J. Pharm. Pharmacol., 1964, **16**, 455–459 Received February 24, 1964

Absolute configuration of dextropropoxyphene at the C-3 asymmetric centre

A. F. CASY AND J. L. MYERS

The configuration at the C-3 asymmetric centre of dextropropoxyphene has been related by a stereospecific route to that of the analogous centre of (−)-isomethadone and hence to (*R*)-α-methyl-β-alanine.

THE well-known stereochemical specificity of analgesics related to 3,3-diphenylpropylamines (Beckett & Casy, 1955) extends to analogues in which the two phenyl groups are placed on adjacent carbon atoms (see Table 1). Dextropropoxyphene [α-(+)-I] has achieved considerable

$$Me_2N\cdot\overset{4}{C}H_2\cdot\overset{3}{C}H(Me)\cdot\overset{2}{C}(O\cdot CO\cdot Et)(Ph)\cdot\overset{1}{C}H_2\cdot Ph$$

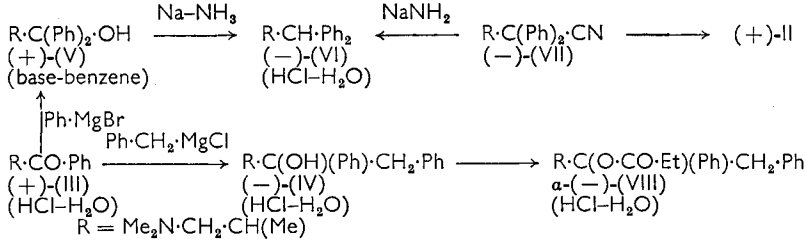
(I)

success as a clinical analgesic useful in the relief of mild to moderate pain (Beckett & Casy, 1962). This diastereoisomer possesses asymmetric centres at C–2 and C–3; the aim of the present work was to relate the configuration at C–3 of dextropropoxyphene to that of the analogous centre present at C–5 in (−)-isomethadone (II). The stereospecific

$$Me_2N\cdot\overset{6}{C}H_2\cdot\overset{5}{C}H(Me)\cdot\overset{4}{C}(Ph)_2\cdot\overset{3}{C}O\overset{2}{C}H_2\cdot\overset{1}{M}e$$

(II)

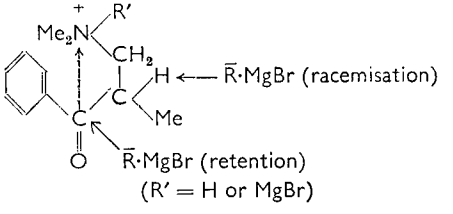
reaction sequence employed is shown below. The (+)-Mannich base (III) (obtained by resolution of racemic material by means of (−)-dibenzoyltartaric acid) was added to excess of benzylmagnesium chloride



when partially racemised α-(−)-4-dimethylamino-3-methyl-1,2-diphenylbutan-2-ol (IV) was isolated, together with the α-racemate. Reaction between the (+)-Mannich base (III) hydrochloride and the same Grignard reagent gave the optically pure α-(−)- and the partially racemised α-(−)-aminobutanol (IV). Reaction between the (+)-Mannich base (III) or the corresponding hydrochloride and phenylmagnesium bromide gave partially racemised 3-dimethylamino-2-methyl-1,1-diphenylpropan-1-ol

From the School of Pharmacy, Chelsea College of Science and Technology, Manresa Road, London, S.W.3.

(V) (base, dextrorotatory in benzene; HCl, laevorotatory in water). Some loss of optical activity had been anticipated in the reactions of the (+)-Mannich base (III), because its asymmetric centre is adjacent to a carbonyl group and is thus prone to base-catalysed racemisation (Eliel, 1962). The greater degree of retention of optical purity that follows the use of the (+)-Mannich base (III) hydrochloride may be a result of the positively charged nitrogen atom in the molecule enhancing the reactivity of the carbonyl group towards Grignard addition and reducing the possibility of base-catalysed racemisation. The optically pure amino-



propanol (V), obtained by resolution of racemic material by means of (+)-camphor-10-sulphonic acid, was used for the stage (V) to (VI); the (+)-aminopropanol (V) gave the (−)-aminopropane (VI) hydrochloride after treatment with sodium in liquid ammonia. As the (+)-amino-cyanide (VII), the precursor of (−)-isomethadone, is converted by sodamide to the (+)-aminopropane (VI) hydrochloride (Beckett, Kirk &

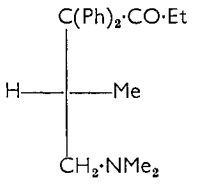
TABLE 1. ACTIVITIES OF ESTERS OF α-4-AMINO-3-METHYL-1,2-DIPHENYLBUTAN-2-OL IN THE HOT-PLATE TEST (IN MICE) (EDDY, 1959)

$X{\cdot}CH_2{\cdot}CH(Me){\cdot}C(O{\cdot}CO{\cdot}R)(Ph){\cdot}CH_2{\cdot}Ph$

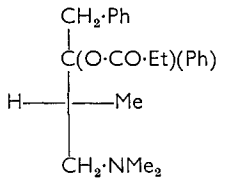
R	X	Form	ED50 mg/kg
Et	NMe_2	α-(±) (propoxyphene)	25·4
Et	NMe_2	α-(+) (dextropropoxyphene)	7·5
Me	-N⟨ ⟩	α-(±)	4·77
Me	-N⟨ ⟩	α-(+)	2·37

Thomas, 1962), it follows that (+)-isomethadone has the same configuration as the (−)-aminopropane (VI) hydrochloride. The last compound is related, through the (+)-Mannich base (III), to the α-(−)-butanol (IV), which gives laevopropoxyphene (VIII) on propionylation (Pohland & Sullivan, 1955). Thus (+)-isomethadone and laevopropoxyphene have identical configurations at C–5 and C–3 respectively; (−)-isomethadone and dextropropoxyphene, i.e., the more analgesically active members of the two enantiomorphic pairs, must therefore be related in the same sense. Beckett, Kirk & Thomas (1962) established the absolute configuration of (−)-isomethadone by relating this isomer to (*R*)-(−)-α-methyl-β-alanine.

Hence the absolute configuration of dextropropoxyphene at C–3 is also known.*

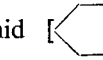


(*S*)-(−)-Isomethadone



3-(*R*)-(+)-Propoxyphene

While this work was in progress Sullivan, Beck & Pohland (1963) reported the absolute configuration of dextropropoxyphene to be 2(*S*):3(*R*). Their method for the C–3 centre involved conversion of the Mannich base (III) to the benzoyl ester of 1-dimethylamino-2-propanol by a Baeyer-Villiger oxidation. This rearrangement has been shown to proceed with retention of configuration in a number of cases, but retention has not been established in the case of amino-ketones.

With the recent report (Portoghese, 1964) that the more analgesically active enantiomer of phenampromid [ N·CH$_2$·CH(Me)·N(CO·Et)(Ph)] also has the same configuration as (−)-isomethadone, the importance of spatial configuration in analgesics possessing the structural entity >N·CH$_2$·CH(Me) is now established. This finding lends further support to the hypothesis, based originally on the results of a stereochemical study of enantiomers of methadone and related compounds (Beckett & Casy, 1954), that an overall optimum spatial configuration is one of the essential requirements for a molecule if it is to induce an analgesic response.

Experimental

Resolution of β-dimethylamino-α-methylpropiophenone (III). The Mannich base (III) (9·55 g) was added to a warm solution of (−)-dibenzoyltartaric acid (17·9 g) in acetone (200 ml). The product, after storage at 0° for 18 hr, deposited the dibenzoyltartrate (9·2 g), m.p. 115–116·5°, $[\alpha]_D^{20}$–53 (*c* 1·0 in EtOH). The rotation of the salt was unchanged on further recrystallisation. The base, liberated from the salt with dilute aqueous ammonia solution and extracted with ether, gave a hydrochloride (4 g), m.p. 161–162°, $[\alpha]_D^{20}$ + 48 (*c* 1·0 in EtOH) [Pohland, Peters & Sullivan (1963) report m.p. 153–155°, $[\alpha]_D^{25}$ + 47 (*c* 1·0 in EtOH)].

Grignard addition to the (+)-Mannich base (III). (*a*) The (+)-Mannich base (III) (15 g) in ether (50 ml) was added to a Grignard reagent prepared from benzyl chloride (19·9 g), magnesium (4·85 g) and ether (250 ml). The mixture was heated under reflux for 4 hr, cooled and poured onto crushed ice and ammonium chloride. Hydrogen chloride was passed through the dried ethereal phase and the precipitated hydrochloride

* In applying the nomenclature of Cahn, Ingold & Prelog (1956) the sequences CH$_2$·NMe$_2$, C(Ph)$_2$·CO·Et, Me, H and C(O·CO·Et)(Ph)·CH$_2$Ph, CH$_2$·NMe$_2$, Me, H obtain in isomethadone and propoxyphene respectively.

(17 g, m.p. 226–230°) crystallised from methanol-ethyl acetate (4 : 1). After two recrystallisations α-(±)-4-dimethylamino-3-methyl-1,2-diphenylbutan-2-ol hydrochloride (10 g), m.p. and mixed m.p. 238-239° was obtained. A second crop of crystals (3·5 g) m.p. 189–192°, $[\alpha]_D^{21}$ — 19·0 (*c* 1·0 in H_2O) had m.p. 234–235°, $[\alpha]_D^{21}$ — 29 (*c* 1·0 in H_2O) after further recrystallisation. [Pohland & Sullivan (1953) report m.p. 231–232° for α-(±)-(IV)].

(*b*) A suspension of the finely powdered (+)-Mannich base (III) hydrochloride (15·0 g) in ether (150 ml) was added to a Grignard reagent prepared from benzyl chloride (38·1 g), magnesium (7·2 g) and ether (350 ml). The product was heated under reflux for 8 hr, decomposed and processed as described in (*a*) above to give the crude hydrochloride (11·2 g), m.p. 226–230°. Fractional crystallisation of the salt from methanol-ethyl acetate gave the partially racemic α-(−)-aminobutanol (IV) hydrochloride (4·8 g), m.p. 233–234·5°, $[\alpha]_D^{21}$ — 16 (*c* 1·0 in H_2O) and the optically pure α-(−)-aminobutanol (IV) hydrochloride (2·5 g), m.p. and mixed m.p. 246–247°, $[\alpha]_D^{21}$ — 53 (*c* 1·0 in H_2O) [Pohland & Sullivan (1955) report m.p. 246–247°, $[\alpha]_D^{20}$ — 53 (*c* 1·0 in H_2O)].

(*c*) The (+)-Mannich base (III) (4·75 g) in ether (25 ml) was added to a Grignard reagent prepared from bromobenzene (6·28 g), magnesium (1·26 g) and ether (50 ml). The product was heated under reflux for 2 hr, decomposed and processed as described above to give 3-dimethylamino-2-methyl-1,1-diphenylpropan-1-ol (V) hydrochloride (7·5 g), m.p. 240°. This salt melted at 244° after recrystallisation from ethanol-ether [Perrine (1953) reports m.p. 242·5° for racemic material) and had $[\alpha]_D^{21}$ — 14·0 (*c* 1·0 in H_2O or EtOH]. The free base, crystallised from light petroleum (b.p. 40–60°), had m.p. 92–92·5° [Perrine (1953) reports m.p. 92·8–93·3° for racemic material) and $[\alpha]_D^{21}$ + 13 (*c* 1·0 in benzene)].

(*d*) A suspension of the (+)-Mannich base (III) hydrochloride (5·0 g) in ether (125 ml) was added to a Grignard reagent prepared from bromobenzene (13·8 g), magnesium (2·1 g) and ether (50 ml). The product was heated under reflux for 4 hr, decomposed and processed as described above to give the aminopropanol (V) hydrochloride (5·0 g), m.p. 240°, $[\alpha]_D^{21}$ — 29·9 (*c* 1·0 in H_2O), $[\alpha]_D^{21}$ — 21·6 (*c* 1·0 in EtOH). The free base, crystallised as above, had m.p. 90–91°, $[\alpha]_D^{21}$ + 48·2 (*c* 1·2 in benzene).

Resolution of 3-*dimethylamino*-2-*methyl*-1,1-*diphenylpropan*-1-*ol.* A solution of the racemic aminopropanol (V) (26·9 g) and (+)-camphor-10-sulphonic acid (23·2 g) in acetone (100 ml) was seeded (seed material obtained by leaving the oil left after evaporating some of the above solution to stand in a desiccator until it solidified) and stored at room temperature for 48 hr. The mother liquors were decanted, the crystals dissolved in hot acetone (150 ml) and reseeded; the crystals which separated had $[\alpha]_D^{17}$ — 27·9 (*c* 1·0 in H_2O). One more recrystallisation from acetone (150 ml.) (no seed added) gave material $[\alpha]_D^{16}$ — 29·1 (*c* 1·0 in H_2O). The free base (V), liberated as usual, had m.p. 90°, $[\alpha]_D^{20}$ + 53·4 (*c* 1·2 in benzene) and gave a hydrochloride, m.p. 241–242°, $[\alpha]_D^{17}$ — 71·3 (*c* 1·0 in H_2O).

(−)-3-*Dimethylamino*-2-*methyl*-1,1-*diphenylpropane* (*VI*). Sodium (0·9 g) was added portionwise over 30 min to a vigorously stirred suspension of the (+)-aminopropanol (V) (3·5 g) in liquid ammonia (80 ml) containing ethanol (2 ml). The solvent was allowed to evaporate and the residue decomposed with ice and extracted with ether. The residue (3·1 g) from this extract gave the (−)-aminopropane (VI) hydrochloride, m.p. 198–199°, $[\alpha]_D^{17}$ − 52·5 (*c* 1·0 in H_2O). (Found: C, 74·9; H, 8·3; N, 4·6. Calc. for $C_{18}H_{24}Cl$ N: C, 74·6; H, 8·35; N, 4·8%). The (+)-aminopropane (V) hydrochloride derived from (+)-3-dimethylamino-2-methyl-1,1-diphenylpropyl cyanide (Beckett, Kirk & Thomas, 1962) had m.p. 199–201°, $[\alpha]_D^{20}$ + 53·8 (*c* 1·0 in H_2O). The infra-red spectra of the two samples were superimposable.

Acknowledgments. We thank Dr. A. Pohland for the gift of authentic samples of α-(+)- and α-(−)-4-dimethylamino-3-methyl-1,2-diphenylbutan-2-ol hydrochloride and for advice on the resolution of the Mannich base (III).

References

Beckett, A. H. & Casy, A. F. (1954). *J. Pharm. Pharmacol.*, **6**, 986–999.
Beckett, A. H. & Casy, A. F. (1955). *Ibid.*, 7, 433–455.
Beckett, A. H. & Casy, A. F. (1962). *Progress in Medicinal Chemistry.* Vol. 2, p. 76. Edited by Ellis, G. P. and West, G. B. London: Butterworths.
Beckett, A. H., Kirk, G. & Thomas, R. (1962). *J. chem. Soc.*, 1386–1388.
Cahn, R. S., Ingold, C. K. & Prelog, V. (1956). *Experientia*, **12**, 81–94.
Eddy, N. B. (1959). *Chem. Ind.*, 1462–1469.
Eliel, E. L. (1962). *Stereochemistry of carbon compounds*, p. 35. New York: McGraw-Hill.
Perrine, T. D. (1953). *J. org. Chem.*, **18**, 898–903.
Pohland, A., Peters, L. R. & Sullivan, H. R. (1963). *Ibid.*, **28**, 2483.
Pohland, A. & Sullivan, H. R. (1953), *J. Amer. chem. Soc.*, **75**, 4458–4461.
Pohland, A. & Sullivan, H. R. (1955). *Ibid.*, **77**, 3400.
Portoghese, P. S. (1964). *Chem. Ind.*, 582.
Sullivan, H. R., Beck, J. R. & Pohland, A. (1963). *J. org. Chem.*, **28**, 2381–2385.