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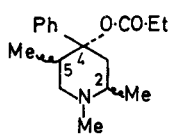
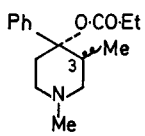
Analgesic potency and stereochemistry of trimeperidine and its isomers and analogues

Reports on the analgesic trimeperidine (γ-promedol) and its isomers that have appeared since 1956 (Prostakov & Mikheeva, 1962) have failed to provide either pharmacological detail or firm evidence of stereochemistry. A generous gift of the precursor 4-piperidone by Dr. N. S. Prostakov has enabled us to investigate these compounds and to apply modern physical techniques to solving their stereochemistry that were not available when the work was originally done. We isolated three 1,2,5-trimethyl-4-propionyloxy-4-phenylpiperidines (I) which corresponded



I



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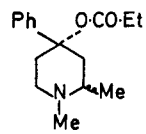

III

with the isomeric γ-, β- and α-forms of the Russian workers. The compounds were assayed for their analgesic properties in mice by the hot-plate test along with analogues lacking 2-methyl (α- and β-prodine, II) or 5-methyl substituents (III). We thank Dr. E. L. May of the National Institutes of Health for these data. Hot-plate ED50 values and stereochemical findings, given in Table 1, enable the following points to be made:

(1) The high activities of the promedol isomers and the fact that replacement of *N*-methyl by *N*-phenethyl in γ-promedol has a potency enhancing effect (Portoghese, 1965), provide good evidence of these esters having a morphine-like action at the analgesic receptor.

(2) The fact that the most active promedol isomer (β-) is equipotent with β-prodine (β-II) further demonstrates the superiority of *cis* 3-Me/4-Ph geometry over the *trans* arrangement in 4-phenylpiperidine analgesics (Casy, 1968; Casy, Chatten & Khullar, 1969).

Table 1. *Stereochemical findings and hot-plate ED50 values*

Compound	Configuration*	Hot-plate ED50 in mice mg/kg, subcutaneous inj.
γ-I	*cis* 2Me/4Ph, *trans* 5Me/4Ph	1·6
γ-I†		0·91
β-I	*cis* 2Me/4Ph/5Me	0·18
α-I	*trans* 2Me/4Ph, *cis* 5Me/4Ph	0·58
α-II	*trans* 3Me/4Ph	0·92
β-II	*cis* 3Me/4Ph	0·18
α-III	*trans* 2Me/4Ph	1·32
β-III	*cis* 2Me/4Ph	1·37
Pethidine	—	4·7

* The preferred conformation of γ-I is a chair with 4-phenyl equatorial; there is evidence that significant skew-boat populations (with 4-phenyl pseudo-equatorial) arise in the case of β- and α-I.
† *N*-Methyl replaced by *N*-phenethyl.

(3) The similar orders of activity of the isomeric analogues of the promedols that lack a 5-methyl substituent (α- and β-III) shows that the orientation of the 2-methyl group has little influence upon the activity of 4-phenylpiperidine analgesics.

In view of recent studies of brain levels of α- and β-II in mice (Abdel-Monem, Larson & others, 1970), it is probable that potency differences between isomeric promedols are due to differences in their affinities for the receptors rather than distribution and metabolism.

Details of evidence establishing the stereochemistry of the promedol isomers and their 2-methyl analogues will be given elsewhere.

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September 17, 1970

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Lipid depletion of bacteria induced by biotin deficiency and its relation to resistance to antibacterial agents

Previous communications from this laboratory have shown that Gram-positive bacteria grown in the presence of glycerol increase in lipid content and that this is accompanied by an increase in resistance to penicillins (Hugo & Stretton, 1966a, b), and phenols (Hugo & Franklin, 1968). We now report that bacteria grown under conditions of biotin deficiency are depleted in their lipid content and this in turn is accompanied by a decrease in resistance to a variety of antibacterial agents.

The organisms used were *Staphylococcus aureus* (Oxford) NCTC 6571 which includes biotin amongst its growth requirements, and *Escherichia coli* T94A (strain 58–278 M), obtained from Professor W. W. Umbreit, which requires biotin and phenylalanine for growth. The biotin requirement of the *E. coli* can be alleviated by the presence of aspartate in the medium. The Oxford staphylococcus was grown in nutrient broth and the cells contained 68·4 μg/mg dry weight lipid in agreement with previous findings (Hugo & Stretton, 1966a, b; Hugo & Franklin, 1968). Growth in Difco biotin assay medium at half strength and supplemented with 2 μg/litre of biotin (optimum 10 μg/litre) produced cells in which the lipid content had fallen to 55·4 μg/mg dry weight, significantly less (19%) than the nutrient broth grown cells.

E. coli was grown in the synthetic medium of Gavin & Umbreit (1965), biotin deficient cells were obtained by growth in this medium from which biotin had been omitted and biotin adequate cells in the same medium containing 10 μg/ml of biotin. Biotin-adequate cells had a lipid content of 179 μg/mg dry weight and biotin deficient cells, 109 μg/mg dry weight, a decrease of 39%.

The biotin adequate and biotin deficient cells of both species were challenged with a series of antibacterial agents. Table 1 gives the minimum inhibitory concentrations.