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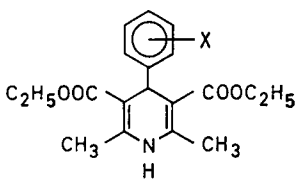
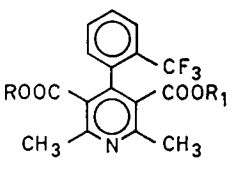
Dihydropyridines with potent hypotensive activity prepared by the Hantzsch reaction*

In 1882, Hantzsch discovered a simple procedure for the synthesis of substituted pyridines by a route in which 1,4-dihydropyridines are the intermediates. Since dihydropyridines have been implicated in various biochemical processes, we thought it of interest to evaluate some of the Hantzsch-type products for pharmacological activity. The only previous report of biological studies is that of Phillips (1949) in which weak analgesic and curare-like activity was reported for certain dihydropyridines.



I, X = H

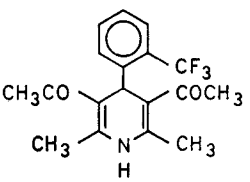
II, X = 2-CF_3 (SKF 24260)



III, R and R_1 = Et

IV, R = H, R_1 = Et

V, R and R_1 = H



VI,

In our studies, compound I was found to produce marked hypotension of long duration when administered intravenously to the anaesthetized dog; however, it had no activity when administered orally, even at high doses.

An extensive study of structural parameters—*N*-substitution, the 2,6-alkyl groups, modification of the ester groups, replacement by other electronegative substituents, and the nature of the 4-substituent—showed that the essential feature for imparting oral activity was the nature of the 4-substituent. Substituents studied at the 4-position included alkyl, cycloalkyl, aryl, and heteroaryl (Belgian patent) groups†. The optimum oral activity was found among those dihydropyridines containing the heteroaryl and substituted phenyl groups. However, the heteroaryl-containing compounds displayed overt signs of toxicity in animals, so the greatest effort was devoted to substituted phenyl compounds, of which *ortho* compounds had the greatest activity. 3,5-Dicarbethoxy-2,6-dimethyl-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine (II, SKF 24260) m.p. 144·5–146°, was singled out for further study. This compound is a potent hypotensive agent in rats, guinea-pigs, rabbits and dogs, and is active by the oral, intravenous and intraduodenal routes.

SKF 24260 produces significant blood pressure lowering of long duration in the anaesthetized dog at doses of 0·01 mg/kg (i.v.), and marked hypotension at 0·1 mg/kg. This effect is not significantly reduced by ganglionic or anti-acetylcholine agents or by antihistamines. Autonomic effects are characterized by a graded reduction in pressor

* For Part I see Loev, B. & Snader, K. M. (1965). *J. org. Chem.*, **30**, 1914.

† Subsequent to this work, coronary dilating activity was reported for certain dihydropyridines [Belgium patent (1967) 689377].

responses to standards such as adrenaline, noradrenaline, tyramine, bicarotid occlusion, and angiotensin. It also inhibits the depressor and chronotropic effects of isoprenaline. Doses required for this β-adrenoceptor blocking action were higher than those needed to produce hypotension. Studies in the anaesthetized dog showed that cardiac output is either increased or unchanged at a time when blood pressure is much reduced.

In the neurogenic hypertensive (Grimson, 1941), renal hypertensive (Green, Saunders & others, 1952), and normotensive dogs, SKF 24260 produces blood pressure lowering lasting up to 8 h after oral administration of 1 mg/kg. Hypotension in the normotensive animals was accompanied by tachycardia; this chronotropic effect is markedly reduced by pretreatment with propranolol. Increased heart rate is not observed in the neurogenic dog whose buffer (baroreceptor reflex) nerves have been sectioned, and all evidence indicates the tachycardia to be reflex in nature.

SKF 24260 is more potent than hydralazine; at equi-hypotensive doses the compounds produce essentially the same degree of tachycardia; however, the blood pressure effects produced by hydralazine gradually disappear within several days of daily dosing, whereas there was no evidence of tolerance to SKF 24260 after 21 days of daily dosing.

The compound appears to exert its effect chiefly by direct vascular dilation, but may also act by slight catecholamine depletion or some form of cns inhibition.

It has a very high 'therapeutic ratio'. In dogs it causes no overt side effects at 40 mg/kg; no obvious deleterious effects on the myocardium could be found in cardiac output or ecg studies. The ratio of LD50 in normal rats to the minimal effective dose in metacorticoid hypertensive rats is 490.

Testing in man with moderate essential hypertension, at oral doses of 5 to 7 mg (0·1 mg/kg), confirmed the hypotensive activity and potency (Walker, Meister & Familiar, 1972).

From a consideration of the possibility that the oral activity of SKF 24260 compared to the oral inactivity of I may have been due to the formation of an active metabolite from the former, we synthesized several possible metabolites, III-V. None of these had significant hypotensive activity at doses up to 80 mg/kg orally in the metacorticoid hypertensive rat (Green & others, 1952). Replacement of the carbethoxy group in I by another electronegative group (acetyl, VI) significantly decreased the potency.

We wish to thank Mrs. Marjorie M. Goodman for technical assistance in the preparation of some of these compounds.

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