Communications to the Editor

3-Piperidyl-1,1-di(2′-thienyl)-but-1-ene as a Potent Antitussive

During the course of work on antitussives which are potent but not habit-forming, it has been found that 3-dimethylamino-1,1-di(2′-thienyl)-but-1-ene(Ohton),[1] an analgesic of thiophene series, possessed an antitussive action several times that of codeine.[2] Therefore, antitussive action and other pharmacological properties of the derivatives of this series were examined. As a result, it has been found that one of such derivatives, 3-piperidyl-1,1-di(2′-thienyl)-but-1-ene hydrochloride[1] (tentatively designated as compound No. 13), possessed a potent antitussive action far above that of morphine and Methadone, and the gist of this study is described herein.

Methods and Materials : Compound No. 13 used for the experiment comes as white prismatic crystals (hydrochloride, m.p. 188~189°), slightly soluble in water. The antitussive action was examined by the "Coughing Dog method" of Kasé,[3,4] the dose necessary to depress coughing for 20~30 minutes taken as being effective, from which 50% antitussive dose (AtD_{50}) was calculated. Analgesic action was tested by the Eddy-Leimbach's hot plate method.[5] Of the antispasmodic actions tested, anticholinergic and antibarium activities were respectively compared with those of atropine and papaverine, antihistaminic activity with that of Benadryl as a standard, all by the Magnus method. Local anesthetic activity was tested by comparing the concentration at which the disappearance of corneal reflex in rabbits and anesthesia by intracutaneous injection in humans occurred, with that of procaine.

Results : The experimental results thereby obtained are shown in the accompanying table. LD_{50}, AtD_{50}, and AD_{50} listed in the table were calculated by Van der Waerden's method. AtD_{50} of the compound No. 13 was about 1.5 times that of morphine, about 1.8 times that of Methadone, and about 4 times that of Ohton. However, the mainte-

Tabel I. Antitussive and Other Pharmacological Activities of Compound No. 13

Pharmacol. Actions / Name of Drug	Antitussive action (Dog, intravenous)			Analgesic action (Mouse, subcutaneous)			Antispasmodic (Rabbit, intestine)		Antihistaminic (Guinea pig, intestine) (Benadryl=100)	Local Anesthesia (Procaine=1.0)		Toxicity LD_{50}	
	(A)	(B)	(C)	(D)	(E)	(F)	(G)	(H)		(I)	(J)	(K)	(L)
No. 13	0.31 ±0.04	1.5	61.6	0.090 ±0.007	0.8	13.6	2	100	5	10	5~10	1.23 ±0.05	19.1 ±0.8
Ohton	1.28 ±0.05	0.4	19.5	0.089 ±0.001	0.8	14.1	10	100	5	0.2		1.26 ±0.02	24.9 ±0.02
Morphine Hydrochloride	0.45 ±0.01	1.0	383.9	0.073 ±0.009	1.0	44.9	—	—	—	—		3.28 ±0.26	172.8 ±7.6
Methadone	0.58 ±0.07	0.8	51.7**	0.030 ±0.001	2.4	12.3	2	100	—	—		0.37 ±0.05	30*

(A) = AtD_{50}(mg./kg.), (B) = Ratio of Effect(Morphine=1.0), (C) = LD_{50}/AtD_{50}, (D) = AD_{50} (mg./10 g.), (E) = Ratio of Effect (Morphine=1.0), (F) = LD_{50}/AD_{50}, (G) = Anticholin. (Atropine=100), (H) = Antibarium (Papaverine=100), (I) = Rabbit, (J) = Human, (K) = Mouse(Subcut.)(mg./10 g.), (L) = Dog(Intraven.)(mg./kg.).
* Minimal Lethal Dose(M.L.D.) ** M.L.D./AtD_{50}

1) D. W. Adamson, A. F. Green : Nature, **165**, 122(1950); D. W. Adamson, W. M. Duffin, A. F. Green : *Ibid.*, **167**, 153(1951); A. F. Green : Brit. J. Pharmacol., 8, 2(1953).
2) Y. Kasé : Japan. J. Pharmacol., **4**, 118(1955).
3) Y. Kasé : This Bulletin, **2**, 298(1954).
4) Y. Kasé : Japan. J. Pharmacol., **4**, 130(1955).
5) N. B. Eddy, D. Leimbach : J. Pharmacol. Exptl. Therap., **107**, 385(1953).

nance period of antitussive action in the same dose by intravenous injection was slightly shorter than that of morphine and Methadone. Besides the potent antitussive action, the compound No. 13 possessed analgesic activity equal to that of Ohton, neurotropic and musculotropic antispasmodic activities, antihistaminic activity equal to that of Ohton, and local anesthetic action over 5 times that of procaine, both in humans and rabbits. However, intracutaneous application of a more concentrated solution (over 0.5%) of the compound No. 13 caused local necrosis of the skin.

LD_{50} of the compound No. 13 was approximately the same as that of Ohton in mice and dogs. The therapeutic index, LD_{50}/AtD_{50}, of its antitussive action was larger than that of Ohton or Methadone. At below lethal dose of the compound No. 13, mice display the Straub's tail-raising effect and the mice which had escaped death excrete red-tinted urine. General symptoms in a dog given intravenous injection of the same dose (0.8 mg./kg.) were the most marked with Methadone, followed by morphine, compound No. 13, and Ohton. The compound No. 13 never caused any emesis and anorexia, and the degree of hypnosis and salivation in dogs were much less than those caused by morphine and Methadone. The action of the compound No. 13 on respiration, blood pressure, and cardiac movemets was equal qualitatively and quantitatively to that of Methadone. The constriction of bronchial muscles caused by the inhalation of 0.2% histamine aerosol in guinea pigs[6] was inhibited by the preliminary administration of the compound No. 13, but to $^1/_{10}$ of that by Benadryl and $^1/_6$ of that by Ohton. The respiratory depression or cessation caused by the overdosage of the compound No. 13 was completely restored with Coramine and other analeptics.

Continued daily dose of 1.0 mg./kg. of the compound No. 13 by intravenous injection in dogs for 20 days indicated that there was neither acute tolerance nor cumulative action in antitussive effect. On the contrary, the same continued daily administration of 0.8 mg./kg. of morphine in dogs indicated such tolerance within 5~10 days.[4] By the daily intravenous administration of 1.0 mg./kg. of the compound No. 13 in dogs for one week no changes in blood or urine could be recognized.

Chemico-Pharmacological Department
Faculty of Pharmacy
University of Kumamoto.
Oemachi, Kumamoto.

Yoshitoshi Kasé (加瀬佳年)
Tenmin Kaku (加来天民)
Yôko Yamamoto (山本陽子)
Mizushi Tanaka (田中 瑞)
Yoshikuni Takasaki (高崎能邦)
Kazuhiko Nagao (長尾和彦)

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6) J. W. E. Harisson, J. L. Ambrus, C. M. Ambrus : J. Am. Pharm. Assoc., Sci. Ed., **40**, 226(1951).