4-ALKOXYPIPERIDINES RELATED TO REVERSED ESTERS OF PETHIDINE

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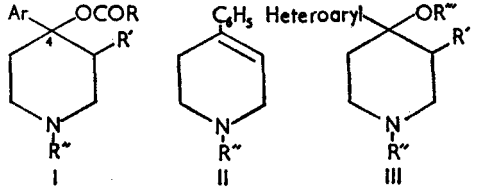
IN reversed esters of pethidine (I) the ester function at C(4) is important for analgesic activity as the corresponding alcohols are inactive. Since hydrolysis has been established as a major metabolic pathway in such

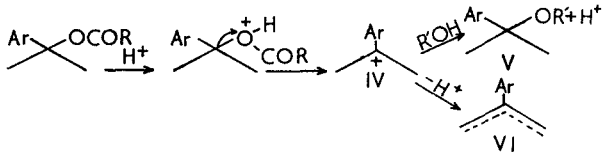


compounds as pethidine, anileridine and ethoheptazine (Way and Adler, 1960), species differences in activity may, in part, arise from differences in enzyme hydrolysis rates. It follows that introduction of factors that hinder hydrolysis may result in esters that have high activity.

One method of slowing hydrolysis is to introduce steric factors in the vicinity of the ester function. This is illustrated by the work of Levine (1955) on ester hydrolysis in human serum and by work on acetylcholine analogues (Beckett, Harper and Clitherow, 1961; Thomas and Stoker, 1961). The steric influence of an *ortho* methyl group in 4-phenylpiperidines is well demonstrated by its interference with the conjugation of 4-phenyltetrahydropyridines (II) (Fullerton, 1960). The same group might be expected to impede the hydrolysis of the corresponding 4-*o*-tolyl esters and this retardation could result in such esters having analgesic potencies greater than those of their less hindered counterparts. The ester [I, R=R'=Me; R''=$(CH_2)_2$Ph; Ar=*o*-tolyl] is, in fact, a highly active analgesic in mice with a potency greater than that of its 4-phenyl analogue (Beckett, Casy and Kirk, 1959). Keats, Telford and Kurosu (1960) found the same 4-*o*-tolyl ester to be 3–4 times more potent than morphine against post-operative pain in man.

During the syntheses of some heteroaryl counterparts of such reversed esters (I, Ar=Heteroaryl) it was found that certain members could be readily converted, with acid, into the 4-alkoxy analogues (III, R'''=alkyl), some of which possessed significant analgesic activity in mice. Some flexibility in the structure of the oxygen function at C(4) is already evident in pethidine and its reversed esters, and the present work has shown that an ether function at this position may also satisfy structural requirements for analgesia. Since ethers are more stable than esters and probably

less prone to enzyme attack, their substitution for ester groups represents another potential means of retarding metabolic deactivation of piperidine analgesics.



Transformation of esters into the corresponding ethers is considered to proceed via carbonium ions generated by acid-catalysed alkyl-oxygen fission of the esters (Casy, Beckett and Armstrong, 1961). The ions further react either with an alcohol (serving as a nucleophile) giving ethers (V) or by proton loss giving olefins (VI). In some instances the latter have been isolated together with the ethers.

The generation of carbonium ions and their fate depend in large measure upon the electronic nature of the 4-aryl substituent. Carbonium ion formation is facilitated by C(4)-substituents of high electron releasing power [e.g., 4-(*p*-methoxylphenyl) and 2-furyl]. Esters substituted with groups of poorer electron releasing power (e.g., phenyl, *p*-tolyl) or of electron withdrawing character (e.g., 2-pyridyl) are stable under the same acid conditions.

The fate of the carbonium ion depends upon the size and nature of the nucleophilic reagent: ethers result from unbranched alcohols, olefins from their branched isomers. The corresponding ethers would display considerable steric hindrance and their formation is thus contraindicated. Electronegative substituents in the β-position of the attacking reagent do not affect the reaction path, for example, both ethanol and β-chloroethanol give ethers. With allyl alcohol, on the other hand, the olefin results whilst with n-propanol, which is similar in size, the n-propoxy ether is obtained.

A series of 4-alkoxypiperidines (III) have been tested for their analgesic properties in mice and a number found to be more active than morphine (Casy, Beckett, Hall and Vallance, 1961). One of the more active members [III, Heteroaryl=2-furyl; R′=Me; R″=$(CH_2)_2$Ph; R‴=Et] has been examined in detail in mice and shown to be a true morphine-type analgesic from the following results:

(1) It is active in both the hot plate and tail pinch procedures;

(2) Its analgesic properties are antagonised by small amounts of nalorphine;

(3) Mice develop tolerance to its analgesic effects;

(4) It produces mydriasis at low dose levels;

(5) It gives a positive Straub tail effect at low dose levels and has a Straub Index (Shemano and Wendel, 1960) similar to that of morphine indicating the two compounds have similar degrees of addiction liability.

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