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Y. Kase, T. Yuizono, and H. Serikawa;* and S. Yamamoto, T. Yamasaki, T. Fushimizu, N. Katayama, T. Moriya, and T. Nozuhara†: *d*-3-Dimethylamino-1,1-diphenylbutyl Ethyl Sulfone as a Long-acting Antitussive.

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During the course of studies to find a structure-activity relationship in antitussive action,[1~5] it has been found that dextrorotatory compounds of some analgesics are suitable as antitussive, because most of them are nearly devoid of analgesic action, while still maintaining potent antitussive effect.[6] Such antitussives could be used clinically without regard to habituation or addiction which is a characteristic and undesirable effect of potent analgesics such as morphine is apt to cause.

As a result of such studies, it has been found that dextrorotatory compound of 3-dimethylamino-1,1-diphenylbutyl ethyl sulfone hydrochloride (designated as Win-1161-3), synthesized by Klenk, *et al.*[7~8] and by Tullar, *et al.*[9] and whose pharmacological activities remained unclarified, possesses a potent and long-acting antitussive effect, a slight analgesic action, and does not show any other undesirable action, such as depression of respiratory and cardiovascular system, in antitussive dose. An excellent antitussive effect has been demonstrated also in clinical trial. The gist of this study is described herein.

Methods and materials

d-3-Dimethylamino-1,1-diphenylbutyl ethyl sulfone used for the experiment comes as white crystals (hydrochloride, m.p. 197°), easily soluble in water. The solution was prepared just before administration. The antitussive effect was evaluated by Kasé's method.[4] The dose necessary to depress coughing for 20~30 mins. is taken as being effective, from which 50% antitussive dose (AtD_{50}) was calculated by Litchfield-Wilcoxon's method.[10] Analgesic action was examined by a modification of the Eddy-Leimbach's hot-plate method[11] and by Haffner's method[12] with mice, and by pinching a pad of a dog with a hemostat.

Results

I. Pharmacology

1) Antitussive effect: The comparison of antitussive effect of Win-1161-3 with other control drugs is shown in Table I.

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Table I. Antitussive Effect of Win-1161-3 in Dogs (intravenous administration)

Drug	AtD_{50} (mg./kg.)	No. of dogs tested	Ratio of effect to codeine	LD_{50}/AtD_{50}
Win-1161-3	2.08 (1.72～2.51)	35	1.8	12.5
Codeine phosphate	3.67 (3.11～4.33)	60	1.0	26.6
Morphine-HCl	0.41 (0.35～0.48)	138	8.9	426.8
Methadon-HCl	0.11 (0.07～0.17) *b)*	48	33.4	260.9
Ohton*a)*	0.85 (0.70～1.03)	30	4.3	27.2

a) 3-Dimethylamino-1,1-di(2′-thienyl)but-1-ene hydrochloride.
b) The AtD_{50} values for Methadon which were reported in the previous papers[3~5] should be corrected to the present one.

According to AtD_{50}, Win-1161-3 is only 1.8 times that of codeine and therapeutic index (LD_{50}/AtD_{50}) is relatively small. However, the effect of Win-1161-3 is very persistent when the dose once exceeded the threshold. The average duration (in min.) of antitussive effect of Win-1161-3 in comparison with that of codeine in the same dog was as follows: 3 mg./kg. intravenous, in 12 dogs, Win-1161-3 : codeine = 520.8 : 27.5(mins.); 6 mg./kg. oral, in 7 dogs, Win-1161-3 : codeine = 801.4 : 59.3 (min.). This shows that the duration of Win-1161-3 is 18.9 times that of codeine by intravenous injection and 13.5 times of that of codeine by oral adminstration.

The reason why AtD_{50} of Win-1161-3 is relatively large and therapeutic index so small can be explained as follows: The maximal antitussive effect of Win-1161-3 was observed 30～60 mins. after the administration even by intravenous route. During this relative latent period the amplitude and frequency of coughing on a smoked paper gradually decreased. Therefore, the AtD_{50} of Win-1161-3 was calculated by a different way from that used for evaluation of usual rapid-acting antitussive like Ohton. When the *net* duration of effect (total duration minus relative latent period) by any dose exceeds the standard duration (20～30 mins.), the dose is taken as being effective and, therefore, AtD_{50} thus calculated should be apparently larger than that of other rapid-acting drugs. Accordingly, therapeutic index should also be apparently smaller.

2) Toxicity: LD_{50} of the drug in mice and dogs are shown in Table II. Judging from the LD_{50} in mice, the toxicity of Win-1161-3 is 1.87 times that of codeine, 30% that of Methadon. Below the lethal dose of Win-1161-3, mice showed the Straub's tail phenomenon, excitation, jumping, and convulsion. General symptoms with antitussive dose in dogs were anorexia, salivation, and increase in respiratory rate, but no vomiting or hypnosis was observed.

Table II. Acute Toxicity in Mice and Dogs

Drug	Route	Mice LD_{50}(mg./10 g.)	Dogs LD_{50}(mg./kg.)
Win-1161-3	s.c.	1.02 (0.83～1.26)	
	i.p.	0.36 (0.27～0.48)	
	i.v.		25.9 (22.2～30.2)
Codeine phosphate	s.c.	1.91 (1.78～2.05)	
	i.v.		97.8 (73.0～131.1)
Morphine-HCl	s.c.	3.54 (2.89～4.34)	
	i.v.		175.0 (156.8～195.3)
Methadon-HCl	s.c.	0.31 (0.27～0.35)	
	i.v.		28.7 (25.0～32.9)
Ohton	s.c.	1.37 (1.23～1.54)	
	i.v.		23.1 (18.5～28.8)

s.c.- subcutaneous i.p.- intraperitoneal i.v.- intravenous

3) Analgesic and other effects: An analgesic activity approximately equal to that of Dolantin was recognized by the hot-plate method and by Haffner's method in mice. However, no analgesic effect was manifested in a dog with antitussive dose. The effect of Win-1161-3 on respiration, blood pressure, and cardiac movements was tested in urethan-anesthetized rabbits, but the effect was not so marked even with intravenous dose of 5 mg./kg., which is twice the dose of AtD_{50} in the dog. Continued daily dose of 2～3 mg./kg. of Win-1161-3 by intravenous injection in dogs for 2 weeks indicated that there was neither acute tolerance nor cumulation in antitussive effect. An important property of Win-1161-3 is that the drug is easily decomposed in aqueous solution, but it shows durable effect by oral administration. Similar phenomenon was reported[6] in antitussive effect of *d*-Isomethadon, and this may suggest that unknown chemical changes occur *in vivo* after oral administration.

II. Clinical Trial

The drug was administered orally to 54 in- and out-patients suffering from severe coughing at

the 2nd Internal Clinic of this University. The classification of patients was pulmonary tuberculosis with cavity, bronchitis, and bronchial asthma. Average daily dose of the drug administered orally was 1~2 mg. for the children and 4~6 mg. for adults. The classification of the effect was as follows: For pulmonary tuberculosis (17 patients), remarkably effective (5/17), effective (12/17), ineffective (0/17); for bronchial asthma and bronchitis (20 patients), remarkably effective (16/20), effective (1/20), ineffective (3/20). It seemed that 6 mg. is sufficient to maintain the effect for a day for adults. The antitussive effect of the drug (3~4 mg.) was compared with those of Dextromethorphan (40 mg.) and codeine (60 mg.) in 17 tuberculosis patients. The effect was the most marked with Win-1161-3, followed by Dextromethorphan and codeine. No side-effect (especially tolerance and cumulation) was observed in 4 tuberculosis patients who were given 6 mg. daily dose of the drug for 40~50 days.

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Shigehiko Sugasawa and Seiichi Takano: 2-(2-Pyridyl)indole Methiodide.**

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By heating 2-(2-pyridyl)indole with methanolic methyl iodide solution in a sealed tube at 100° for two hours Sugasawa, *et al.*[1] obtained a crystalline product. When purified from hydrous ethanol this compound formed yellow needles of m.p. 194°(decomp.), having U. V. $\lambda_{max}^{50\%EtOH}$ at 325 mμ(log ε 4.34), which they took for the methiodide of the original base but was later found to be erroneous.

The methiodide of 2-(2-pyridyl)indole was now found to be conveniently prepared by heating the indole with pure dimethyl sulfate in benzene solution to form the methyl methosulfate of the base and then treating it with potassium iodide. The methiodide thus prepared came as faint yellow needles of m.p. 227~228° (decomp.), having U. V. $\lambda_{max}^{95\%EtOH}$ at 252 mμ (log ε 3.95) and 373 mμ (log ε 4.19).

According to the suggestion of Dr. Swan the compound of m.p. 194°(decomp.) obtained by Sugasawa, *et al.* was reinvestigated.

This compound was now obtained as a crystalline solid, which formed faint yellow needles of m.p. 197~199°(decomp.) with the same U. V. maximum as was described before, and was now found to be a mixture of the methiodide and the hydriodide of 2-(2-pyridyl)indole. This mixture could not be separated through crystallization from a variety of solvents, but when hydrous methanolic solution of this compound was basified with sodium hydrogen carbonate, there separated a basic substance, which could be collected in benzene. From this solution colorless rhombic pillars of m.p. 152~153° were recovered, which was found to be identical with 2-(2-pyridyl)indole.

The aqueous layer was extracted continuously with chloroform and thus a compound of m.p. 225~226°(docomp.) was recovered, which was proved to be the methiodide of 2-(2-pyridyl) indole by direct comparison with an authentic specimen prepared as above.

When roughly equal portions of the methiodide and the hydriodide of the base

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** This paper concerns a correction of the erroneous description of 2-(2-pyridyl)indole methiodide published in this Bulletin, **4**, 16(1956) by Sugasawa *et al.* One of the present writers (S.S.) is grateful to Dr. G.A. Swan, Chemistry Department, King's College, University of Durham, Newcastle-upon-Tyne, England, who drew his attention to this error and gave him an opportunity to make a correction by his own hands.

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