6124 = YB-2 = propranolol which roughly corresponds to 30, 10, 5 and 1. The duration of blocking activity was comparatively shorter in Kö1366 and C-3 than in other 4 agents as indicated in Figure 1.

The present result of β-adrenergic blocking activity on the inotropic response is almost the same to that on the chronotropic response of the excised and blood-perfused sino atrial node preparation of dog. We conclude that there may be probably no difference in the β-blocking activity of 6 compounds between on the chronotropic and inotropic responses in dog.

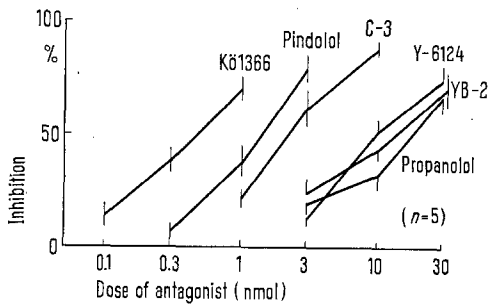

Fig. 2. Dose-effect curves for 6 β-adrenergic blocking agents on the positive inotropic response caused by 0.3 nmol of norepinephrine. Oridinates: Percent inhibition of the positive inotropic response to norepinephrine. Abscissas: Dose of antagonists. Each points indicate the means and vertical bars refer to S.E.

Zusammenfassung. Es wurde die Potenz sechs β-adrenergischer Blockierungsmittel auf positiv inotrope Wirkung von Noradrenalin am isolierten, Blut zuführenden Papillarmuskel des Hundes vergleichend untersucht. Die Reihenfolge der Wirksamkeit: Köl366 > pindolol > C-3 > Y-6124 = YB-2 = propranolol (30:10:5:1).

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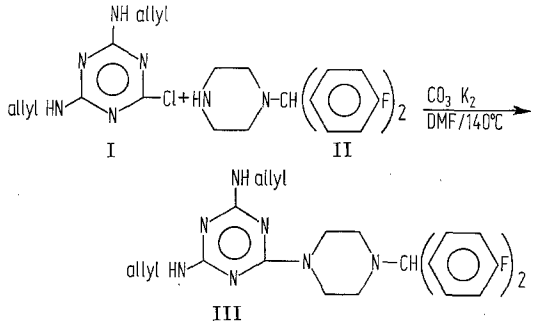
A Long Acting Respiratory Stimulating Agent: 1-(4,6 *Bis* allylamino-2-s-triazinyl)-4-(*Bis p*-fluorobenzhydryl) Piperazine (S 2620)

Todays respiratory stimulants for treatment of respiratory insufficiency are potent CNS stimulating substances; they induce convulsions even in the presence of CNS depressants such as barbiturates. Besides, they increase oxygen consumption and CO_2 production, so that the resulting hyperventilation does not parallel the concomitant arterial Pa CO_2 lowering. We searched for compounds which act on the respiratory tract by the intermediary of both carotid and aortic chemoreceptors and without CNS stimulating activity and selected among 50 piperazine derivatives[1] the title compound (S 2620) III which was synthesized according to the following scheme:



2-Chloro-4,6-bis allylamino-s-triazine I was prepared according to reference[2]. 1-(*Bis p*-fluorobenzhydryl) piperazine II was prepared through condensation of *bis-p* fluorobenzhydryl chloride and anhydrous piperazine. 1-(4,6-*Bis* allylamino-2-s-triazinyl)-4-(*bis p*-fluorobenzhydryl) piperazine III has mp 181 °C. The *bis* (methane sulfonate) of III has mp 243 °C (dec); UV $\lambda_{max.}^{EtOH}$ nm (log ε); 227 (4,52), 246 (4,53), 271_{Sh} (3,28).

In anaesthetized and unanaesthetized dogs, S 2620, administered by the i.v. (0.2 to 3 mg/kg) or oral route (2 to 5 mg/kg), induced a long lasting increase of ventilation without changes of oxygen consumption, carbon dioxide production and respiratory quotient. The arterial Pa CO_2 decreases with the increase of blood pH. Neither intracisternal nor intravertebral injection of S 2620 had any significant effect on respiration. The respiratory stimulation is abolished by vagotomy and carotid bodies denervation. In consequence, S 2620 is a long lasting chemoreflex stimulant without complication of cortical excitation.

The stimulating effect of S 2620 upon respiration is not influenced during oxygen administration, metabolic acidosis and alkalosis, after i.v. injection of mecamylamine, hexametonium, atropine, eserine and reserpine. The LD_{50} (mice) of III (*bis* methane sulfonate) were found 210 mg/kg (i.v.), 390 mg/kg (i.p.) and > 2 g/kg (p.o.).

In clinical studies, the effect of acute and chronic administration of S 2620 used for treatment of acute respiratory insufficiency has been observed in patients with chronic pulmonary emphysema and hypercapnia as in barbiturate intoxication. In every case, S2620 leads to hyperventilation with a long lasting lowering of arterial Pa CO_2 as well as to an increase in arterial oxygenation. Full reports of the chemistry and pharmacology[3] of this new agent will be presented in the near future.

Résumé. La (*Bis* allylamino-4,6 s-triazinyl-2)-I (*bis p*-fluorobenzhydryl)-4 pipérazine est un stimulant respiratoire à longue durée d'action et dépourvu d'action stimulante du système nerveux central.

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[1] Manuscript in preparation.
[2] R.D. DUNLOP and J. H. GARDNER, J. Am. chem. Soc. *55*, 1665 (1933).
[3] M. LAUBIE and F. DIOT, J. Pharmac., in preparation.