Stereochemistry of Methadol Diastereomers

Sir:

Previous investigations (1, 2) have shown that catalytic or lithium aluminum hydride reduction of methadone (I) proceeds stereospecifically to afford α-methadol (II*a*), while sodium in propanol reduction gives rise to a mixture of diastereomers in which the β-isomer (II*b*) predominates. The stereochemistry of these isomers is of great interest because of the remarkable changes in the configurational selectivity of analgesic receptors (Table I) which takes place in the α-series. Such changes recently have been rationalized in terms of differing modes of analgesic–receptor interactions (3).

In this paper evidence is presented which leads to the complete stereochemical assignment and conformational preference of these diastereomers.

Quaternization of racemic α- and β-methadol with methyl iodide afforded the corresponding methiodides, IV*a* (4) and IV*b*, m.p. 189–191°. Pyrolysis of IV*a* and IV*b* proceeded stereospecifically to give rise to isomeric tetrahydrofuran derivatives V*a*, m.p. 90–91° (4), and V*b*, m.p. 61–63°, respectively. Catalytic hydrogenation of VI which was obtained by the method of Easton (5, 6), afforded a mixture of V*a* and V*b* in 60% yield, whose composition was estimated by NMR analysis to be in a ratio of 2 to 1. Molecular models (Stuart-Briegleb) indicate that the top face of VI is more accessible to the hydrogenation catalyst than is the side which is *cis* to the C-5 methyl group. This strongly suggests that V*a* corresponds to the *cis*-isomer and V*b* represents the *trans*-diastereomer.

In view of the stereospecificity of the ring closure to V and the reported (7) formation of optically active VI from enantiomers of methadone methiodide, it is evident that the cyclization of IV*a* and IV*b* involves inversion at the C-6 asymmetric center. The relative stereochemistry of II*a* and II*b* therefore can be designated as (3S:6S) or (3R:6R) and (3R:6S) or (3S:6R), respectively. This assignment was corroborated by determining the dissociation constants of α- and β-methadol in methanol. The pKa of II*a* is 8.15 while that of II*b* is 7.85. According to the current concepts (8) concerning the base strength of diastereomeric amino alcohols, the pKa of these diastereomers is a reflection of the difference in the ability of the protonated species of II*a* and II*b* to form intramolecular hydrogen bonds of the type illustrated by formula VII. The diastereomer which is hydrogen bonded more strongly is more highly dissociated. The fact that α-methadol (II*a*) is a stronger base therefore indicates that there is less steric hindrance to intramolecular hydrogen bond formation. Molecular models show that this is consistent with the stereochemistry proposed above for II*a* and II*b*, since it can be seen that the cyclic hydrogen bonded conjugate acid of β-methadol (VIII*b*) has both the methyl and ethyl groups on the same side of the *quasi* ring, whereas the less hindered α-isomer (VIII*a*) has these groups on opposite sides.

High resolution infrared studies of II*a* and II*b* in carbon tetrachloride show that the bases are intramolecularly hydrogen bonded in as high a concentration as 0.25 *M*, thus indicating strong association. This was substantiated by NMR analysis of the bases in deuterochloroform. The hydroxylic protons of II*a* and II*b* resonate at unusually low field (8.6 and 7.9 p.p.m., respectively) and have peak half-widths of 30 and 23 c.p.s., respectively. The fact that the hydroxy-

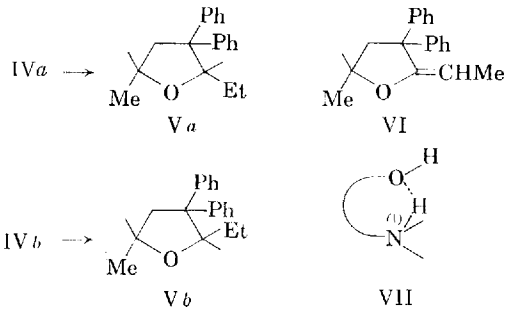
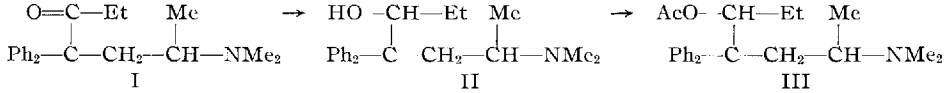
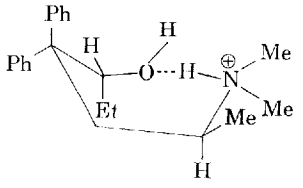


TABLE I.—ANALGESIC ACTIVITY OF METHADOLS AND ACETYLMETHADOLS (2)

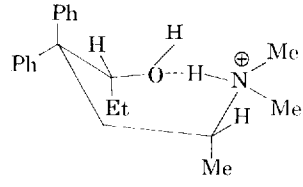


Configuration	ED_{50}[a]	Isomer	ED_{50}[a]	Isomer	ED_{50}[a]
S-(+)	25.7	*a*, (−)-α	3.5	(−)-α	1.8
		b, (+)-β	63.7	(+)-β	4.1
R-(−)	0.8	*a*, (+)-α	24.7	(+)-α	0.3
		b, (−)-β	7.6	(−)-β	0.4

[a] mg./Kg. injected subcutaneously in mice.



VIII *a*

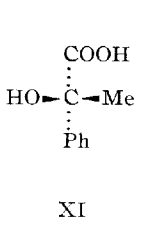


VIII *b*

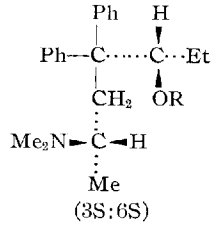
ylic proton resonance for II*a* is broader than that of II*b* indicates that the former free base forms stronger intramolecular hydrogen bonds than does the latter. The conformation of the bases, therefore, are very similar to the hydrogen bonded conjugate acids.

Further evidence for the stereochemistry of the methadols was obtained by application of Prelog's rule (9). Treatment of (−)-II*a* with benzoylformyl chloride produced in 95% yield the benzoylformate ester hydrochloride (IX), m.p. 195°, $[\alpha]_D^{25}$ −74.9°, which was converted to its methiodide (X), m.p. 208°, $[\alpha]_D^{25}$ −42.8° (70% yield). Reacting either IX or X with methylmagnesium iodide followed by saponification, afforded (80% over-all yield from X) S-(+)-atrolactic acid (XI), $[\alpha]_D^{25}$ +4.3° (1% in 1 *N* NaOH), corresponding to 8% optical purity (10). In accordance with Prelog's rule (9), the stereochemistry at C-3 therefore is assigned to the S-series.

Since the absolute configuration of (+)- and (−)-methadone, which are precursors of optically active α- and β-methadol (see Table I) has been determined (11), the complete absolute stereochemistry is as shown below. The (+)-α- and (−)-β-series are the mirror image forms corresponding to the projection formulas.

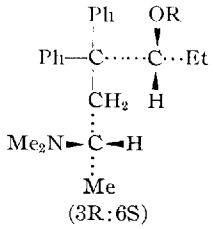


XI



(3S:6S)

II*a*, R = H
III*a*, R = Ac
} (−)-α



(3R:6S)

II*b*, R = H
III*b*, R = Ac
} (+)-β

Possible reasons for the changes in analgesic receptor stereoselectivity will be discussed fully in a definitive publication.

(1) Pohland, A., Marshall, F. J., and Carney, T. P., *J. Am. Chem. Soc.*, **71**, 460(1949).
(2) Eddy, N. B., May, E. L., and Mosettig, E. J., *J. Org. Chem.*, **17**, 321(1952).
(3) Portoghese, P. S., *J. Med. Chem.*, **8**, 609(1965).
(4) Easton, N. R., Nelson, S. J., and Fish, V. B., *J. Am. Chem. Soc.*, **77**, 2547(1955).
(5) Easton, N. R., and Fish, V. B., *ibid.*, **76**, 2836(1954).
(6) Easton, N. R., *et al.*, *ibid.*, **80**, 2519(1958).
(7) Easton, N. R., Nelson, S. J., and Fish, V. B., *J. Org. Chem.*, **25**, 847(1960).
(8) King, J. F., in "Technique of Organic Chemistry," Part I, vol. XI, Interscience Publishers, Inc., New York, N. Y., 1963, Chap. VI, p. 318.
(9) Eliel, E., "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 114.
(10) McKensie, A., *J. Chem. Soc.*, **97**, 1016(1910).
(11) Beckett, A. H., and Casy, A. F., *ibid.*, **1955**, 900.

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