*J. Pharm. Pharmac.*, 1975, 27, 497–501 *Received September* 27, 1974

# Synthesis and characteristics of the enantiomers of the cyclic metabonate† of methadone

A. H. BECKETT, E. E. ESSIEN* AND C. ANTIRI-PENROSE

*Department of Pharmacy, Chelsea College (University of London), Manresa Road, London, SW3 6XL, U.K.*

2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (II), a cyclic metabonate of methadone was synthesized from methadone (I) and methadone-*N*-oxide (III). *m*-Chloroperbenzoic acid was used to oxidatively demethylate I while sulphur dioxide reductively demethylated III to give II. The importance of these syntheses lies in the fact that there is no attack on the asymmetric carbon atom in I or III, thus providing direct methods of obtaining the optical isomers of II.

In metabolic studies (*in vitro* and *in vivo*) of methadone (I), *N*-oxidation of the drug to give methadone-*N*-oxide (III) and mono-*N*-demethylation followed by spontaneous rearrangement of the molecule to give methadone cyclic metabonate (II) have been reported (Fig. 1) (Beckett, Taylor & others, 1968; Beckett, Mitchard & Shihab, 1971; Beckett, Vaughan & Essien, 1972; Pohland, Boaz & Sullivan, 1971). Attempts have been made to synthesize the cyclic metabonate (II) from materials unrelated to methadone, such as 3,3-diphenyl-3-cyano-1-methylpropylisocyanate (Beckett & others, 1968).

These methods have often proved lengthy and tedious. In a previous attempt to synthesize *N*-demethylmethadone (Harper, Jones & Simmonds, 1966) the desired product was not obtained. On treating 1,5-dimethyl-3,3-diphenyl-2-pyrrolidone with ethyl-lithium Pohland & others (1971) isolated a product which was identified as II. We now report new methods of synthesis of the cyclic metabonate (II) starting from methadone (I) and methadone-*N*-oxide (III).

## MATERIALS AND METHODS

Methadone hydrochloride was supplied by Burroughs Wellcome & Co. The (+)- and (−)- isomers of methadone were obtained as their hydrochloride salts from Sterling-Winthrop Research Institute, Rensselaer, New York. *m*-Chloroperbenzoic acid and liquefied sulphur dioxide were obtained from BDH Ltd. The purity of samples obtained was checked by t.l.c. and g.l.c.

### *Thin-layer chromatography (t.l.c.)*

Chromatograms were run on glass plates (20 × 20 cm) spread to 0·5 mm with a slurry of silica gel G (Merck) in water (1:2) and activated by heating at 110° for 1 h. The solvent system used was methanol–benzene–n-butanol–ammonia (0·88)–water

* Present address: Faculty of Pharmacy, University of Ife, Ile-Ife, Nigeria, West Africa.

† The term metabonate is used to define a product of metabolism formed by non-enzymic changes other than proton transfer in a metabolite. These changes may occur in the biological system or during isolation or during analytical procedures (Beckett, 1971).

(60:10:15:5:10 by volume) (Shihab, 1971). Dragendorff's reagent was used for detection of spots.

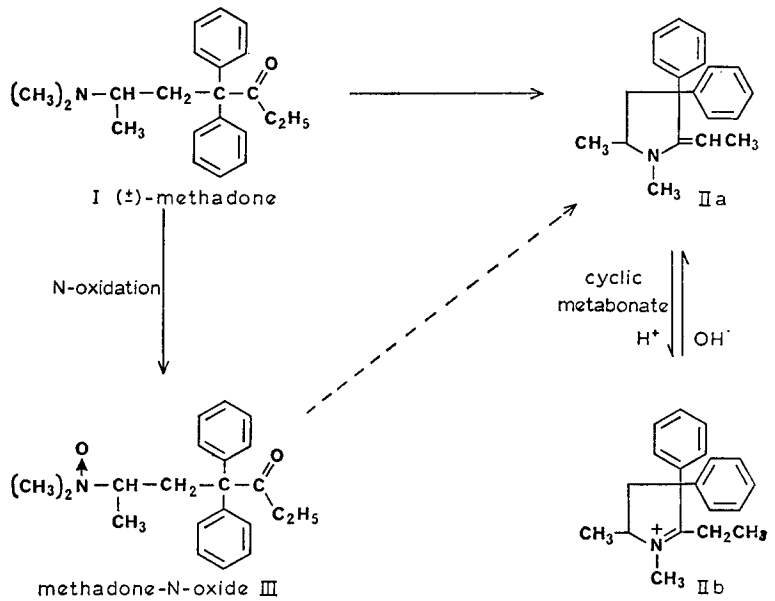


FIG. 1. Metabolism of (±)-methadone (Beckett & others, 1968, 1971, 1972).

*Gas-liquid chromatography (g.l.c.)*

A Perkin-Elmer F11 chromatograph with a flame ionization detector was used. The column was a 1 metre glass tubing ¼ inch o.d. packed with acid washed chromosorb G, DMCS treated and coated with 1% Apiezon L and 1% KOH. Nitrogen was the carrier gas (108 ml $min^{-1}$) at oven temperature of 205°, injection block temperature, 250°; hydrogen and air pressure being 23 and 25 lb $in^{-2}$ respectively. The internal marker used for g.l.c. determinations was amitriptyline.

*G.l.c.-mass spectrometry*

Mass spectra were obtained by gas chromatography linked with mass spectrometry using a Perkin-Elmer Model 270 mass spectrometer at an ionizing potential of 70 eV.

*Nuclear magnetic resonance spectroscopy (nmr)*

Nmr spectra of the compounds in $CDCl_3$ and $D_2O$ were recorded on a Perkin-Elmer R-10 spectrometer incorporating a Northern Scientific 544 CAT, using tetramethylsilane as the internal standard.

*Optical rotatory dispersion (ORD)*

The ORD spectra of (+)- and (−)-isomers of methadone (I) and the corresponding cyclic metabonates (IIa) were recorded in methanol (spectrograde) using a Bellingham Stanley Bendix-Ericsson polarimetric 62 equipped with a 250 W supersil xenon lamp. The instrument was operated under constant nitrogen purging. Samples for analysis were weighed out on a Cahn electrobalance.

*Synthesis of the cyclic metabonate (II)*

A. From methadone-*N*-oxide (III). Sulphur dioxide was passed into a methanolic solution (20 ml) containing 1 g of methadone-*N*-oxide (prepared by the Upjohn and

Co. method, 1958) for 40 min. Oxygen-free nitrogen was bubbled through the solution to expel excess $SO_2$ gas. Methanol was then evaporated off under reduced pressure. The resulting syrupy residue containing about equal amounts of cyclic compound (II) and methadone (I) (g.l.c. analysis) was purified as described below.

B. From methadone (I). To a solution of methadone (1 g) in 20 ml of dry chloroform was added, with gentle but constant stirring, a solution containing 1·86 g *m*-chloroperbenzoic acid in 20 ml of dry chloroform (1:2·5 molar ratio of I to the acid). The mixture was kept for 3½ h in the dark and then excess sodium hydroxide solution (20%) was added. The chloroform layer was separated; it was evaporated to dryness under reduced pressure to yield a residue containing cyclic compound (II) and methadone (I) in a 2:1 ratio (g.l.c. analysis).

*Purification*

Aqueous solutions (pH 4; 30 ml) of the reaction products from A and B (see methods above) were separately extracted with ether to remove methadone elimination product and some methadone (and unreacted organic acid in method B). Subsequent extractions of the aqueous solutions with benzene removed methadone-*N*-oxide and more methadone. The pH of the aqueous solutions was adjusted to 8·5 and the cyclic compound (II) was extracted with benzene. The benzene extracts were evaporated under reduced pressure to yield IIa (38 and 50% in methods A and B respectively). Analysis for (±)-cyclic compound, calculated for $C_{20}H_{23}N$: C, 86·6; H, 8·3; N, 5·1. Found: C, 81·9; H, 8·1; N, 4·5*. To a solution of IIa (only (±)-cyclic product) in dry ether was added excess oxalic acid in dry ether dropwise until there was no more precipitation. The product obtained was washed five times with sodium-dried ether and dried under nitrogen to yield the acid oxalate* of IIb (yield = 40%), m.p. 68–70°. Analysis calculated for $C_{22}H_{25}NO_4$: C, 71·9; H, 6·8; N, 3·8. Found: C, 67·8; H, 6·6; N, 3·4*.

The yield of the cyclic compound was more in method B than in A. The former had the added advantage that methadone was the starting material; whereas in the latter method (A) a two step synthesis to obtain initially methadone-*N*-oxide (III) and subsequently the cyclic compound was involved. Using various molar ratios of methadone and *m*-chloroperbenzoic acid and different reaction times (Fig. 2) a good yield (50%) of the desired cyclic compound was obtained by reacting one mole of methadone with 2·5 molar equivalent of *m*-chloroperbenzoic acid for 3½ h.

*Properties of the synthetic cyclic compound*

The synthetic cyclic metabonate (IIa) and its acid oxalate salt were highly hygroscopic and unstable and had to be protected from light. The products obtained by both methods A and B had identical physico-chemical characteristics as shown by t.l.c., g.l.c., g.c-mass spectrometry and nmr. These properties were also identical to those of the cyclic metabonate (II) obtained metabolically from incubations of methadone (I) with fortified guinea-pig liver preparations (Beckett & others, 1971), and from the urine of patients receiving methadone. The (+)- and (−)-cyclic metabonates prepared from (+)- and (−)-methadone respectively were identified by g.l.c. and t.l.c. using the (±)-cyclic product as reference. The t.l.c. characteristics of the synthetic and the metabolically produced cyclic compounds were identical ($R_F$ 0·59). $R_F$ values for methadone and methadone-*N*-oxide were 0·79 and 0·74 respectively.

* Compounds are unstable (see later).

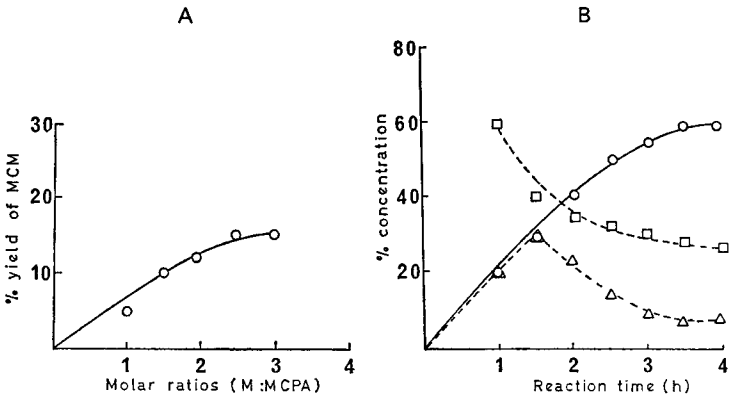


FIG. 2. Reaction of *m*-chloroperbenzoic acid with methadone. A—Percentage yield of methadone cyclic metabonate (MCM) with various molar ratios of methadone (M) and *m*-chloroperbenzoic acid (MCPA). B—Percentage concentration of methadone and its products at different reaction times. □ = methadone; △ = methadone-*N*-oxide; ○ = methadone cyclic metabonate.

The g.c.-mass spectra of the synthetic cyclic compound showed diagnostic ions which were identical with those already reported (Shihab, 1971; Pohland & others, 1971). The base peak at *m/e* 277 was consistent with the molecular ion ($M^+$). Other prominent ion peaks included the peaks at *m/e* 262 ($M^+-15$) which is attributed to the loss of the C–Me group. With the loss of a phenyl group from the molecular ion, the result was an ion peak at *m/e* 200 ($M^+-77$).

Nmr studies provided additional proof of the structure of the synthetic cyclic metabonate. The nmr spectrum of the acid oxalate salt in $D_2O$ showed a triplet (3H) at 9·29$\tau$ attributed to the terminal methyl of the 2-$CH_2$ $CH_3$ group; a diagnostic feature of the endocyclic alkene structure (IIb). The doublet (3H) at 8·35$\tau$ is for the -CH$CH_3$. A prominent singlet at 6·20$\tau$ suggests the presence of $-N^+-CH_3$. The base was extracted into $CDCl_3$ on addition of a few drops of NaOH. The spectrum of the base in $CDCl_3$ was complicated and on expansion showed singlets at 7·22 $\tau$ (minor) and 7·37 $\tau$ (major) in the ratio of 2:3. Other signals observed include singlets at 8·28 and at 9·05$\tau$. A pair of doublets at 8·83$\tau$ (minor) and 8·88 $\tau$ (major) J = 6Hz, could be attributed to the -CH-$CH_3$ protons.

The singlets at 7·22 and 7·32$\tau$ are due to the -N-$CH_3$ of the *cis*-and *trans*-structures whilst those at 9·05 and 8·28$\tau$ are due to the vinylic methyl protons (see Hassan & Casy, 1970). Singlets were observed instead of the expected doublets because in the presence of $D_2O$ (used previously as the solvent for the acid oxalate salt), the vinylic methine protons have been exchanged for deuterium and therefore could not split the methyl protons. The appearance of the $-N^+-CH_3$ signal downfield compared with the $-N-CH_3$ signal may be due to the anisotropic effect of the charged nitrogen in the acid salt. The above nmr results support the earlier findings (Beckett & others, 1968; Hassan & Casy, 1970) that the cyclic metabonate of methadone as the free base IIa (Fig. 1) exists as the *cis*-and *trans*-mixture but on salt formation (hydroiodide by previous workers), the exocyclic double bond migrates to the endocyclic position as shown in IIb (Fig. 1).

Earlier workers (Crabbe, Demoen & Janssen, 1965) reported that (—)-methadone in cyclohexane gave a positive Cotton effect in the region of 300 nm (maximum and minimum: 316 and 268 nm respectively). In this present work, (—)-methadone in methanol gave a negative Cotton effect in the region of 300–350 nm (maximum 320, minimum 282 nm). This inversion of Cotton effects in different solvents has been

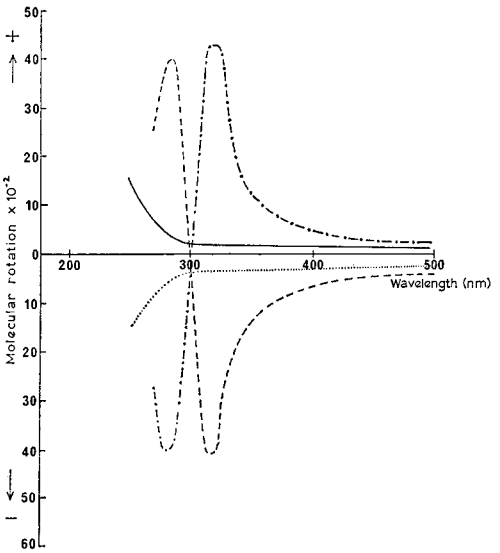


FIG. 3. ORD curves of (+)- and (−)-methadone and their corresponding cyclic metabonates. ——— cyclic metabonate of (+)-methadone, ····· cyclic metabonate of (−)-methadone; −·−·−·−· (+)-methadone HCl; − − − (−)-methadone HCl.

reported for other asymmetric ketones, e.g. for *trans*-6-chloro-3-methylcyclohexanone and 12β-hydroxy-12-methyl-20-ketopregnane when passing from non-polar solvents like iso-octane and n-heptane to the polar solvent methanol (Crabbe, 1965).

The optical curves produced by (+)- and (−)-isomers of II (bases only) obtained from (+) and (−)-methadone respectively were similar but with opposite rotational values, (see Fig. 3); the isomers of II showing almost plain absorption in the carbonyl absorption region (280–334 nm; compared with the optical curve for isomers of methadone). This also confirms the absence of the carbonyl group in the cyclic products. Thus, the present methods make it possible to compare the optical values of II obtained from urine of patients receiving methadone, with reference enantiomorphs to determine the stereoselective metabolism of methadone in man.

*Acknowledgements*

The authors thank Mr. G. R. McDonough for the help given in the running and interpretation of the nmr spectra. One of us (C.A.) acknowledges The Ghana Government for her post-graduate award.

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