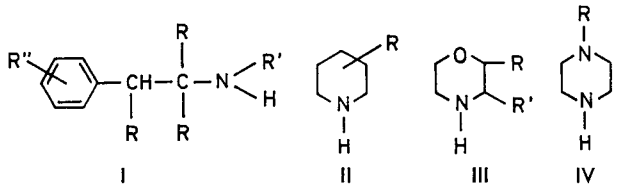
N-Oxidation of primary and secondary amines to give hydroxylamines—a general metabolic route

Aralkylamines (I), in which R = H or lower alkyl, R′ = H, alkyl, hydroxy- and cyano-alkyl, aralkyl and ring substituted aralkyl, and R″ = electron attracting or repelling groups e.g. trifluoromethyl, halogeno, alkyl, alkoxy groups have been shown to yield hydroxylamines upon incubation with microsomal preparations from various species (Beckett, 1971; Beckett, Van Dyk & others, 1971; Beckett & Al-Sarraj, 1972,



I II III IV

and unpublished work); the metabolism of some of these compounds has been investigated *in vivo* in various species and the excretion of hydroxylamines has been demonstrated. Some of these compounds are used medicinally e.g. amphetamine, ethylamphetamine, fenfluramine, phentermine, chlorphentermine, cyanoethylamphetamine.

Primary and secondary aliphatic amines and phenacylalkylamines also yield hydroxylamines metabolically. So do secondary amines in which the nitrogen atom is part of the ring system. Typical examples are compounds based on the piperidine structure II in which R = H, alkyl or aryl with or without other substituents, on the morpholino structure (III) in which R = H, alkyl or aryl and R′ = H or alkyl and on the piperazino structure (IV) in which R = alkyl, aralkyl and aryl. These are metabolized to hydroxylamines *in vitro;* some of these e.g. phenmetrazine (Beckett & Salami, 1972) have also been shown to give hydroxylamines *in vivo* in animals and man.

The incorporation of the above basic structures into more complicated systems does not prevent hydroxylamine formation e.g. pipradrol, normorphine, norcodeine, nortriptyline are metabolized to their corresponding hydroxylamines.

Many tertiary amino-compounds are dealkylated to secondary amines *in vitro* and *in vivo* and these secondary amino-metabolites can be further metabolized by *N*-oxidation to give hydroxylamines e.g. dimethylamphetamine is first demethylated and the secondary and primary amines produced are then converted to their corresponding hydroxylamines; phendimetrazine yields not only phenmetrazine but also the hydroxylamine of this compound (Beckett & Salami, 1972).

The metabolically produced hydroxylamines vary greatly in chemical stability; some are oxidized to oximes, others to C-nitroso compounds while others are stable under normal conditions; some can be reduced polarographically while others undergo anodic oxidation under the same conditions. Thus their stability in the biological system varies greatly.

In vivo, many of the hydroxylamines are excreted as their conjugated forms.

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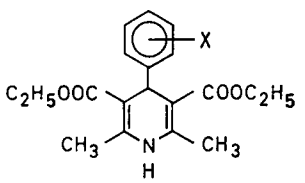
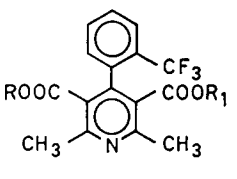
Dihydropyridines with potent hypotensive activity prepared by the Hantzsch reaction*

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

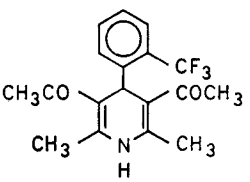
II, X = 2-CF_3 (SKF 24260)



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].