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Applications of Piperidine for the Development of New Drugs. I. New Potent Respiratory Stimulants

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Piperidine, one of alicyclic amines, shows not only nicotine-like synaptotropic actions but also a marked respiratory stimulant action due to the chemoreflex of carotid body. Accordingly, in expectation of preparing some potent respiratory stimulants, two series of compounds were synthesized by the substitution of the pyridine ring in the nikethamide structure for a piperidine ring and the substitution of morpholino groups in the dimorpholamine (dim.) for two piperidino groups or similar piperidine ones. Among them, N,N′-dibutyl-N,N′-bis(piperidinocarbonyl)ethylenediamine (VII) was the most potent in respiratory stimulant action.

In rabbits, the respiratory stimulant action of VII was 4 to 5 times as potent as that of dim. and the duration of the effect was twice as long as that of dim. Its toxicity in mice was about a half that of dim. Furthermore, the significance of the role of piperidino group in manifestation of pharmacological activities was demonstrated.

Piperidine, one of alicyclic amines, possesses nicotine-like actions on the peripheral synapses and chemoreceptors and, furthermore, a minute amount of it causes a marked respiratory stimulation through carotid body reflex concomitantly with a rise of blood pressure in dogs and cats.[2]

Pyrrolidine shows similar but weaker pharmacological properties than piperidine not only in actions on synapses and chemoreceptors but also in stimulant action on respiration.[2]

Piperazine and morpholine are of quite different nature, that is, they do not show definite nicotine-like actions but cause weak respiratory stimulation due to respiratory reflex induced by a transitory and precipitous fall of blood pressure without any action on the carotid body chemoreceptors.[2]

Thus, piperidine is the most active among the alicyclic amines in respiratory stimulant action. Accordingly, the respiratory stimulant action would be remarkably strengthened if this pharmacological activity is given to a known respiratory stimulant by the introduction of a piperidine nucleus.

1) Location: *a) 1-5 Oehon-machi, Kumamoto; b) Yoshitomi-machi, Chikujo-gun, Fukuoka.*

2) Y. Kasé, T. Miyata, and T. Yuizono, *Japan. J. Pharmacol.*, **17**, 475 (1967).

Based on the idea mentioned above, two series of compounds were synthesized. 1) Niketham ide-type compounds. Six compounds were synthesized by the substitution of the pyridine ring in the niketham ide (abbreviated as nik.) structure for a piperidine ring as shown in Table I. 2) Dimorpholamine-type compounds. Dimorpholamine (dim.) is one of the most potent respiratory stimulants at the present time and has two morpholine nuclei in its chemical structure. As described above, morpholine is devoid of stimulant action on the carotid body chemoreceptor, so new compounds in which two morpholine nuclei were substituted for two piperidine nuclei, N,N′-dibutyl-N,N′-bis(piperidinocarbonyl)ethylenediamine and its five derivatives were synthesized.

As the authors had expected, it was found that all of the nik.-type compounds had more potent respiratory stimulant action than the parent compound, nik. However, the compound possessing the most potent respiratory stimulant action was found to be N,N′-dibutyl-N,N′-bis(piperidinocarbonyl)ethylenediamine (VII) in the dim.-type ones.

In rabbits, the respiratory stimulant action of VII was 4 to 5 times as potent as that of dim. and the duration of the effect was twice as long as that of dim. It showed antagonistic action to the respiratory depression caused by morphine and by pentobarbital in rabbits. Its toxicity in mice was about a half that of dim. The authors[3] had briefly reported the respiratory stimulant action of the compound comparing with that of dim.

This paper deals with the synthesis and pharmacology of the above-mentioned nik.-type and dim.-type compounds and shows a predominant pharmacological activity of VII among the compounds tested.

Experimental

I. Chemistry

A Nik.-type Compounds——3-(N,N-Diethylcarbamoyl)piperidine(I) has been described by A. Lassls, *et al.*[4]

3-(Piperidinocarbonyl)piperidine (II): A mixture of 25 g of the nicotinoylpiperidine, 0.5 g of PtO_2, 32 ml of 4N HCl and 100 ml of water was hydrogenated at room temperature and 35 atm for 20 hr. The catalyst was filtered and K_2CO_3 was added to make the solution distinctly alkaline. The free base extracted into 100 ml of benzene, and the benzene solution was removed *in vacuo* to give a light amber oil, which was distilled to yield 18 g (70%) of (II), bp 120—125° (0.3 mmHg). *Anal.* Calcd. for $C_{11}H_{20}ON_2$: C, 67.30; H, 10.27; N, 14.27. Found: C, 67.42; H, 10.05; N, 14.45.

1-Methyl-3-(N,N-diethylcarbamoyl)piperidine (III) has been described by A. Lassls, *et al.*[4]

1-Methyl-3-(piperidinocarbonyl)piperidine (IV) was prepared from 23 g of the 1-methyl-3-(piperidinocarbonyl)pyridium iodide, 90 ml of water and 0.3 g of PtO_2 in the same manner as described for the preparation of (II) to give a product of 11 g (76%), bp 183° (22 mmHg); maleate: mp 129—131°. *Anal.* (maleate). Calcd. for $C_{16}H_{26}O_5N_2$: C, 58.86; H, 8.03; N, 8.58. Found: C, 59.06; H, 8.02; N, 8.62.

1-Phenethyl-3-(N,N-diethylcarbamoyl)piperidine (V) has been described by J. Same, *et al.*[5] Hydrochloride, recrystallized from the mixture of ethanol and ethyl acetate, had mp 174—176°. *Anal.* Calcd. for $C_{18}H_{28}ON_2$–HCl: C, 66.54; H, 8.99; N, 8.62. Found: C, 66.30; H, 8.87; N, 8.57.

1-Phenethyl-3-(piperidinocarbonyl)piperidine (VI): A mixture of 7 g of the 3-(piperidinocarbonyl)-piperidine, 6.6 g of phenethyl bromide and 5 g of fine powdered K_2CO_3 in 70 ml of benzene was heated at reflux for 15 hr. The benzene solution was washed with water and extracted with 5% hydrochloric acid. By the same treatment as (II), 9.5 g (89%) of (VI) was obtained, bp 197—198° (0.75 mmHg); hydrochloride: mp 168° (from the mixture of ethanol and ethylacetate). *Anal.* Calcd. for $C_{14}H_{28}ON_2$–HCl: C, 67.73; H, 8.68; N, 8.32. Found: C, 67.75; H, 8.62; N, 8.25.

B Dim.-type Compounds——N,N′-Dibutyl-N,N′-bis(piperidinocarbonyl)ethylenediamine (VII): A solution of 5 g of the N,N′-dibutylethylenediamine and 6.5 g of triethylamine in 50 ml of dry benzene was stirred and treated dropwise with 9 g of the piperidine-N-carbonylchloride[6] in 20 ml of dry benzene at 0—5°, then refluxed for 5 hr. After cooling, the organic phase was washed with 30 ml of 5% HCl, then 30 ml of 5%

3) Y. Kasé, A. Nakanishi, A. Kawasaki, T. Miyata, K. Katsukawa, M. Nakanishi, and T. Tsumagari, *Arch. Intern. Pharmacodyn.*, **163**, 133 (1966).
4) A. Lassls, W.M. Marine, and P.D. Waller, *J. Org. Chem.*, **21**, 958 (1956).
5) J. Same, W.F. Minor, and Y.G. Perron, *J. Am. Chem. Soc.*, **81**, 711 (1959).
6) W.R. Boon, *J. Chem. Soc.*, **1947**, 313.

NaOH, and dried over Na_2SO_4. The solvent was removed *in vacuo*, to give a product of 8.2 g (70%), bp 185° (0.05 mmHg). *Anal.* Calcd. for $C_{22}H_{42}O_2N_4$: C, 66.96; H, 10.78; N, 14.20. Found: C, 66.73; H, 10.70; N, 14.02.

N,N′-Dibutyl-N,N′-bis(1-methyl-3-piperidylcarbonyl)ethylenediamine (VIII): A mixture of 15 g of the N,N′-dibutyl-N,N′-bisnicotinoylethylenediamine dimethyliodide, 0.4 g of PtO_2 and 80 ml of water was hydrogenated at 55—60° and 30 atm, for 20 hr. By the same treatment as (II), 7.5 g (79%) of (VIII) was obtained, bp 218° (0.05 mmHg). *Anal.* Calcd. for $C_{22}H_{46}O_2N_4$: C, 68.20; H, 10.97; N, 13.26. Found: C, 67.90; H, 10.82; N, 12.95.

N,N′-Dibutyl-N,N′-bis[3-(N,N′-diethylcarbamoyl)piperidinocarbonyl]ethylenediamine (IX) was prepared from 1.5 g of the N,N′-dibutylethylenediamine-N,N′-biscarbonylchloride,[7] 1.1 g of triethylamine and 1.85 g of the 3-(N,N-diethylcarbamoyl)piperidine in the same manner as described for the preparation of (VII) to give a product of 1.85 g (65%), which was purified with column chromatography (alumina).

N,N′-Dibutyl-N,N′-bis[(4-piperidino-4-carbamoyl)piperidinocarbonyl]ethylenediamine (X): A solution of 7.1 g of the 4-piperidino-4-carbamoylpiperidine in 70 ml of dry benzene and 4 g of triethylamine was stirred and treated dropwise with 5 g of the N,N′-dibutylethylenediamine-N,N′-biscarbonylchloride in 20 ml of dry benzene at 0—5°, then refluxed for 5 hr. After cooling, a crystalline solid was separated and washed with water, then dried. Recrystallization from ethanol, yielded 5 g (46%) of (X), mp 195—198° (decomp); dihydrochloride: mp 213—215° (from ethanol–ether). *Anal.* Calcd. for $C_{34}H_{62}O_4N_8$: C, 63.12; H, 9.66; N, 17.32. Found: C, 62.34; H, 9.46; N, 17.60. Calcd. for $C_{34}H_{62}O_4N_8$–2HCl: C, 56.73; H, 8.96; N, 15.57. Found: C, 56.40; H, 8.99; N, 15.33.

N,N′-Dibutyl-N,N′-bis(pyrrolidinocarbonyl)ethylenediamine (XI) was prepared from 17.2 g of the N,N′-dibutylethylenediamine, 23 g of triethylamine and 27.5 g of pyrrolidine-N-carbonylchloride[8] in the same manner as described for the preparation of (VII) to give a product of 28 g (76%), bp 165° (0.02 mmHg). *Anal.* Calcd. for $C_{20}H_{38}O_2N_4$: C, 65.54; H, 10.45; N, 15.28. Found: C, 65.56; H, 10.53; N, 15.12.

N,N′-Dibutyl-N,N′-bis(4-methylpiperazinocarbonyl)ethylenediamine (XII): A solution of 6.5 g of the N-methylpiperazine in 70 ml of dry toluene was stirred and treated dropwise with 9.5 g of the N,N′-dibutylethylenediamine-N,N′-biscarbonylchloride in 20 ml of dry toluene at 0—5°, then refluxed for 2 hr. After the solvent was removed *in vacuo*, residue was dissolved in water and saturated with K_2CO_3. The free base was extracted into 100 ml of chloroform, then washed with water and dried. The chloroform solution was removed *in vacuo* to give a product of 9.3 g (89.5%). Dimaleate: mp 165—167° (from acetone). *Anal.* (dimaleate). Calcd. for $C_{30}H_{52}O_{10}N_6$: C, 54.87; H, 7.92; N, 12.80. Found: C, 54.39; H, 7.72; N, 12.55.

II. Pharmacology

All of the nik.-type compounds were dissolved in physiological saline solution. Some of dim.-type compounds (VII, IX and X), however, were sparingly soluble in water, so they were dissolved in physiological saline after emulsification with gelatin, which showed no significant effects on respiration and blood pressure in laboratory animals even if a considerably large amount of it was given. Although VIII, XI and XII were soluble in water, gelatin was also added to its solution in order to obtain equal experimental conditions.

Toxicity——*dd*-Strain male mice, weighing 15—20 g, were used. Each of the test compounds was administered intraperitoneally to more than 10 groups, each of which consisted of 8 mice, and toxic symptoms were observed. The 50% convulsive dose (CD_{50}), LD_{50} and their fiducial limits ($p=0.05$) were calculated from the manifestation of convulsions and mortality of animals within 24 hours by the method of Litchfield and Wilcoxon.[9]

Awakening Action from Anesthesia——*dd*-Strain male mice weighing 16—20 g were used. Two groups, each consisting of 8 mice, were used for each compound. Five minutes after intraperitoneal administration of 10 mg/kg and 20 mg/kg of the test compounds, 70 mg/kg of sodium hexobarbital was administered intraperitoneally. The time between loss and regain of the righting reflex was taken as the duration of anesthesia. Control experiments with hexobarbital alone, were carried out 4 days before the administration using the same animals.

The statistical significance of the results was tested by means of the Fisher's F-test.

Effects on Respiration and Blood Pressure——Eighty-two albino rabbits weighing around 2.5 kg were anesthetized with urethane (1.2 g/kg, *s.c.*) and the blood pressure of the common carotid artery was recorded on a smoked paper by the routine mercury manometer method and respiration (intratracheal pressure) was also recorded simultaneously with a Marey's tambour *via* tracheal cannula. The test compounds were administered through a fine polyethylene plastic tube previously indwelled in the femoral vein.

Antagonism against the Respiratory Depression caused by Morphine and by Pentobarbital——Fifty-seven male albino rabbits weighing 2.5 to 3 kg were used. Blood pressure of the common carotid artery

7) W.R. Boon, *J. Chem. Soc.*, **1947**, 315.
8) R.A. Franz, *C.A.*, **54**, 573^e (1960) (U.S. Patent 2868328).
9) J.T. Litchfield and F.T. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

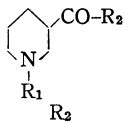
and respiration of urethanized animals were recorded on a smoked paper by the same procedures as described above. When the respiratory rate was decreased to 1/4—1/2 by intravenous doses of 4 to 8 mg/kg of morphine hydrochloride, the test compounds were given intravenously. In the case of pentobarbital, when the respiratory rate was decreased to less than a half by intravenous doses of 10 to 15 mg/kg of sodium pentobarbital, the test compounds were given intravenously. In both the cases mentioned above, the efficacies of the test compounds were compared with those of dim. and nik.

Result and Discussion

Toxicity

The LD_{50} and CD_{50} of the compounds are shown in Table I. With exceptions of two nik.-type compounds (V and VI) which have a phenethyl group at the position of R_1, the toxicities of the test compounds were weaker than those of the original compounds. Among them, the toxicity of VII, which contains two piperidine nuclei instead of morpholine ones in the dim. structure and shows the most powerful respiratory stimulant action (see the succeeding section), was about a half that of dim.

Table I. LD_{50} and CD_{50} in Mice

Compd. No.	A. Nikethamide-type R_1		LD_{50} mg/kg	CD_{50} mg/kg
I	H	diethylamino	810 (650—1010)	≒LD_{50}
II	H	piperidino	495 (472— 520)	no convulsions
III	CH_3	diethylamino	880 (704— 990)	781 (631—962)
IV	CH_3	piperidino	680 (554— 850)	516 (427—624)
V	phenethyl	diethylamino	165 (132— 206)	≒LD_{50}
VI	phenethyl	piperidino	148 (124— 176)	≒LD_{50}
Nikethamide			249 (199— 311)	181 (159—212)

	B. Dimorpholamine-type R-CO-N-CH_2-CH_2-N-CO-R		
	R	C_4H_9 C_4H_9	
VII	piperidino	140 (123—159)	104 (94—115)
VIII	1-methyl-3-piperidyl	194 (179—210)	≒LD_{50}
IX	3-(N,N-diethylcarbamoyl)piperidino	221 (176—276)	≒LD_{50}
X	4-piperidino-4-carbamoylpiperidino	>1000	no convulsions
XI	pyrrolidino	167 (143—194)	71.6 (61.8—83.4)
XII	4-methylpiperazino	630 (473—838)	no convulsions
Dimorpholamine	morpholino	80 (73—87)	62 (55—70)

The test compounds were given intraperitoneally to mice. Figures in parenthesis show the fiducial limits ($p=0.05$) CD_{50}, 50% Convulsive doses.

II, X and XII showed no convulsions even at the dose levels of their LD_{50}. The CD_{50} of I, V, VI, VIII and IX were approximately equal to the corresponding LD_{50}, in other words, convulsions were inevitably followed by death. The ratios of LD_{50} to CD_{50} (LD_{50}/CD_{50}) in III, IV and VII were 1.13, 1.32 and 1.35. On the other hand, those of the parent compounds (nik. and dim.) were 1.38 and 1.29, respectively. The ratio of XI which showed the lowest CD_{50} value was 2.74.

Awakening Action from Anesthesia

Pretreatment with a dose of 10 mg/kg of the test compounds caused no significant change in the duration of anesthesia ($p=0.05$). With an increased dose of 20 mg/kg, VII and dim. caused a significant decrease in the duration of anesthesia ($p=0.05$), while other compounds

including the nik.-type ones and nik. itself showed no significant action. As for the awakening action from anesthesia, VII was a little more potent than dim.

Effects on Respiration and Blood Pressure

As shown in Fig. 1 (A,B), all of the nik.-type compounds showed a respiratory stimulant action 2 to 5 times as potent as that of nik. but they were only 1/100 to 1/250 as potent as dim.

In contrast to this, VII, one of dim.-type compounds, showed more potent respiratory stimulant action than dim. The effect of VII was 4 to 5 times as potent as that of dim., and the duration of the effect was twice as long as that of dim. when the doses with which the same degree of respiratory stimulation occurred were administered. XI also showed respiratory stimulant action almost as potent as that of dim. The respiratory stimulant actions of other dim.-type compounds (VIII, IX, X and XII) were far weaker than that of dim.

All of the nik.-like compounds, especially V and VI caused pronounced blood pressure fall. On the other hand, actions of VII and XI on blood pressure were similar to that of dim., that is, they caused a transitory fall followed by a slight rise. Other dim.-type compounds (VIII, IX, X and XII) caused moderate blood pressure fall.

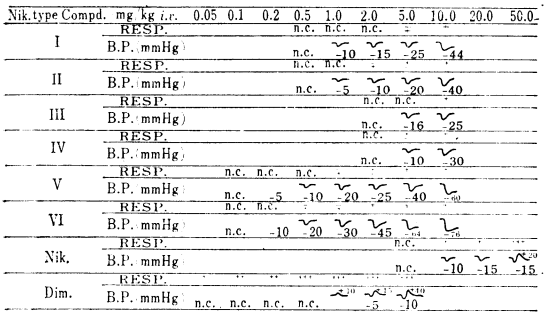


Fig. 1A. Effects on Respiration and Blood Pressure (Nikethamide-type Compounds)

Urethanized male rabbits weighing 2.2—2.8 kg. RESP., respiration; ±～+++, degree of respiratory stimulation; n.c., no change; B.P., blood pressure in mmHg; numerals, degree of blood pressure rise or fall

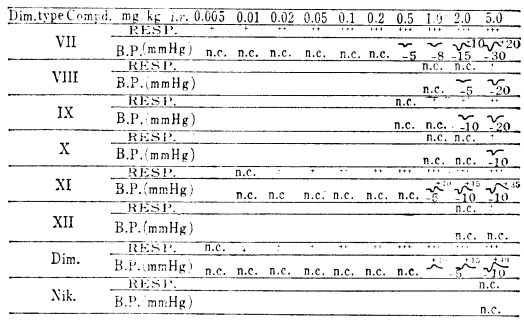


Fig. 1B. Effects on Respiration and Blood Pressure (Dimorpholamine-type Compounds)

Antagonism against the Respiratory Depression caused by Morphine and by Pentobarbital

a) Morphine-induced Respiratory Depression——Two nik.-type compounds, V and VI, showed antagonistic actions to the respiratory depressant action of morphine with an intravenous dose of 1.0 mg/kg. Thus, the actions of V and VI were 10 times as potent as that of nik. and equal to that of dim. (Fig. 2A). Other nik.-type compounds (I, II, III and IV) were as potent as nik. in this respect. It is of interest that V and VI showed a marked antagonism against the respiratory depression by morphine, though they were able to cause only a slight respiratory stimulation in intact animals.

Antagonistic action of VII, which showed the most potent respiratory stimulant action in intact animals, was the most potent among the compounds tested, being 4 to 5 times as potent as that of dim. (Fig. 2B). The potency of XI was twice that of dim. Other dim.-type compounds (VIII, IX, X and XII) also showed weak antagonistic action against the respiratory depression by morphine.

b) Pentobarbital-induced Respiratory Depression——All of nik.-type compounds showed more potent antagonistic action against pentobarbital-induced respiratory depression than that of nik. Their actions, however, were rather weaker than that of dim.

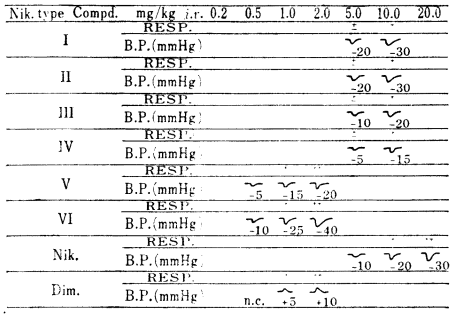


Fig. 2A. Antagonism to the Morphine-induced Respiratory Depression (Nikethamide-type Compounds)

Urethanized male rabbits weighing 2.2—2.8 kg. When the respiratory rate was decreased to 1/4—1/2 by intravenous administration of 4 to 8 mg/kg of morphine, the test compounds were administered intravenously. RESP., respiration; —, no antagonism: ±～+++, degree of antagonism. Other abbrebiations are the same as those shown in Fig. 1.

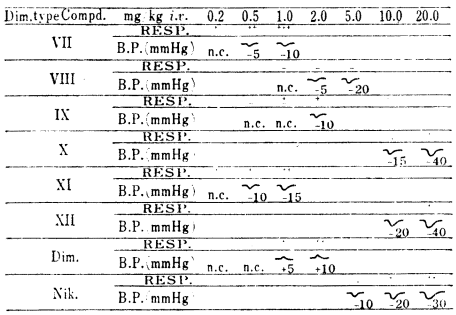


Fig. 2B. Antagonism to the Morphine-induced Respiratory Depression (Dimorpholamine-type Compounds)

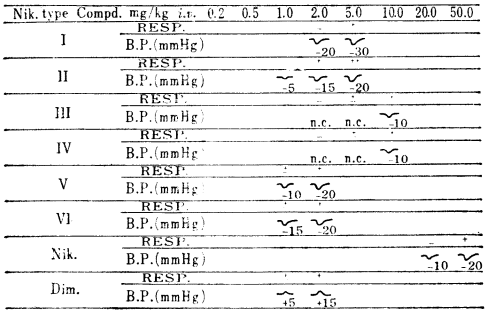


Fig. 3A. Antagonism to the Pentobarbital-induced Respiratory Depression (Nikethamide-type Compounds)

Urethanized male rabbits weighing 2.2—2.8 kg. When the respiratory rate was decreased to less than a half by intravenous administration of 10 to 15 mg/kg of pentobarbital, the test compounds were administered intravenously. Abbreviations are the same as those shown in Fig. 1 and 2.

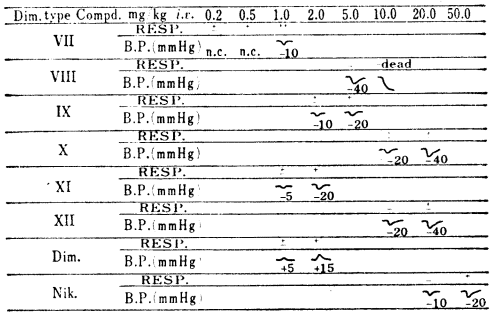


Fig. 3B. Antagonism to the Respiratory Depressant Action of Pentobarbital (Dimorpholamine-type Compounds)

On the other hand, VII among dim.-type compounds was a powerful antagonist to pentobarbital. It was 4 to 5 times as potent as dim. The potency of compound XI was equal to that of dim. Other dim.-type compounds (VIII, IX, X and XII) showed a weak antagonistic action against the respiratory depression induced by pentobarbital.

As shown above, a dim.-type compound, VII, showed a remarkable antagonism to the respiratory depressant actions of morphine and pentobarbital.

Structure-Activity Relationship

All of the 6 nik.-type compounds showed respiratory stimulant actions more potent than that of nik. itself. Thus, the substitution of a pyridine ring in the structure of nik. for a piperidine nucleus, yielded compounds of stronger respiratory stimulant activities than the parent substance. Consequently, nicotinic acid amide, a main component of nik. structure, seems not to be indispensable for the exhibition of respiratory stimulant activity, though it shows CNS stimulant action without any other nicotine-like actions; in other words, amide

of nipecotic acid, which is an isomer of pipecolic acid, a precursor of piperidine in the living body,[10] also seems to contribute to the respiratory stimulant actions of the nik.-type compounds.

Although replacement of diethylamino(aliphatic amino) moiety in a substituent at 3-position with piperidine(alicyclic amino) group (II, IV, VI) little influenced upon the activities tested, but it tended to increase toxicity.

A comparison of I with III and V, or that of II with IV and VI, shows that there is no significant influence of the substituent at 1-position upon respiratory stimulant activity. It is noted, however, that 1-phenethyl compounds (V, VI) are much more toxic and active both in the antagonistic actions to morphine- or pentobarbital-induced respiratory depression and in the depressor action, than the corresponding nonsubstituted or 1-methyl compounds. In this regard, it is well known that the introduction of a phenethyl group to some analgesics increases an analgesic activity. In contrast to nik.-type compounds described above, it is remarkable that the compound VII, one of dim.-type compounds, in which two morpholino groups in the dim. structure were substituted for two piperidino nuclei, showed the most potent respiratory stimulant actions among all the compounds tested. The activity of VII was 4 to 5 times as potent as that of dim. and the duration of effect was twice as long as that of dim. The compound XI which possesses two pyrrolidino groups instead of two morpholino ones also showed respiratory stimulant action a little more potent than dim. The compounds XII possessing 4-methylpiperazino group, however, showed rather weak respiratory stimulant action. Thus, the activity decreased in the following order; VII>XI>dim.>XII. Both piperidine and pyrrolidine themselves cause a marked respiratory stimulation, on the other hand, neither morphine nor piperazine does so. Therefore, the result seems to represent the activities of 4 alicyclic amines themselves (piperidine, pyrrolidine, morpholine and piperazine) in respiratory stimulant action. Furthermore, it is evident from the comparison of VIII with VII that the substitution of a piperidino group for a 3-piperidyl group results in a striking decrease in respiratory stimulant activity. The introduction of diethylcarbamoyl group at 3-position of piperidine ring in structure of VII yielded the compound IX, possessing a similar chemical structure to I in nik.-type compounds. Although IX had been expected to show more potent respiratory stimulant action than that of VII, it only showed a very weak action. Similarly, the introduction of a piperidino group together with a carbamoyl one at 4-position of piperidine ring in structure of VII also markedly weakened the respiratory stimulant activity as well as other pharmacological activities (*e.g.*, toxicity).

Thus, VIII, IX, X and XII showed rather weak respiratory stimulant action, that is, they are not so potent as dim. but more potent than nik. Accordingly, dim.-type compounds, especially VII showed powerful, respiratory stimulant action, in comparison with nik.-type compounds. However, it might be saying too much that the introduction of 1-piperidine carboxylic acid amide is superior to that of 3-piperidine carboxylic acid amide (nipecotamide) for manifestation of respiratory stimulant activity.

At all events, the results obtained from the present investigations offer an additional evidence for our previous findings,[11] the significant role of a piperidino group for manifestation or augmentation of pharmacological activities.

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10) Y. Kasé, M. Kataoka, and T. Miyata, *Life Sciences*, **6**, 2427 (1967); Y. Kasé, Y. Okano, Y. Yamanishi, M. Kataoka, K. Kitahara, and T. Miyata, *Life Sciences*, **9**, 1381 (1970).

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