

The configuration of dextromoramide

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THE (+)-enantiomorph of 2,2-diphenyl-3-methyl-4-morpholinobutyryl-pyrrolidine [dextromoramide, (+)-I] is a potent analgesic in mice [the (-)-isomer is almost inactive]§ and knowledge of its configuration is of importance in relation to the stereospecificity of the analgesic receptor site (Beckett & Casy, 1965). This paper describes the correlation of dextromoramide (I) with (-)-isomethadone (VII), of known configuration (Beckett, Kirk & Thomas, 1962).

Treatment of levomoramide [(-)-I] with sodamide removed the amide function and gave the (-)-hydrocarbon II; by analogy therefore dextromoramide [(+)-I] must be related to the enantiomorph (+)-hydrocarbon II. This was shown to have the same configuration as the (+)-nitrile III and the (-)-ketone IV by chemical methods of unambiguous stereochemistry (see Fig. 1). These three compounds II, III and IV of related configuration were correlated with the dimethylamino-analogues (+)-V, (+)-VI and (-)-VII [(-)-isomethadone], also of identical configuration, by a method based upon comparisons of molecular rotatory changes in solvents of increasing polarity (cf. Beckett & Casy, 1957), and also by optical rotatory dispersion studies.

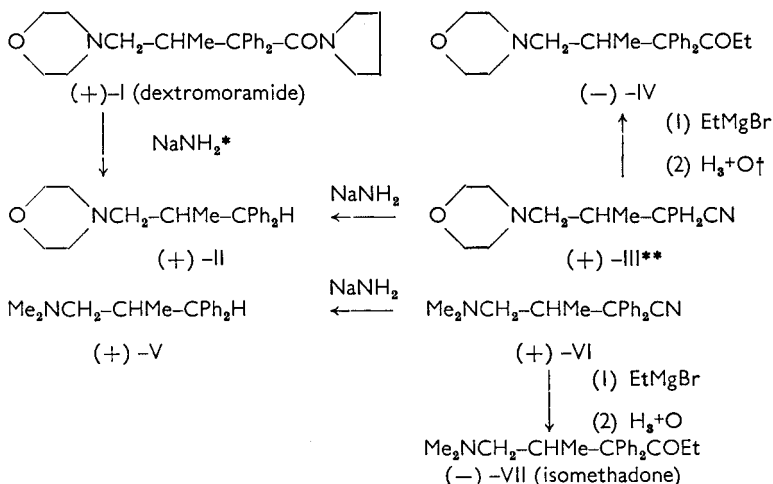


FIG. 1. Reactions employed in configurational studies.

* Relationship established using (-)-I(levomoramide). ** Resolved by means of camphor-10-sulphonic acid. † Refluxed 7 hr with conc. HCl




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§ ED50 mg/kg mice (hotplate test): (±) 1.25, (+) 0.64, (-) > 150 (Janssen & Jageneau, 1957).

Molecular rotational values for the morpholino-compounds (II–IV) and for the dimethylamino-derivatives (V–VII) are recorded in Table 1. Within each trio of compounds, displacement of the sign of $[M]$ (caused by increases in solvent polarity) is not uniform in direction, nor are regular variations in $[M]$ values observed. It is important to note, however, that the $[M]$ values of *corresponding members* of the two groups are displaced in the *same* direction: $[M]$ values of the nitriles III and VI, for example, are both displaced towards increasing dextrorotation as solvent polarity increases. Corresponding members also show the same form of variation in the value of $[M]$: thus for both the ketones IV and VII, $[M]$ values in benzene are contrary to the overall laevorotatory trend. These results indicate the configurational identity of the pairs II–V, III–VI and IV–VII.

Evidence for the configurational identity of the nitriles III and VI and the ketones IV and VII is also provided by optical rotatory dispersion data*. The former pair exhibit positive plain curves (rotations recorded to

TABLE 1. MOLECULAR ROTATIONS $[M]_D$ AT $21^\circ \pm 2^\circ$ (c 1–1.5%)^{*} OF 3-DIMETHYLAMINO AND 3-MORPHOLINO-1,1-DIPHENYL-2-METHYLPROPANE DERIVATIVES (A-CH₂-CHMe-CPh₂-B)

Compound	A	B	Solvent				Direction of sign displacement as solvent polarity increases
			C ₆ H ₁₂	C ₆ H ₆	EtOH	H ₂ O**	
II		H	+62	+59	+117	+126	+
V	Me ₂ N-	H	+70	+90	+134	+156	+
III		CN	+131	+108	+151	+196	+
VI	Me ₂ N-	CN	+151	+149	+192	+236	+
IV		COEt	-160	-61	-112	-279	-
VII	Me ₂ N-	COEt	-95	zero	-69	-232	-

Notes. * Variations due to concentration and temperature are much less than those due to change of solvent
 ** Hydrochloride

275 $m\mu$) and the latter, negative Cotton effects ($[\alpha]_{316} - 3730^\circ$, trough; $[\alpha]_{277} + 5060^\circ$, peak; the curve then flattens and rises again near 256 $m\mu$). In both cases the curves are virtually superimposable. Hence, *like* configurations are assigned to the (+)-hydrocarbon V, related to (-)-isomethadone (VII), and to (+)-II, related to dextromoramide: it follows that dextromoramide has the same configuration as *S*-(-)-isomethadone. Since it has already been shown that dextropropoxyphene (at its 3-C centre) and (-)-phenampromid have likewise the same configuration as *S*-(-)-isomethadone (Casy & Myers, 1964, and references cited), configurational identity among the more pharmacologically active enantiomorphs of

* Recorded on a Polarmatic 62 photoelectric spectropolarimeter, in water (conc. 1 mg/ml).

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analgesics containing the structural feature $>NCH_2CHMe$, is therefore firmly established.

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References

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