LETTERS TO THE EDITORS

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A New Analgesic Drug Analogous to *iso*Amidone

In the course of our search for new analgesics free from undesirable side-effects, 6-piperidino-4 : 4-diphenyl-5-methyl-3-hexanone (III) (the piperidyl analogue of *iso*amidone) has been synthesized by the following route :

$Ph_2CH.CN + ClCHMe.CH_2NC_5H_{10}$ →
(I)

$Ph_2C(CN).CHMe.CH_2NC_5H_{10}$ →
(II) (HCl, m.p. 225–226°)

$Ph_2C(CEt : NH).CHMe.CH_2NC_5H_{10}$ →
(2HCl, m.p. 193°)

$Ph_2C(COEt).CHMe.CH_2NC_5H_{10}$
(III) (HCl, m.p. 197–198°)
(HBr, m.p. 208–209°)

In the combined synthesis of amidone and *iso*amidone it has been shown that at least two isomeric nitriles are formed by the condensation of diphenylacetonitrile (I) and 1 (or 2)-chloro-2-(or 1)-dimethylaminopropane, owing to ring formation in the latter[1], and in view of the isolation of a third isomer of amidone[2] other chemical mechanisms may also operate. As the synthesis shown in the above scheme does not, therefore, establish the structure of the product, this was elucidated by the process of exhaustive methylation on the penultimate nitrile (II) on lines similar to those described by Schultz, Robb and Sprague[3].

Degradation of the nitrile (II) gave *N*-methylpiperidine (picrate, m.p. 222° [4]) and 2 : 2-diphenyl-3-methylbutenenitrile, m.p. 64–65°, apparently identical with that obtained by the American workers[3]. On hydrogenation it gave 2 : 2-diphenyl-3-methyl-*n*-butylamine, of which the phenyl urea derivative, m.p. 204–205°, was identical with a specimen synthesized by an independent method. Work is now proceeding with the view of isolating any other isomer of (III) that may be formed.

The piperidyl analogue of *iso*amidone has proved of considerable pharmacological interest, since it shows the smallest degree of undesirable side-actions of any of the active analgesic drugs we have yet studied. The methods used for the assessment of toxicity, analgesic and respiratory depressant activities have been described[5,6], and the results obtained with this compound are shown in the accompanying table, together with the figures previously reported for amidone and *iso*amidone. In all cases morphine has been used as the standard for the measurement of analgesic and respiratory depressant actions.

'Piperidyl *iso*amidone' (III) shows the same effects in acute animal toxicity experiments as amidone or *iso*amidone, death in all cases resulting from acute cardiac failure. All these compounds differ from morphine in this respect, since they are many times more toxic upon rapid intravenous injection than is morphine, although the toxicities in sub-acute experiments are very much more similar to that of morphine. All the compounds referred to, with the exception of morphine, are toxic to the isolated rabbit heart (Langendorff's preparation) at concentrations stronger than 1 part in 100,000, although 'piperidyl *iso*amidone' alone shows appreciable coronary dilator activity in concentrations below this figure.

Compound	Toxicity (I.V. mice) mgm./kgm.	Analgesic activity: Equi-active doses mgm./kgm.	Analgesic activity: Approximate ratio	Respiratory depressant activity: Equi-active doses mgm./kgm.	Respiratory depressant activity: Approximate ratio
Morphine	—	3·0	1·0	4–5	1·0
Amidone	12·5–25*	2·2–2·5	1·3	2·5	1·4–2·0
*iso*Amidone	40	3·0	1·0	7–10	0·4–0·7
'Piperidyl *iso*amidone'	25	3·0	1·0	12	0·3–0·4

* The toxicity of amidone and its optical isomers in mice is greatly influenced by the strain of animals employed, the published figures showing very wide variations.

In man 'piperidyl *iso*amidone' in doses of 12·5 mgm. produced no appreciable side-actions. When the dose was increased to 25 mgm., some of the volunteers described a sensation of warmth, were flushed and slightly dizzy, although the symptoms were less pronounced than those we have observed with other analgesic drugs. This drug was without significant effect upon the cardio-vascular system.

The depressant effect of 'piperidyl *iso*amidone' upon the respiratory response in human subjects to the inhalation of 5 per cent carbon dioxide in oxygen was examined by Prescott, Thorp *et al.*[7], and shown to be far less than that produced by equivalent analgesic doses of morphine, pethidine, amidone, *iso*amidone or Hoechst compound 10582, and to be approximately one third that of morphine.

From the table it would appear that *iso*amidone itself should be a superior drug to amidone; but in a few patients given *iso*amidone it was found that the duration of analgesic action was too short for the drug to be of real value. On the other hand, 'piperidyl *iso*amidone' produced analgesia similar in duration to that of amidone, and has shown sufficient promise to warrant an extensive examination and clinical trials, particularly in obstetrics, and the results of this work will be reported elsewhere.

Note added, January 10. Recently a second nitrile hydrochloride, m.p. 199–200°, isomeric with the hydrochloride of (II), has been isolated and converted into the corresponding ethyl ketone (6-piperidino-4 : 4-diphenyl-3-heptanone, $Ph_2C(COEt).CH_2.CHMe.NC_5H_{10}$) (HCl, m.p. 118–120°). Preliminary results obtained by Dr. A. C. White and Mr. A. F. Green, using young rats, indicate that this ketone is approximately twice as active as morphine analgesically, yet only equal to it as a respiratory depressant.

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[6] Thorp, Walton and Ofner, *Nature*, **160**, 605 (1947).
[7] Prescott, Ransom, Thorp and Wilson, [*Lancet*, **256**, 340 (1949)].