262. *Configurational Studies in Synthetic Analgesics. Part IV.* The Configuration of (−)-Isomethadone.*

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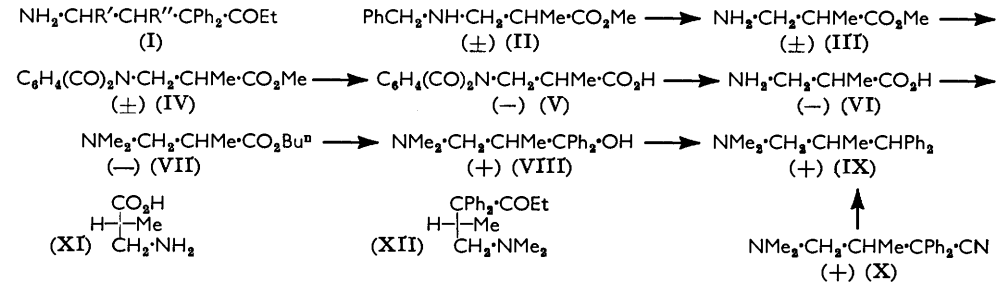
The configuration (XII) of (−)-isomethadone has been related to (−)-α-methyl-β-alanine (XI) by a series of reactions not involving the asymmetric centre.

The analgesic activity of methadone-type compounds (I; R′ = Me, R″ = H) resides mainly in one member of each enantiomorphic pair and the more active isomers possess identical configurations.[1] In the isomethadone series of compounds (I; R′ = H, R″ = Me), the analgesic activity exhibited by racemic mixtures is also due mainly to one of the isomers. For example, in mice (−)-isomethadone is 40 times as active as its enantiomorph.[2] The absolute configuration of (−)-isomethadone has now been determined as follows, since the configuration of (−)-α-methyl-β-phthalimidopropionic acid (V) has been previously established.[3] In the chart the symbols (±), (+), and (−) denote those isomers with which the reactions were carried out. Some preliminary work was done with racemic material.



N-Benzyl-α-methyl-β-alanine methyl ester (II), prepared by condensing benzylamine with methyl methacrylate,[4] was debenzylated by hydrogenation in the presence of 10% palladium–charcoal, the product (III) being isolated as hydrochloride. The latter was converted into the phthalimido-derivative (IV) which was saponified by acetic acid and aqueous 10% hydrochloric acid, to give α-methyl-β-phthalimidopropionic acid; use of aqueous alkali led to loss of the phthaloyl as well as the ester group. α-Methyl-β-phthalimidopropionic acid (V), $[\alpha]_D^{21}$ −20·1° (*c* 1·5 in $CHCl_3$), was obtained by resolution with brucine, a modification of the method described by Bregant and Balenovic [3] being used. This substantially pure isomer was hydrolysed to α-methyl-β-alanine hydrochloride (VI) by a mixture of concentrated hydrochloric acid and glacial acetic acid.

Reductive methylation [5] of the amino-acid (VI), followed by esterification, gave (−)-n-butyl β-dimethylaminoisobutyrate (VII), which with phenylmagnesium bromide gave (+)-3-dimethylamino-2-methyl-1,1-diphenylpropan-1-ol (VIII), whence sodium in liquid ammonia afforded the (+)-amine (IX). From the specific rotation of this compound it was obvious that partial racemisation had occurred.

The nitrile of (±)-isomethadone was resolved by the method of Larsen *et al.*[6] The (+)-nitrile (X), the precursor of (−)-isomethadone,[6] was converted into (+)-3-dimethylamino-2-methyl-1,1-diphenylpropane (IX) by sodamide in refluxing toluene. The infrared

* Part III, Beckett and Casy, *J.*, 1957, 3076.

[1] Beckett, in " Progress in Drug Research," ed. by Jucker E., Vol. I, Birkhauser, Basle, 1959, p. 455 and refs. there cited.
[2] Leimbach and Eddy, *J. Pharmacol.*, 1954, **110**, 135.
[3] Bregant and Balenovic, *Tetrahedron*, 1959, **5**, 44.
[4] Phillips, Ph.D. Thesis, London, 1958.
[5] Bowman and Stroud, *J.*, 1950, 1342.
[6] Larsen, Tullar, Elpern, and Buck, *J. Amer. Chem. Soc.*, 1948, **70**, 4194.

spectra of this base and its hydrochloride were identical with those of the corresponding products derived from the alcohol (VIII).

It follows that the (+)-nitrile (X) and (−)-isomethadone (XII) are stereochemically related to (−)-α-methyl-β-alanine (XI). In the terms proposed by Cahn, Ingold, and Prelog [7] (−)-isomethadone is (*S*)-isomethadone.

Experimental

Equiv. wts. of bases were determined by titration with 0·02N-perchloric acid in glacial acetic acid with Oracet Blue as indicator.[8] Hydrochlorides were titrated in the same solvent in the presence of mercuric acetate by Pifer and Wollish's method.[9]

(±)-N-*Benzyl-α-methyl-β-alanine Methyl Ester* (II).—Benzylamine (160 g.), methyl methacrylate (225 g.), and methanol (100 c.c.) were left at room temperature for 6 weeks and then distilled to give the amino-ester (II) (261 g.), b. p. 99°/0·3 mm. (Found: equiv., 210. Calc. for $C_{12}H_{17}NO_2$: equiv., 207). Phillips [4] gives b. p. 96°/0·3 mm.

(±)-*Methyl β-Amino-α-methylpropionate* (III).—The amino-ester (II) (261 g.) was shaken in absolute ethanol (500 c.c.) with hydrogen at room temperature and pressure in the presence of 10% palladium–charcoal (20 g.). In 14 hr. 1 mol. of hydrogen was absorbed. The mixture was filtered, acidified with ethanolic 10% hydrochloric acid, and concentrated to give, on cooling, needles of *methyl β-amino-α-methylpropionate hydrochloride* (155 g.), m. p. 110·5° (Found: C, 39·5; N, 9·4%; equiv., 156. $C_5H_{12}ClNO_2$ requires C, 39·2; N, 9·1%; equiv., 153·5).

(±)-*Methyl α-Methyl-β-phthalimidopropionate* (IV).—The amino-ester (III) (120 g.), phthalic anhydride (120 g.), and anhydrous sodium acetate (240 g.) were refluxed, with stirring, in glacial acetic acid (600 c.c.) for 2 hr., then cooled and diluted gradually with water. The crystals formed recrystallised from ethanol–water (1 : 1) as needles of *methyl α-methyl-β-phthalimidopropionate* (151 g.), m. p. 89° (Found: C, 63·2; H, 5·25; N, 6·0. $C_{13}H_{13}NO_4$ requires C, 63·2; H, 5·3; N, 5·5%).

(±)- *and* (−)-α-*Methyl-β-phthalimidopropionic Acid*.—The ester (IV) (190 g.) dissolved when refluxed in glacial acetic acid (400 c.c.) and aqueous 10% hydrochloric acid (400 c.c.) for 2 hr. The mixture was cooled and diluted with water. The crystals which separated recrystallised from ethanol–water (1 : 3) as leaflets of the (±)-acid (145 g.), m. p. 162°. Bregant and Balenovic [3] give m. p. 161°.

The acid (154 g.) and brucine (260 g.) were dissolved in ethanol (1300 c.c.) and left at 0° for 10 days. The crystals formed had $[\alpha]_D^{24·5}$ −31·5° (*c* 1·506 in $CHCl_3$). A second crop of crystals, obtained from the mother-liquor, had $[\alpha]_D^{25}$ −37° (*c* 1·504 in $CHCl_3$). Fractional crystallisation of the combined crops from absolute ethanol gave the substantially pure brucine salt of low solubility which had $[\alpha]_D^{22}$ −39·7° (*c* 1·503 in $CHCl_3$). Bregant and Balenovic [3] report $[\alpha]_D$ −44°. The free acid (V) was obtained by the addition of 4N-hydrochloric acid (1700 c.c.) to a suspension of the brucine salt (100 g.) in water (3000 c.c.). Fractional crystallisation of the first two crops of crystals gave the (−)-acid (V) (9·8 g.), m. p. 145—146°, $[\alpha]_D^{21}$ −20·1° (*c* 1·5 in $CHCl_3$). Bregant and Balenovic [3] report m. p. 145—146°, $[\alpha]_D^{17}$ −24·4° (*c* 0·98 in $CHCl_3$).

(−)-*n-Butyl β-Dimethylamino-α-methylpropionate* (VII).—The phthalimido-acid (V) (9·8 g.) was refluxed for 8 hr. in glacial acetic acid (24 c.c.) and concentrated hydrochloric acid (30 c.c.), then left overnight. The precipitated phthalic acid was filtered off, and the filtrate washed with ether (3 × 20 c.c.) and evaporated. The residue (5·2 g.) was shaken in water with hydrogen at room temperature and pressure in the presence of 10% palladium–charcoal (3·0 g.) and a 40% solution of formaldehyde (11·6 c.c.). After 1 hr. absorption ceased, and the mixture was filtered and evaporated under reduced pressure. The residual crude acid (4·0 g.) was dissolved in dry butan-1-ol (60 c.c.), and dry hydrogen chloride passed through the solution for 1 hr. The solution was then heated at 100—110° and passage of hydrogen chloride continued for a further 5 hr. The product was evaporated under reduced pressure, the residue made just alkaline with aqueous 50% sodium hydroxide, ether added, and the mixture made into a slurry with anhydrous potassium carbonate. The solution was decanted and dried (Na_2SO_4), the ether evaporated, and the residual oil distilled, to give the ester (VII) (3·6 g.), b. p. 98·5°/16 mm., $[\alpha]_D^{21·5}$ −17·8° (*c* 1·526 in EtOH). It gave a *picrate*, m. p. 100° (Found:

[7] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.

[8] Beckett and Tinley, "Titrations in Non-Aqueous Solvents," The British Drug Houses Ltd., Poole.

[9] Pifer and Wollish, *J. Amer. Pharm. Assoc., Sci. Ed.*, 1951, **40**, 609.

C, 46·1; H, 5·8; N, 13·5%; equiv., 416. $C_{16}H_{24}N_4O_9$ requires C, 46·1; H, 5·8; N, 13·45%; equiv., 416·4).

(+)-NN-*Dimethyl-2-methyl-3,3-diphenylpropylamine* (IX).—(*a*) The amino-ester (VII) (3·0 g.) in dry toluene (10·0 c.c.) was added dropwise to an ice-cold solution of phenylmagnesium bromide (1·17 g.) and bromobenzene (7·54 g.). The product was stirred for 1 hr. at room temperature, added to ice containing ammonium chloride (2·8 g.), and acidified with glacial acetic acid. The solid which separated was filtered off, and the base liberated with dilute aqueous ammonia and extracted with chloroform. The chloroform extract was dried (Na_2SO_4), the chloroform evaporated, and the residue crystallised, to give (+)-3-dimethylamino-2-methyl-1,1-diphenylpropan-1-ol (VIII) (3·9 g.), m. p. 91°, $[\alpha]_D^{21·5}$ +8·7° (*c* 1·508 in EtOH), whose infrared spectrum was identical with that of an authentic sample.[10] This alcohol (3·5 g.) was suspended in liquid ammonia (80 c.c.) containing ethanol (2·0 c.c.), and sodium (0·9 g.) was added during 50 min. with stirring. The whole was left until the ammonia had evaporated, then the residue was decomposed with ice and extracted with ether. The extract was dried (Na_2SO_4) and evaporated and the residue distilled, to give the *amine* (IX) (2·2 g.), b. p. 133°/1·2 mm., $[\alpha]_D^{22·5}$ +27·1° (*c* 1·58 in $CHCl_3$) (Found: C, 85·2; H, 8·9; N, 5·4%; equiv., 257. $C_{18}H_{23}N$ requires C, 85·4; H, 9·1; N, 5·5%; equiv., 253). It gave a *hydrochloride*, m. p. 187—188°, $[\alpha]_D^{22}$ +11·2° (*c* 1·01 in EtOH) (Found: C, 73·9; H, 8·45; N, 4·6%; equiv., 297. $C_{18}H_{24}ClN$ requires C, 74·6; H, 8·35; N, 4·8%; equiv., 290).

(*b*) The nitrile (88 g.) from (±)-isomethadone was resolved by the method of Larsen *et al.*,[6] giving a (+)-nitrile (13·0 g.), $[\alpha]_D^{22}$ +71° (*c* 0·906 in 96% EtOH) {Larsen *et al.* give $[\alpha]_D$ +70° (*c* 1·50 in EtOH)}. The (+)-nitrile (5·0 g.) was refluxed in dry toluene (20 c.c.) with sodamide (5·0 g.) for 12 hr. The mixture was cooled and filtered, and the toluene distilled off. The residue was distilled, to give the (+)-amine (IX) (4·2 g.), b. p. 120°/0·7 mm., $[\alpha]_D^{23}$ +43·1° (*c* 1·5 in $CHCl_3$) (Found: C, 86·1; H, 9·3; N, 5·7%), and its hydrochloride, m. p. 199—201°, $[\alpha]_D^{22}$ +27·3° (*c* 0·99 in EtOH) (Found: C, 73·9; H, 8·1; N, 4·8%; equiv., 292).

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[10] Perrine, *J. Org. Chem.*, 1953, **18**, 898.