Since the caudate nucleus of the rat appears to contain both β-adrenergic- and dopamine-receptors[15], interaction of dopamine, "dopamine-like" drugs or dopamine antagonists with both types of receptors could occur. In line with this hypothesis is the recent finding of the blockade by the potent neuroleptics pimozide and clozapine of a noradrenaline sensitive adenylate cyclase in slices of rat limbic forebrain[17]. Furthermore, investigations in vivo show significant differences between the actions of apomorphine and piribedil, since the effects of piribedil are reduced by reserpine or tyrosine hydroxylase inhibition, whereas those of apomorphine are not[18,19]. It has also been suggested, on the basis of a variety of experimental data, that some endogenous release of dopamine must always exist for piribedil to exert its full dopamine receptor stimulating activity[20]. Thus the mechanism of action of piribedil remains to be elucidated. Whether or not it is related to noradrenergic mechanisms rather than dopaminergic mechanisms needs further investigation.

Summary. Using isolated retinas of the rabbit, we have shown that the effects of antiparkinsonian drugs such as piribedil and S-584 are not related to direct stimulation of dopamine-receptors.

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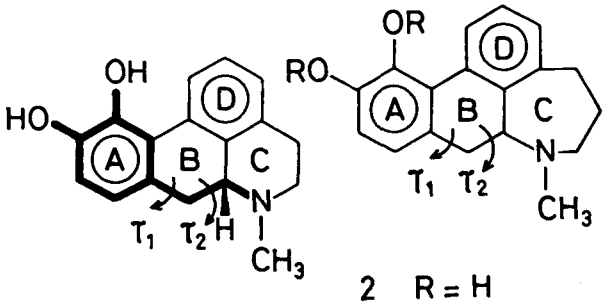
[21] Acknowledgments. The author wishes to thank Miss CHRISTIANE BLANK for excellent technical assistance, and Dr. J. C. ARNAUD, from "Les Laboratoires Servier" for the generous gift of piribedil and piribedil metabolite S-584.

Conformations and Biological Properties of Apomorphine and its Phenanthro[10,1-b, c] azepine Homologue[1]

Most drug-receptor interactions are stereospecific and preferentially involve a particular conformation of the drug molecule. The stimulating effect of apomorphine (**1**) on dopamine receptors is very stereoselective. Only the (–)-enantiomer, which has the *R*-configuration[2], is biologically active[3,4]. This action may be attributed to that structural fragment of the apomorphine molecule which corresponds to dopamine. The conformation of this fragment has torsion angels in the $-CH_2-CH_2-N$ moiety which are fixed as anticlinal (τ_1) and antiplanar (τ_2) by the rest of the molecule.



1

2 R = H

3 R = CH_3

The values of τ_1, τ_2 observed in the crystal structure analysis of apomorphine hydrochloride[5] are 146, −178° and 133, −178° in the two independent molecules in the crystallographic asymmetric unit. These values contrast with those observed in the crystal structure of the flexible molecule dopamine in the form of its hydrochloride[6] where $\tau_1 = \pm 99°$, $\tau_2 = 180°$. In solution, however, the fractional population of this rotamer is only 0.43[7] and it is possible for dopamine to take up a conformation similar to that seen in apomorphine by rotation about the ring-C_α bond. Since, however, the conformation of the catecholamine moiety in apomorphine is different from the observed crystal conformation of dopamine, the relevance of the crystal conformation of dopamine to any arguments concerning dopamine receptors is called in question. The conformations of rigid analogues with high agonist activity are more likely to provide suitable indicators.

Recently, we have synthesized 11,12-dihydroxy-7-methyl-4,5,6,7,7a,8-hexahydrophenanthro[10,1-b,c]azepine (**2**)[8], which is a homologue of apomorphine (**1**). Contrary to expectation, this compound had no dopaminergic action. Oral doses up to 100 mg/kg had no effect on the general behaviour of mice, nor did 50 mg/kg i.p. affect the catalepsy induced by tetrabenazine. In rats, i.v. doses of between 0.5 and 20 mg/kg produced neither stereotypies nor gnawing. Apomorphine, when given under the same conditions, induced gnawing within 30 min, with an ED_{50} of about 0.3 mg/kg i.v.

There are two possible explanations for the inactivity of the apomorphine homologue **2**: either the nitrogen atom is not pseudoequatorial to ring B, as in apomorphine, but axial, and the molecule thus does not fit the receptor; or the nitrogen atom is equatorial and the receptor is unusually sterically sensitive in the region to which the C-ring of apomorphine binds. To distinguish between these two possibilities, we have completed a crystal structure analysis of the dimethoxy analogue **3**. NMR-spectra have shown that **2** and **3** have identical conformations.

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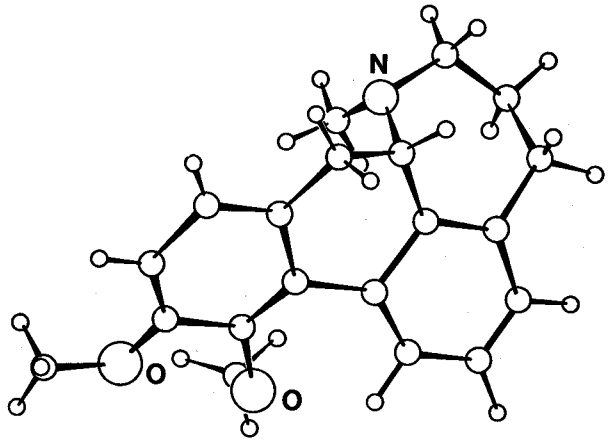
The result of the crystal structure analysis is shown in the Figure. The nitrogen atom is axial to the B-ring, and the N-methyl group is also, unusually, axial to the seven-membered ring. This conformation is quite different from that of apomorphine and is sufficient explanation for the biological inactivity of **2**. The torsion angles of interest, τ_1 and τ_2, are -146 and $+86°$, respectively. Interestingly, for molecules with the same absolute configuration at the asymmetric centre, the sense of the twist between the two benzene rings is opposite in apomorphine and in this homologue **2**.



0,0-Dimethyl derivative of apomorphine homologue (**3**): perspective drawing of the structure as observed in crystals of the base.

Summary. 11,12-Dihydroxy-7-methyl-4,5,6,7,7a,8-hexahydrophenanthro[10,1-b,c]-azepine (**2**), a homologue of apomorphine (**1**), has been found to be devoid of dopaminergic effects. The biological differences between apomorphine and this homologue are explained in terms of differences in conformation of the two molecules.

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The Process of Survival of Denervated and Freely Autotransplantated Skeletal Muscle

Survival of free autotransplants of entire skeletal muscles was first demonstrated by STUDITZKY[1,2], but the importance of previous denervation was emphasized by THOMPSON[3]. Successful autotransplantations have later been reported by several authors[4–10]. In a series of investigations on denervated cat muscle autotransplants[7,11–13], we have analyzed the various phases of early survival, revascularization and reinnervation of the graft. Those studies resulted in the finding that the muscle fibres undergo differential changes in the superficial and deep regions of the graft within the first week after the transplantation[7]. In particular, three concentric zones could be clearly distinguished where differential histochemical changes were demonstrated. However, the nature of these changes could not be clearly established by light microscopy. An ultrastructural study was therefore undertaken in order to define more precisely the process of survival of the graft.

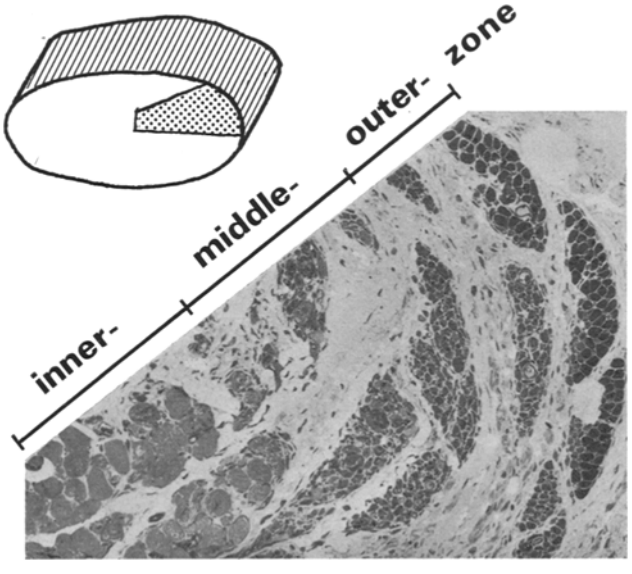

Fig. 1. Survey of muscle graft 8 days after transplantation. 3 zones are distinguished (outer, middle and inner zone). The boundaries between the different zones are not clear-cut and their relative extension varies in different parts of the transplant. × 60.

Materials and methods. The transplantations were made in two stages[7]. Primarily, a denervation of the m. peroneus longus of adult cats was made. Secondarily, 3 weeks after denervation, the muscles (diameter 8–9 mm, length 4 cm) were transplanted. By blunt dissection a tunnel was created under the fascia of one of the intercostal muscles. In this way the fibres of the transplant ran at approximately right angles to the intercostals. Both ends of the grafts were then sutured to the intercostal fascia under slight tension. The muscles were removed 2, 8 or 15 days after transplantation and processed for electron microscopy, i.e. treated with 2.5% glutaraldehyde for 16 h, cut into slices, postfixed in 1% osmium tetroxide and plastic embedded. For simplicity, only the findings after 8 days of transplantation will be described here.

Results and discussion. Three zones could be distinguished in the graft (Figure 1): an outer zone composed of a few layers of muscle fibres with slightly reduced diameter, a middle zone comprizing several fascicles of very small muscle fibres interspersed with numerous other cells, and an inner zone where large pale muscle fibres were observed at sites surrounded and penetrated by small cells.

Outer zone (Figure 2). The surface of the muscle fibres displayed small papillary projections of the basement membrane which contained cytoplasmic evaginations. The contractile material showed a tendency to become confluent into large fields. This was apparently related to an altered distribution of sarcotubular system elements. Triads were frequently seen transversely oriented. Honeycomb tubular structures derived from the T-systems were also seen. At variance with the control,