C, decomp.) (from EtOH)	Yield (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	94～97/2	picrate	174～175	80	47.49	4.48	18.46	47.41	4.58	18.35
		oxalate	178		55.00	6.66	11.66	55.23	6.70	11.92
C_2H_5	105～110/2	picrate	162～163	80	48.85	4.83	17.81	49.04	4.78	17.25
		oxalate	166～167		56.69	7.08	11.02	56.25	7.16	10.64
C_3H_7	110～115/2	picrate	160	80	50.12	5.16	17.20	49.77	5.40	17.39

Ethyl 2-Methyl-3-[2-(N-methylanilino)ethylamino]propionate (IXa)——A mixture of N-methy-N-phenylethylenediamine (20 g.) and ethyl methacrylate (20 g.) was allowed to stand at room temperature (15～20°) for 10 days and then warmed at 50° for 10 hr. The product was fractionally distilled and a fraction of $b.p_3$ 165～170° was collected (14.2 g.), which formed a colorless transparent oil and was characterized as the crystalline hydrogen oxalate, which separated in colorless plates (from EtOH), m.p. 212°(decomp.) (Table V).

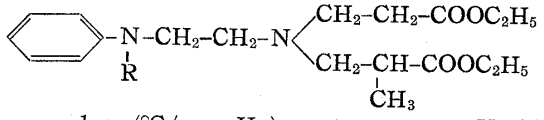
TABLE V. 

R	b.p. (°C/mm. Hg)	Yield (%)	Oxalate m.p. (°C, decomp.) (from EtOH)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	165～166/3	50	212	57.67	7.34	7.91	57.50	7.19	8.06
C_2H_5	156～159/1	47	219～220	58.75	7.60	7.60	58.55	7.39	7.56
C_3H_7	175～180/4	40	213～214	59.68	7.85	7.33	60.04	8.04	7.84

Ethyl 2-{[N-(2-Ethoxycarbonylethyl)phenethylamino]methyl}butyrate (IVa)——A mixture of ethyl 2-(phenethylaminomethyl)butyrate (IIIb) (10 g.) and ethyl acrylate (7 g.) was set aside at room temperature for 10 days and then heated at 75° for 10 hr. The product was fractionally distilled (Table VIa and VIb).

TABLE VIa. 

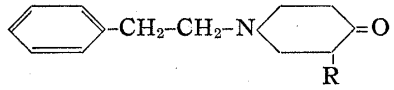
R	b.p. (°C/mm. Hg)	Yield (%)
C_2H_5	175～180/0.3	72
C_3H_7	190～195/0.3	77
iso-C_3H_7	190～195/0.3	72
CH_2=CH-CH_2	190～195/0.3	72

TABLE VIb. 

R	b.p. (°C/mm. Hg)	Yield (%)
CH_3	185～190/1	75
C_2H_5	190～195/1	70
C_3H_7	205～207/1	68

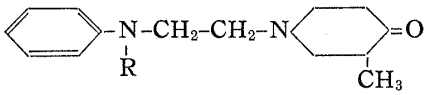
1-Phenethyl-3-ethyl-4-piperidinone (Vb)——To a solution of ethyl 2-[{N-(2-ethoxycarbonylethyl)-phenethylamino}methyl]butyrate (IVb) (7 g.) in toluene (40 cc.), NaH (0.5 g.) was added and the mixture was refluxed in an oil bath kept at 140～145° until the evolution of H_2 had ceased (ca. 4 hr.). When cool, the reaction mixture was acidified with AcOH and extracted with benzene. The residue of the benzene extract was boiled with 10% HCl (30 cc.) for 4 hr. to effect ketonic fission and the mixture was basified with K_2CO_3. The base that liberated was collected in benzene, which was dried and evaporated. The residue was distilled *in vacuo* (Table VIIa and VIIb).

Table VIIa.



R	b.p. (°C/mm. Hg)	Yield (%)	Picrate, m.p. (°C) (from C_2H_5OH)	Analysis (%) Calcd. C	H	N	Found C	H	N
C_2H_5	150~151/3	91	176~177	54.78	5.25	12.17	54.71	5.50	12.17
C_3H_7	155~159/3	81	153~154	55.70	5.50	11.81	55.86	5.82	11.62
iso-C_3H_7	150~153/3	91.7	172~173	55.70	5.50	11.81	55.52	5.90	11.77
CH_2=CH-CH_2	159~160/3	74	176~177	55.93	5.08	11.86	56.10	4.95	11.57

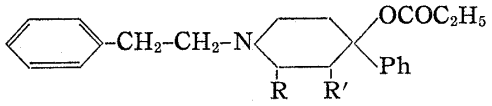
Table VIIb.



R	b.p. (°C/mm. Hg)	Yield (%)	Dihydrochloride m.p. (°C, decomp.) (from EtOH)	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
CH_3	162~165/3	53	192~193	56.43	7.52	8.78	22.26	55.99	7.12	8.43	21.96
C_2H_5	163~165/2	53	194	57.66	7.80	8.40	21.32	57.43	7.56	8.20	21.00
C_3H_7	172~174/1	55	$\frac{1}{2}H_2O$ 178	57.30	8.14	7.86	19.94	56.90	8.60	7.85	19.37

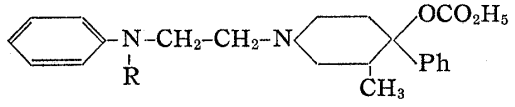
1-Phenethyl-3-methyl-4-phenyl-4-(propionoyloxy)piperidine Hydrochloride (VIa)——To a suspension of metallic Li (0.07 g.) in dehyd. Et_2O, bromobenzene (0.6 cc.) was added in small portions during 30 min. The mixture was warmed for 30 min. until Li metal had disappeared. To this solution 1-phenethyl-3-methyl-4-piperidinone (1 g.) in dehyd. benzene (1.5 cc.) was added with cooling during 30 min. An additional portion of pure benzene (9 cc.) was then added and the whole was refluxed for 1 hr. To the chilled resultant mixture propionic anhydride (1.9 cc.) was added during 15 min. After being heated at 50° for 30 min., the product was decomposed by addition of crushed ice, made alkaline with 10% NaOH solution, and extracted with benzene. The extract was washed, dried, and the solvent was removed. The residue was dissolved in dehyd. Et_2O and the hydrochloride was prepared by introducing dry HCl gas into its Et_2O solution. The salt was purified from a mixture of dehyd. EtOH and AcOEt (Tables VIIIa and VIIIb).

Table VIIIa.



R	R′	Hydrochloride m.p. (°C) (from EtOH)	Yield (%)	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
H	CH_3	204~205	47	71.22	7.74	3.61	9.16	71.30	7.67	3.76	9.01
H	C_2H_5	195~196	47	71.70	8.02	3.48	8.82	72.03	7.94	3.38	9.47
H	C_3H_7	159~160	40	72.20	8.18	3.37	8.54	71.86	8.20	3.01	8.74
H	iso-C_3H_7	167~168	32	72.20	8.18	3.37	8.54	72.14	8.02	3.54	8.76
H	CH_2=CH-CH_2	185~186	15	72.55	7.76	3.38	8.58	72.34	8.01	3.12	8.76
CH_3-	H	195~197	48	71.22	7.74	3.61	9.16	71.52	7.43	3.82	9.24

Table VIIIb.



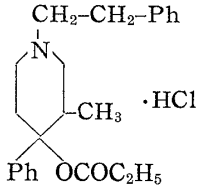
R	Dihydrochloride m.p. (°C) (from EtOH)	Yield (%)	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
CH_3	184~185	20	63.57	7.50	6.18	15.67	63.26	7.13	6.02	15.31
C_2H_5	182~183	20	64.24	7.71	6.00	15.20	64.11	7.53	5.91	14.93
C_3H_7	H_2O 179~180	18	62.52	8.01	5.61	14.23	62.16	7.91	5.42	14.08

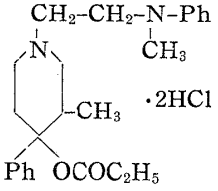
Table IX.

Compound	ED_{50} mg./kg. (Antitussive)	ED_{50} mg./kg. (Analgesic)	LD_{50} mg./kg. (S.C.[a])
Morphine HCl	6.40	3.48	360 (Sulfate[b])
Pethidine HCl	9.65	6.53	165
No. 1	3.34	0.59	60
No. 2	1.02	0.44	ca. 50
No. 3	1.17	1.48	100～150

ED_{50} (Antitussive) : Mechanical stimulation in guinea pigs.
ED_{50} (Analgesic) : Pressure method in mice.
LD_{50} : subcutaneously in mice.

a) L.O. Randoll, G. Lehmann : J. Pharmacol. Exptl. Therap., **99**, 163 (1950).
b) E.L. Way : *Ibid.*, **87**, 265 (1946).

No. 1 

No. 2 

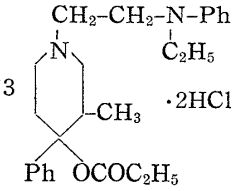
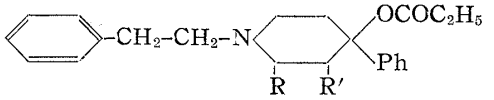
No. 3 

Table X. 

R	R′	ED_{50} mg./kg.	Morphine HCl=1	Pethidine HCl=1
H	CH_3	0.79	10.13	32.28
H	C_2H_5	3.70	2.16	6.89
H	C_3H_7	0.96	8.33	26.56
H	H	1.34	5.97	19.03
CH_3	H	1.16	6.90	21.98
	No. 2	0.51	15.69	50.00

ED_{50} (Analgesic); Hot-plate method in mice.

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Summary

1-Phenethyl- and 1-[2-(N-alkylanilino)ethyl]-3-alkyl-4-piperidinepropionates were synthesized for physiological evaluation as analgesics. Phenethylamine was condensed with formaldehyde and various alkylmalonic acids, followed by decarboxylation and esterification, to furnish the corresponding 2-alkyl-3-phenethylaminopropionates, which were also prepared from the same amine and 2-alkylacrylates. These were then converted to 3,3′-(phenethylimino)dipropionic ester derivatives, which were condensed by the Dieckmann method and the crude keto esters were directly submitted to ketonic fission. 1-Phenethyl-3-alkyl-4-piperidinones thus obtained formed a viscous oil, which was allowed to react with phenyllithium and the products were treated with propionic anhydride, to give the ultimate compounds. From N-alkyl-N-Phenylethylenediamine in place of phenethylamine the corresponding piperidinol propionates were similarly prepared. The results of the pharmacological examination of these compounds were described briefly.

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