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74. Yoshitoshi Kasé and Tomokazu Yuizono : A Contribution of Piperidino Group to Manifestation of Antitussive Activity.

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The fact that a conspicuous property of 3-piperidino-1,1-di(2-thienyl)but-1-ene (the compound (Ⅲ) in Table I) in antitussive effect among other similar derivatives containing dimethylamino (I) or diethylamino (Ⅱ) group in their chemical structure, as already shown by Kasé, *et al.*,[1] called the authors' attentions to the rôle of piperidino group for manifestation of antitussive activity. Some evidences for such an assumption accumulated in the authors' own data on antitussive activity and it was confirmed that an introduction of a piperidino group into a compound possessing a depressant action on the central nervous system to some extent has a possibility of manifesting or strengthening antitussive activity. An introduction of piperidino group seems not to have any definite effect on analgesic activity, that is, its effect on analgesic activity is less than that of dimethylamino group in most cases.

The examples presented in this paper are limited mainly to analgesics, non-analgesic compounds possessing chemical structures similar to analgesics, chlorpromazine derivatives, and adrenergic amines, because of difficulty in obtaining such a series of compounds for this purpose. Naturally more evidences are required to confirm such a hypothesis but it will be able to give a clue to the study of antitussive drugs from a chemical point of view.

Methods

Antitussive effect was evaluated by Kasé's method[2] in unanesthetized dog and in lightly pentobarbitalized cat (20 mg./kg., intraperitoneal). Changes in respiration by coughing caused by mechanical stimulation on the mucosa of tracheal bifurcation through a chronically built tracheal fistula were recorded on a smoked paper. Antitussive effect of a certain drug was determined from the decreases in amplitude and frequency of cough curves, and from the duration of such effect. The dose necessary to depress coughing for 20～30 min. is taken as being effective, from which 50% antitussive dose (AtD_{50}) was calculated by Litchfield-Wilcoxon's method[3] ($p=0.05$). Analgesic effect was examined by the d'Amour-Smith's method[4] in mice.

Results and Discussions

As it is a well-known fact that dimethylamino group strengthens analgesic activity in most cases more potently than other groups such as diethylamino, morpholino, and piperidino, comparison of the effect of piperidino group on antitussive activity with those of other groups was mainly made with the effect of methyl group.

In a series of potent analgesics such as dithienylbutenylamines (series 1), and methadone and sulfamethadone group (series 2), compounds containing a piperidino group as a basic moiety show more potent antitussive activity than those containing methyl or ethyl group. The compound (XIII) (racemate) is about 5 times as potent as the compound (XII) which is *l*-isomer of the compound (X) (racemate) in antitussive effect, inspite of a well-known fact that *l*-isomer is the most potent in analgesic activity. In the case of methadone (VI), however, activity is approximately equal to that of the compound (VII).

In a series of compounds possessing a very weak or non-analgesic activity such as those of series (3) and (4), the above-described characteristics of piperidino group becomes more marked;

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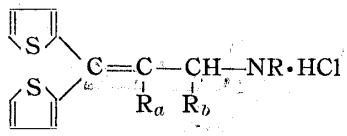
1) Y. Kasé, *et al.* : This Bulletin, **3**, 394(1955).
2) Y. Kasé : Japan. J. Pharmacol., **4**, 130(1955).
3) J. T. Litchfield, F. Wilcoxon : J. Pharmacol. Exptl. Therap., **96**, 99(1949).
4) F. E. d'Amour, D. L. Smith : *Ibid.*, **72**, 74(1941).

TABLE I.

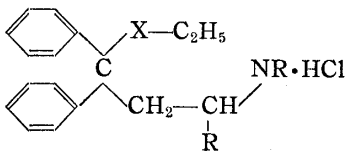
Series 1.



Compd. No.	Generic name or code No.	R_a	R_b	-NR	AtD_{50} (mg./kg.) i.v. Dog	AtD_{50} (mg./kg.) i.v. Cat	AD_{50} (mg./10g.) mouse s.c.
(I)	Ohton	-H	$-CH_3$	$-N<^{CH_3}_{CH_3}$	0.85 (0.70~1.04)	1.49 (1.31~1.71)	0.056 (0.050~0.062)
(II)		〃	〃	$-N<^{Et}_{Et}$	0.96 (0.71~1.29)	1.58 (1.44~1.74)	0.069 (0.051~0.079)
(III)	Piperidino-ohton	〃	〃	-N(H)	**0.27** (0.23~0.30)	**0.64** (0.54~0.76)	**0.058** (0.051~0.067)
(IV)	Iso-ohton (172E)	$-CH_3$	-H	$-N<^{CH_3}_{CH_3}$	*10.7	9.42 (8.44~10.49)	one-tenth as effective as Ohton
(V)	206E	〃	〃	-N(H)	* **8.95**	**6.00** (5.26~6.84)	ineffective

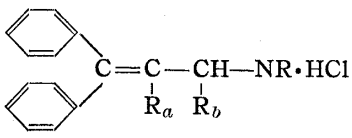
* Minimal effective dose.

Series 2.



Compd. No.	Generic name or code No.	X	R	-NR	AtD_{50} (mg./kg.) Dog i.v.	AD_{50} (mg./10g.) Mouse s.c.
(VI)	Methadone (*d*+*l*)	-CO-	$-CH_3$	$-N<^{CH_3}_{CH_3}$	0.11 (0.07~0.17)	0.035 (0.030~0.041)
(VII)		〃	〃	-N(H)	**0.11** (0.09~0.13)	**0.040** (0.032~0.051)
(VIII)	Ticarda	-CO-	-H	$-N<^{CH_3}_{CH_3}$	1.20 (1.10~1.31)	0.093 (0.080~0.108)
(IX)		〃	〃	-N(H)	**0.59** (0.49~0.73)	**0.073** (0.054~0.100)
(X)	Sulfamethadone (*d*+*l*)	$-SO_2-$	$-CH_3$	$-N<^{CH_3}_{CH_3}$	1.86 (1.57~2.20)	0.087 (0.074~0.102)
(XI)	〃 (*d*)	〃	〃	〃	2.08 (1.72~2.51)	0.24 (0.21~0.28)
(XII)	〃 (*l*)	〃	〃	〃	0.71 (0.56~0.91)	0.025 (0.021~0.029)
(XIII)		〃	〃	-N(H)	**0.15** (0.13~0.18)	**0.037** (0.026~0.052)
(XIV)		$-SO_2-$	-H	$-N<^{CH_3}_{CH_3}$	1.00 (0.80~1.25)	0.16 (0.13~0.19)
(XV)		〃	〃	$-N<^{Et}_{Et}$	1.21 (1.07~1.37)	0.20 (0.17~0.23)
(XVI)		〃	〃	-N(H)	**0.43** (0.34~0.54)	**0.048** (0.037~0.062)

Series 3.

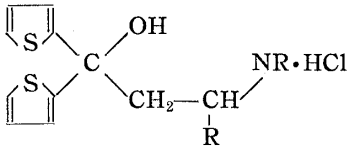


Compd. No.	Generic name or code No.	R_a	R_b	-NR	Antitussive effect (mg./kg.) Cat i.v.	Analgesic effect[a] Mouse s.c.
(XVII)	177E	-COOEt	$-CH_3$	$-N<^{CH_3}_{CH_3}$	ineffective with 20.0	ineffective
(XVIII)	107E	〃	〃	$-N<^{C_2H_5}_{C_2H_5}$	〃	〃

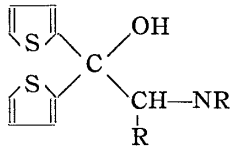
(XIX)	118E	〃	〃	-N⟨H⟩O	〃	〃
(XX)	207E	〃	〃	-N⟨H⟩N-CH_3·2HCl	*15.3	slightly effective
(XXI)	191E	〃	〃	-N⟨H⟩	**2.83** (2.29～3.50)	ineffective
(XXII)	182E	-COOEt	-H	-N$<^{CH_3}_{CH_3}$	ineffective with 20.0	〃
(XXIII)	127E	〃	〃	-N$<^{C_2H_5}_{C_2H_5}$	〃	〃
(XXIV)	154E	〃	〃	-N⟨H⟩O	〃	〃
(XXV)	222E	〃	〃	-N⟨H⟩N-CH_3·2HCl	*20.0[b)]	〃
(XXVI)	170E	〃	〃	-N⟨H⟩	**6.20** (5.20～7.40)	〃
(XXVII)	50E	-H	-COOEt	-N$<^{CH_3}_{CH_3}$	ineffective with 20.0	slightly effective
(XXVIII)	91E	〃	〃	-N$<^{C_2H_5}_{C_2H_5}$	〃	ineffective
(XXIX)	152E	〃	〃	-N⟨H⟩O	〃	〃
(XXX)	167E	〃	〃	-N⟨H⟩N-CH_3·2HCl	*20.0	〃
(XXXI)	92E	〃	〃	-N⟨H⟩	**10.9** (8.7～13.6)	very slightly effective

a) Data on analgesic activity (tested by d'Amour-Smith's method) are cited from the work of N. Sugimoto and N. Shigematsu (Yakugaku Zasshi, **77**, 927, 929(1957)).
* Minimal effective dose.

Series 4.



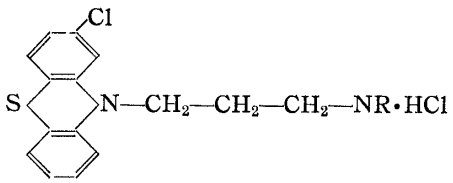
Compd. No.	Code No.	R	-NR	Antitussive effect (mg./kg.) (Cat i.v.)	Analgesic effect (Mouse)
(XXXII)	11	$-CH_3$	-N$<^{CH_3}_{CH_3}$	23.8 (21.6～26.2)	ineffective
(XXXIII)	12	〃	-N$<^{C_2H_5}_{C_2H_5}$	ineffective with 23.8	〃
(XXXIV)	52	〃	-$\overset{+}{N}$$<^{CH_3}_{CH_3}_{CH_3}$	ineffective with 22.1	〃
(XXXV)	3	〃	-N⟨H⟩	***17.4**	〃
(XXXVI)	101	-H	-N$<^{CH_3}_{CH_3}$	ineffective with 20.1	〃
(XXXVII)	14	〃	-N⟨H⟩	**20.1** (17.0～23.7)	〃

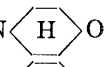
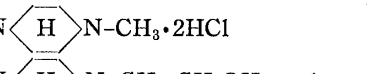
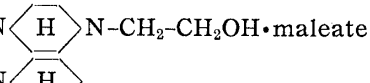


(XXXVIII)	189-A	-H	-N$<^{CH_3}_{CH_3}$	ineffective with 12.8	ineffective
(XXXIX)	196-A	〃	-N⟨H⟩	***12.8**	〃

* Minimal effective dose.

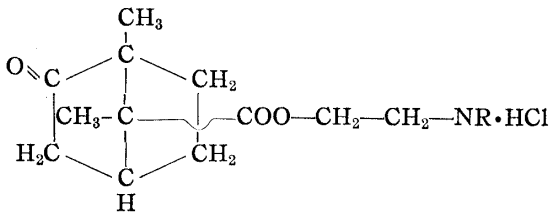
Series 5.

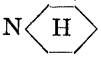


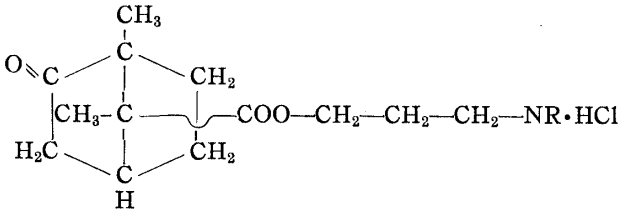
Compd. No.	Generic name or code No.	-NR	Antitussive effect (mg./kg.) Dog i.v.
(XL)	Chlorpromazine	$-N(CH_3)_2$	slightly effective with 20.0
(XLI)	P-24	$-N(C_2H_5)_2$	ineffective with 20.0
(XLII)	P-22		*10.7
(XLIII)	Prochlorperazine		*10.7
(XLIV)	Perphenazine		*20.0
(XLV)	P-21		* **5.2**

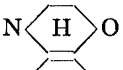
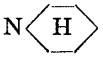
* Minimal effective dose.

Series 6.



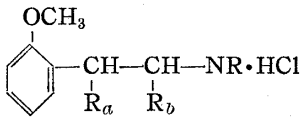
Compd. No.	Code No.	-NR	Antitussive effect (mg./kg.) Cat i.v.
(XLVI)	TE 53	$-N(CH_3)_2$	ineffective with 20.0
(XLVII)	TE 51	$-N(C_2H_5)_2$	〃
(XLVIII)	TE 55		〃
(XLIX)	TE 56		* **5.2**

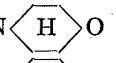
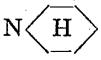


Compd. No.	Code No.	-NR	Antitussive effect (mg./kg.) Cat i.v.
(L)	TE 52	$-N(CH_3)_2$	ineffective with 20.0
(LI)	TE 54	$-N(C_2H_5)_2$	〃
(LII)	TE 57		〃
(LIII)	TE 58		***10.7**

* Minimal effective dose.

Series 7.



Compd. No.	R_a	R_b	-NR	Antitussive effect (mg./kg.) Dog i, v.
Y_1	$-CH_3$	-H	$-N<^{H}_{CH_3}$	ineffective with 20.0
Y_4	〃	〃	$-N<^{H}_{C_2H_5}$	〃
Y_9	〃	〃	$-N<^{CH_3}_{CH_3}$	ineffective with 10.0
Y_{11}	〃	〃		〃
Y_{10}	〃	〃		remarkably effective with **8.0**
M_{36}	-H	$-CH_3$	$-N<^{H}_{C_2H_5}$	ineffective with 5.0
M_8	〃	〃	$-N<^{H}_{isobutyl}$	〃
M_9	〃	〃	$-N<^{H}_{hexyl}$	slightly effective with 5.0
M_{10}	〃	〃		ineffective with 10.0
M_{11}	〃	〃		〃

Data are cited from the Footnote (5).

compounds containing a piperidino group (XXI, XXVI, XXXI, XXXV, XXXVII, XXXIX) are able to manifest antitussive activity exclusively, while an introduction of a piperidino group does not cause any definite effect on analgesic activity, the activity either increases or decreases. In other words, there is no parallelism between antitussive and analgesic effect in the case of piperidino compounds.

In a series of chlorpromazine compounds (series 5), chlorpromazine (XL) showed a slight and indefinite antitussive effect with 20 mg./kg., but the compound (XLV) (piperidino), (XLII) (morpholino), (XLIII) (4-methyl-1-piperazino), and (XLIV) (4-hydroxyethyl-1-piperazino) showed a definite effect with 5.2, 10.7, 10.7, and 20.0 mg./kg., respectively. Also in this series a piperidino group strengthened antitussive activity most potently.

The compounds of isoketopinate series (series 6), whose pharmacological properties other than antitussive activity remain to be clarified, also show distinct activation in antitussive action by introduction of a piperidino group (XLIX, LIII), regardless of the length of side chain.

In a series of adrenergic amines (series 7) (data listed here are cited from Yanagiura's paper[5]) examined by electric stimulation of tracheal mucosa in an unanesthetized dog), only the compound Y_{10} in the first group showed a marked effect and others in this group were ineffective. However, the compound M_{11} containing a piperidino group did not show any antitussive activity with 10 mg./kg., though the compound M_9 containing a hexyl group showed a very weak antitussive effect with 5 mg./kg. This result is contrary to the above-described hypothesis and an only exception in the data described here.

The reason why an introduction of a piperidino group can activate antitussive activity so markedly is unkown and is now under investigation.

The authors wish to express their appreciation to Dr. N. Sugimoto of the Research Institute of the Tanabe Seiyaku Co. Ltd., and to Dr. M. Nakanishi, the Research Institute of the Yoshitomi Pharmaceutical Co., for generously supplying the compounds used for this experiment.

Summary

An introduction of a piperidino group into a certain compound can manifest or strengthen antitussive activity, independent of analgesic activity. This property seems to appear not only in analgesics but also in other compounds possessing depressant action on the central nervous system to some extent.

(Received February 6, 1959)

5) S. Yanagiura : Folia Pharmacol. Japon., **54**, 688(1958).