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STEREOCHEMISTRY OF ISOMETHADOL ISOMERS

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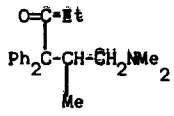
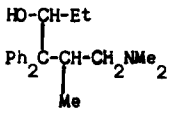
It has been reported (1,2) that the reduction of the potent analgesic, isomethadone (I), with lithium aluminum hydride proceeds in a stereospecific fashion to afford a racemate designated as α-isomethadol (IIa). If, however, the reduction is carried out with sodium and propanol, the major product is the β-racemate (IIb) (2). The four theoretically possible optical isomers of II have also been prepared from enantiomers of isomethadone using the above procedure (2).



I

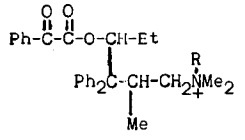


II

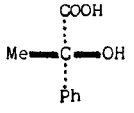
The stereochemistry of IIa and IIb is of interest (3) because these compounds have been reported to show a large difference in analgesic activity. The β-racemate possesses substantial activity, while the α-racemate has been found to be virtually inactive. Moreover, most of the analgesic activity in the active racemate resides in the (+)-enantiomer.

In this communication, evidence is presented which leads to the stereochemical assignment of these diastereomers.

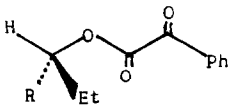
Treatment of (-)-IIa with benzoylformyl chloride produced the benzoylformate ester hydrochloride (III). This was converted to the corresponding methiodide (IV), m.p. 198°, $[\alpha]_D^{24}$+22.5° (C 0.4, MeOH), by treating with silver oxide and then allowing the base to react with methyl iodide. Reaction of IV with excess methylmagnesium iodide in diethyl ether, followed by saponification of the atrolactate ester afforded R-(-)-atrolactic acid (V), $[\alpha]_D^{24}$-14.4° (C 1.29, 1N NaOH), corresponding to 25% optical purity (4) and in an overall yield of 67%.



III, R=H
IV, R=Me



V

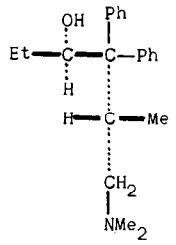


VI, R= Ph_2C-CH-$CH_2NMe_3^+$

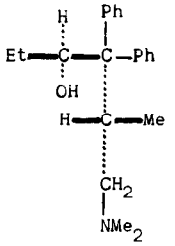
If H, Et, and the R group are considered small, medium and large, respectively, and are in the sequence depicted by formula VI, then according to Prelog's rule (5), approach from the least hindered side by the Grignard reagent should afford the (R)-atrolactate ester. Thus the configuration at C-3 in (-)-IIa is assigned to the (R) series.

Both (-)-IIa and (+)-IIb have been prepared from the (-)-enantiomer of isomethadone (I), whose configuration (6) recently has been established as (5S). The complete stereochemistry of (-)-IIa and (+)-IIb therefore is as shown by projection formulas VIIa and VIIb, respectively.

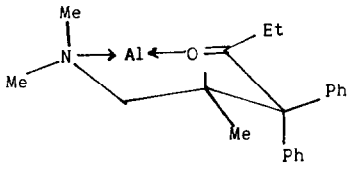
The stereospecificity of hydride reduction of I to IIa might possibly be due to the intramolecular coordination of the aluminum atom of an aluminum hydride species with the amine and carbonyl groups as shown by formula VIII. A similar type of coordination has been proposed (7-10) in order to



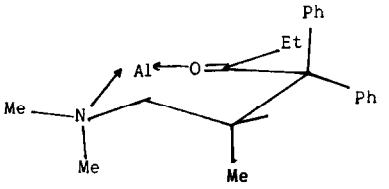
(3R:5S)
VIIa



(3S:5S)
VIIb



VIII



IX

account for the stereochemistry of isomeric glycols and amino alcohols arising from the reaction of ketone precursors with Grignard reagent. In the case of isomethadone, the 5-methyl group would act to stabilize the quasi ring in conformation VIII. The inverted conformation, IX, is not as favorable if one considers the "diaxial-like" interaction between the 5-methyl and N-methyl groups to exert a large destabilizing influence. Stuart-Briegleb models reveal the carbonyl carbon atom of VIII is more accessible from above than below the plane of the quasi ring. If steric approach control (10) is operative, as one would expect in cases of hydride reduction of hindered

ketones, then top-side hydride attack should afford a diastereomer possessing the (3R:5S) configuration. This is consistent with our stereochemical assignment of (-)-α-methadol (VIIa).

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