We have already reported the inhibition of homologous passive cutaneous anaphylaxis (PCA) by 14 newly synthesized compounds related to the chemical structure of disodium cromoglycate (1). Since 1, 3-bis(2-phenyl-4-chromenon-5-yl)-2-ol (compound 1) showed the most potent inhibition of PCA when given orally, the effect of the agent on experimentally-induced atopic type of asthma in guinea pigs was examined.

According to Levine et al. (2), antiserum containing homocytotropic antibody was obtained from guinea pigs which had been immunized with benzylpenicilloyl bovine γ-globulin (BPO_{23-BGG}) mixed with alumina as an adjuvant and which was given i.p. 8 to 12 times monthly. Sera collected from each animal 30 days after the last injection were pooled and frozen at −20°C until use. The antibody titer of this serum was 1 : 1024, as estimated by 7-day homologous PCA. Male Hartley guinea pigs weighing about 350 g were passively sensitized by an intracardiac injection of the antiserum in a dose of 0.5 ml/animal. After 48 hr the animals were anesthetized with urethane and given 0.2 mg/kg of benzylpenicilloyl bovine serum albumin (BPO_{23-BSA}) i.v. as a hapten-specific antigen. The change of respiration was similar to that seen in the case of asthmatic attacks in humans. The expiratory disorder was quite evident and was prolonged considerably as compared to that induced in rats (3). Thus we chose this model for experiments on the atopic type of asthma.

Compound 1 was administered in doses of 1.0 to 20 mg/kg p.o. to guinea pigs 2 hr prior to challenge. The animals were deprived of food for 24 hr before the drug treatment, but water was provided ad libitum. In the case of 1.0 mg/kg, antigen-induced decrease in the rate of respiration showed a tendency toward inhibition while that in the volume of respiration was significantly inhibited. The ratio of the time required to expire against that to inspire (Ex/In) was increased by the antigen treatment 20 to 30% of the value seen before challenge. This increase in the ratio was slightly inhibited by 1.0 mg/kg of the agent. All such changes in the respiration were significantly inhibited by 10 to 20 mg/kg of the agent, as shown in Fig. 1.

To determine the duration of the inhibitory activity of compound 1 on the
experimentally-induced asthma, 10 mg/kg of the agent was given p.o. to guinea pigs, in 5 groups of 4 animals 30 min, 1 hr, 2 hr, 6 hr and 12 hr prior to challenge with antigen, respectively. Thirty-minute pretreatment revealed a moderate inhibition in the asthma. More distinct inhibition was observed by 1-hr to 6-hr pretreatments, and even the 12-hr pretreatment resulted in a fairly potent inhibition, as shown in Fig. 2. This result is in accord with that obtained in the PCA study (1).

In other experiments, the effect of compound 1 given p.o. continuously for 4 weeks on the airway excretion was examined in rats. Increases were observed in the protein level and viscosity of the excretion, however, these increases were far less than seen in cases of continuous dosing of isoproterenol (4). Thus, compound 1 does not appear to have a harmful effect on the airway excretion.

The anti-asthmatic property of compound 1 should prove to be of interest to clinicians wishing to prescribe a long acting clinical oral preparation of the drug for prophylactic treatment of asthmatic attacks.

**Fig. 1.** Effect of compound 1 on experimental asthma in guinea pigs. The agent was administered 10 mg/kg p.o. 2 hr prior to challenge. Each group included 4 animals for compound 1 and 7 animals in the control, respectively. *, †: Statistical significance from the control at p<0.05 and p<0.01, respectively.
FIG. 2. Effect of compound 1 on experimental asthma in guinea pigs. The agent was administered 10 mg/kg p.o. 12 hr prior to challenge. Each group included 4 animals. *, †: Statistical significance from the control at p<0.05 and p<0.01, respectively.

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