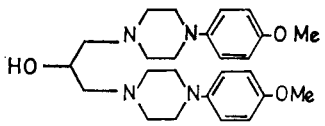
1,3-Bis[4-(*p*-methoxyphenyl)piperazinyl]-2-propanol (Ro 8-2580): a new monoamine depletor

Dopamine, noradrenaline and 5-hydroxytryptamine (5-HT) are depleted by reserpine, benzoquinolizine derivatives, oxypertine (Bak, Hassler & Kim, 1969; Carlsson, Jonasson & Rosengren, 1963), prenylamine and ε-aminocaproic acid (for review see Glowinski, 1970; Haefely, 1968) and, more recently, U-20057 (Johnson & Rudzik, 1970).

The present paper describes a new compound that decreases monoamines and produces slight sedation: 1,3-bis[4-(*p*-methoxyphenyl)-1-piperazinyl]-2-propanol, mol.wt 440·6 (Ro 8-2580).*



Rats from a closed randomized colony (Füllinsdorf strain, 80–160 g) were given single doses of Ro 8-2580 by stomach tube.

For amine determinations the animals were decapitated and the brains and hearts homogenized, extracted (Shore & Olin, 1958) and the content of noradrenaline (modification of Shore & Olin, 1958), dopamine (Bertler, Carlsson & Rosengren, 1958), 5-HT (Bogdanski, Pletscher & others, 1956) and 5-hydroxyindolacetic acid (5-HIAA) (Udenfriend, Weissbach & Brodie, 1958) measured.

For pharmacological investigations the following tests were made in separate animals.

The "openfield" test (Janssen, Jagenau & Schellekens, 1960): the number of "walking" and "rearing" movements (exploratory activity) were noted for 3 min. The catalepsy test (Boissier & Simon, 1963): the animal was considered to be cataleptic if the crossed homolateral limbs remained in this unnatural position for at least 10 s. Prolongation of pentobarbitone sleeping time: the number of animals losing their righting reflex for more than 1 min, 30 min after a intraperitoneal subhypnotic dose of pentobarbitone (12·5 mg/kg) was noted. The locomotor activity of two groups of three rats was measured in activity cages (Lehigh-Valley, Electronics Inc., Mod. A 2497) simultaneously with two control groups; the light beams interruptions were counted every 5 min. The performance of rats on a rotating rod was examined as described by Dunham & Mija (1957). The rectal temperature was obtained by means of a telethermometer equipped with a No. 402 probe (Yellow Springs Instrument Co.).

All three brain amines are below 50% of controls between 2 and 4 h after 100 μmol/kg Ro 8-2580 (Fig. 1); the 5-HT is the least affected (60% below) and dopamine the most (90% below). The 5-HIAA content increased (90% above) as the 5-HT decreased.

The Ro 8-2580-induced decline of 5-HT in brain (60% at 2 h) differs from that of noradrenaline (75%) in brain and heart at 2 and 8 h respectively). The recovery of 5-HT proceeded at a higher rate than that of noradrenaline, regaining its normal brain concentration after about 24 h, whereas the catecholamines, especially noradrenaline in the heart, were only restored at 48 h or even later. The relatively rapid decrease of the brain amines is paralleled by a diminished exploratory activity (rearing

* Synthetized by Dr. A. Edenhofer, Chemical Department, F. Hoffmann-La Roche & Co. Ltd., Basel, Switzerland.

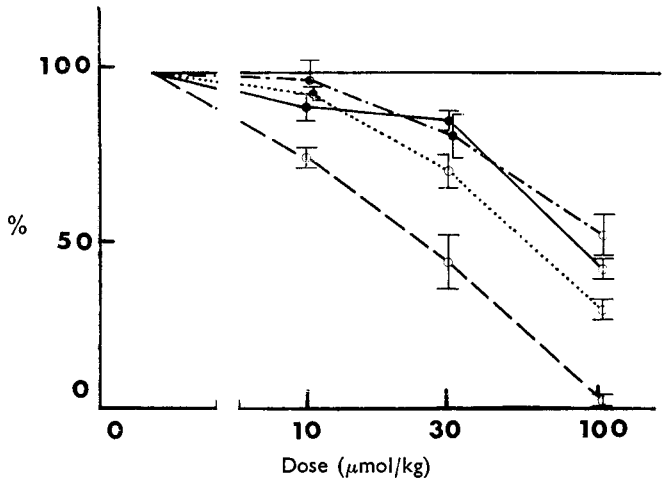


FIG. 1. Decrease of monoamines 2 h after oral application of increasing doses of Ro 8-2580. At time 0, the dose of the depletor was given by mouth. Control animals was taken as 100% (ordinate). Each point represents a mean value of at least three experiments ± standard error. Open circles are significantly different ($P < 0.01$) from controls. — 5-HT, — — dopamine, ··· noradrenaline in brain. —·— Noradrenaline in heart.

and walking); the recovery of the activity after 24 h was quicker than that of the amines. In spite of this difference it appears that motor activity in an unfamiliar environment (exploratory activity) correlates much better with the amine depletion than does the motor activity in a familiar environment (motor activity) which showed a significant diminution during about 3 h only. Decreased performance in the rotarod test had about the same time course. Unexpectedly, Ro 8-2580 neither produced catalepsy nor potentiated pentobarbitone sleeping time nor decreased the temperature.

Interference with the storage capacity constitutes the most likely mechanism for the monoamine lowering effect of Ro 8-2580. The concomitant increase in 5-hydroxyindolacetic acid suggests that the decrease of amine content is not due to inhibition of synthesis but to a depleting action. Ro 8-2580 has about the same duration of action as the benzoquinolizines (e.g. Ro 4-1284) (Pletscher, Brossi & Gey, 1962), U-20057 (Johnson & Rudzik, 1970) and oxypertine (Bak & others, 1969) and therefore differs from the longer acting reserpine. The depletion of catecholamines is more pronounced than that of 5-HT, as also reported for benzoquinolizines (Pletscher & others, 1962).

Many investigators have reported (e.g. Pirch, 1969; Pirch, Rech & Moore, 1967; Faith, Young & others, 1968) that the sedative action of reserpine rapidly recovers within 48 h, while amine content remains low. These observations suggest a dissociation of brain amine content and sedation (Brodie & Costa, 1962; Carlsson & others, 1963). The results of the present study confirm such observations with a new amine depletor.

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