Communications to the Editor

The "Coughing Dog"[1]—An Improved Method for the Evaluation of an Antitussive.

A simple method by which coughing is readily induced in unanesthetized and unbound dogs has been contrived and the cough depressing effect of any drug can be determined quantitatively.

Making of tracheal fistula: A dog weighing 6 kg. or more is anesthetized; the neck is disinfected and the skin there cut open longitudinally for exposure of the trachea, the anterior wall of the trachea is partially incised so as to make there a round hole a trifle larger than a tracheal cannula in diameter, the skin covering the perforated spot is also cut off, the two margins are sewn together and an artificial tracheal fistula is now made. The dog, given ordinary postoperative treatment, is ready for use in two or three days.

Experimental procedures: A well-trained dog is used under no restraint, but most dogs had better be fixed; the end of a sterilized Y-shaped cannula is thrust into the trachea through the fistula and one opening of the cannula is connected by a T-tube to Marey's tambour for respiration to be recorded (See Fig. 1). Coughing is caused by stimulating the tracheal bifurcation mechanically with a nylon-bristled stimulator thrust into the trachea through the other opening of the cannula. Coughing invariably follows the stimulation and ceases with the withdrawal of the stimulator. The cannula needs to be drawn out after each experiment. The experiment can be safely repeated daily over a long period on the same dog.

The cough depressing effects of some drugs evaluated by this method accord well with the results obtained by the 1st method[2].

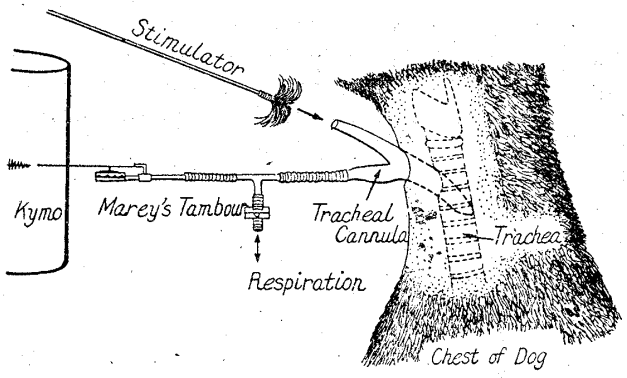

Fig. 1. Arrangement of Apparatus

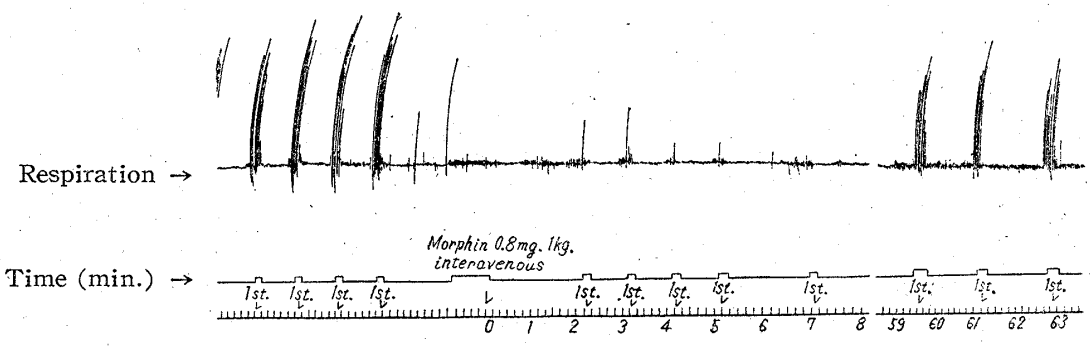

Fig. 2. Cough Depressing Action of Morphine Hydrochloride (0.8 mg./kg. intravenously) (stim.=Stimulation)

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1) Preliminary report was presented at the Annual Meeting of the Japanese Pharmacological Society, on November 8, 1953.
2) Y. Kasé: Japan. J. Pharmacol., **2**, 7 (1952).

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Santonin Analogs. IV. On an Isomeric Tetrahydroalantolactone obtained by the Reduction of Dihydroalantolactone.

A new procedure for obtaining both pure dihydroisoalantolactone (I) and dihydroalantolactone (II) in a good yield and an interesting observation during catalytic hydrogenation of (II) were reported in the 1st[1] and 3rd[2] papers of this series. The present paper is concerned with the preparation of isomeric glycols, (VII) and (XIII), and isomeric lactones, (VI) and (XIV), by the same series of reaction on (I) and (II).

With the use of lithium aluminum hydride, (I) was reduced producing a compound (III), $C_{15}H_{26}O_2$, m.p. 129~131°, $[\alpha]_D^{26}$: +46.0°. (III) was converted to (I) again by a mild oxidation with dichromate. Therefore structure (III) is the logical reduction product.

The structure of (III) was further supported by the following reactions: A methyl hydroxycarboxylate (IV), $C_{16}H_{26}O_3$, m.p. 103~106°, which was obtained by the hydrolysis of (I) with sodium hydroxide and followed by methylation with diazomethane, was oxidized with dichromate to a methyl ketocarboxylate (V), $C_{16}H_{24}O_3$, b.$p_{0.05}$ 95~97°. (V) was reduced with lithium aluminum hydride to yield (III). The same series of reactions were tested for tetrahydroalantolactone (VI) and in this case also the corresponding glycol (VII), $C_{15}H_{28}O_2$, m.p. 111~113°, $[\alpha]_D^{23}$: −7.9°, methyl hydroxycarboxylate (VIII), $C_{16}H_{28}O_3$, m.p. 124~127°, and methyl ketocarboxylate (IX), $C_{16}H_{26}O_3$, b.$p_{0.05}$ 95° (2,4-dinitrophenylhydrazone, m.p. 118~120°), were obtained.

Since (VII) was obtained from (III) by catalytic reduction, the stereochemical configurations of these corresponding derivatives, except one double bond in the series of dihydroalantolactone, were found to be the same.

However, when these reactions were tested for dihydroalantolactone (II), the glycol, $C_{15}H_{26}O_2$, m.p. 78~81°, $[\alpha]_D^{23}$: +29.9°, the structure of which could be proposed as (X) because (X) was converted again to (II) by mild oxidation, was found to give a saturated glycol (XIII), $C_{15}H_{28}O_2$, m.p. 126~128°, $[\alpha]_D^{23}$: +23.9°, by catalytic reduction. This new saturated glycol was different from (VII) in its melting point and possessed an opposite optical rotation. On admixture of (XIII) and (VII), a marked depression of the melting point was observed. Thus, (XIII) is a stereochemically isomeric compound of (VII). The other reactions for (II) gave corresponding compounds as in the case of (I). Thus, (II) was converted into methyl hydroxycarboxylate (XI), $C_{16}H_{26}O_3$, m.p. 103~105°, and (XI) was further oxidized to give methyl ketocarboxylate (XII), $C_{16}H_{24}O_3$, b.$p_{0.08}$ 110~111°(2,4-dinitrophenylhydrazone, m.p. 188~190°).

Furthermore, the isomeric saturated glycol (XIII) was mildly oxidized with dichromate to give a lactone (XIV), $C_{15}H_{24}O_2$, m.p. 134~137°, $[\alpha]_D^{20}$: +37.9°, and this was reduced

1) T. Ukita, R. Matsuda, S. Nakazawa: J. Pharm. Soc. Japan, **72**, 796 (1952).
2) T. Ukita, S. Nakazawa: This Bulletin, **2**, 239 (1954).