Configurational Studies in Synthetic Analgesics.

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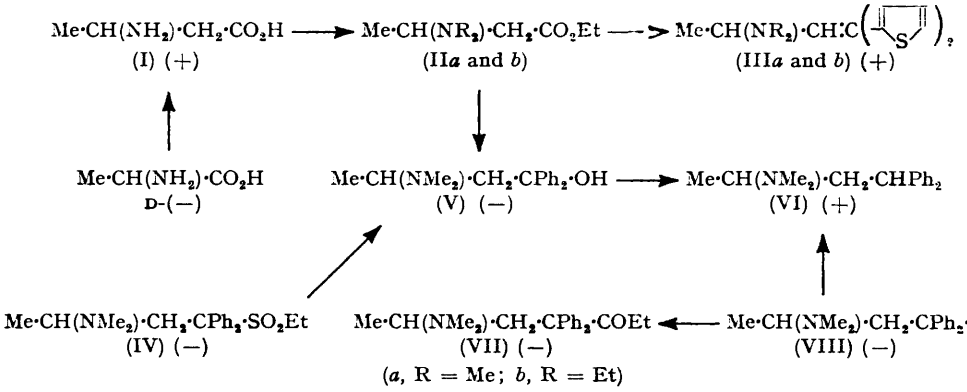
The analgesically active isomers "(−)-Methadone" [(−)-6-dimethylamino-4 : 4-diphenylheptan-3-one] (VII), (−)-3-dimethylamino-1 : 1-diphenylbutyl ethyl sulphone (IV), "(+)-Dimethylthiambutene" [(+)-3-dimethylamino-1 : 1-di-2′-thienylbut-1-ene] (III*a*), and "(+)-Diethylthiambutene" [(+)-3-diethylamino-1 : 1-di-2′-thienylbut-1-ene] (III*b*), have been shown to possess identical configurations which are related to D-(−)-alanine.

It has been shown that, in synthetic analgesics possessing one asymmetric carbon atom, nearly all the analgesic activity exhibited by the racemic mixture resides in one of the isomers. In an investigation of the structural requirements of analgesics it was of importance, therefore, to determine the configuration of certain of these highly active enantiomorphs. The configurations have been determined by reactions outlined in the annexed scheme.

β-Aminobutyric acid (I) was obtained from alanine by application of an Arndt–Eistert reaction according to a modification of the method of Balenović, Cerar, and Fuks (*J.*, 1952, 3316), preliminary work being done on racemic material. The Wolff rearrangement, involving migration of an asymmetric group, has been shown to proceed with retention of configuration (Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 500). *N*-Phthaloylalanine was converted *via* its acid chloride into 1-diazo-3-phthalimidobutan-2-one and the diazo-ketone rearranged to methyl β-phthalimidobutyrate : silver benzoate (see Newman and Beal, *J. Amer. Chem. Soc.*, 1950, **72**, 5163) proved to be more efficient as catalyst than the silver oxide used by the original workers. Treatment of the diazo-ketone with alcoholic ammonia and silver nitrate gave

β-phthalimidobutyramide. The structures of the two products of rearrangement were confirmed by their direct synthesis from β-aminobutyric acid prepared by hydrolysis of ethyl β-aminobutyrate. This ester was obtained by condensing ethyl crotonate with ammonia according to Adamson's method (*J.*, 1950, 885). The β-phthalimidobutyric acid derivatives were hydrolysed to β-aminobutyric acid hydrochloride by a mixture of concentrated hydrochloric acid and glacial acetic acid. The use of 50% hydriodic acid for the hydrolysis (Balenović *et al.*, *loc. cit.*) gave a product which could not be methylated by reductive methylation, probably owing to poisoning of the catalyst by iodine.



The (+) and (−) denote sterically related compounds of the series, and not necessarily those isomers with which the reactions were carried out.

Optically active *N*-phthaloyl-L-alanine, $[\alpha]_D^{18}$ −23·6° (*idem*, *loc. cit.*, report −17·5°), was prepared by heating a mixture of neutralised L-alanine hydrochloride and phthalic anhydride for 15 min. at 170—180° (cf. Bilman, *J. Amer. Chem. Soc.*, 1948, **70**, 1473). The lower value of the specific rotation given by Balenović *et al.* (*loc. cit.*) agrees with the value originally reported by Fischer (*Ber.*, 1907, **40**, 489) for material prepared by heating a mixture of alanine and phthalic anhydride for 7 hr. at 120—125°, a process which was shown to give a partially racemised product. The optical purity of the intermediates used along the route to 3-dimethylamino-1 : 1-diphenylbutan-1-ol (V) is indicated by the numerical identity of the specific rotations of this final product and material obtained by the resolution of the corresponding racemic mixture.

Reductive methylation of β-aminobutyric acid hydrochloride, derived from D-(−)alanine, by the method applied by Bowman and Stroud (*J.*, 1950, 1342) to α-amino-acids, followed by esterification of the product, gave ethyl β-dimethylaminobutyrate (II*a*). This ester with phenylmagnesium bromide gave the (−)-amino-alcohol (V), the hydrolysis product of (−)-3-dimethylamino-1 : 1-diphenylbutyl ethyl sulphone (IV) (Archer and Auerbach, *J. Amer. Chem. Soc.*, 1951, **73**, 1840). The (+)-amino-alcohol (V), obtained by resolution of the racemic compound with (+)-tartaric acid, was dehydrated by Archer and Auerbach's method (*loc. cit.*) to (−)-3-dimethylamino-1 : 1-diphenylbut-1-ene which, on hydrogenation, gave (−)-3-dimethylamino-1 : 1-diphenylbutane (VI). (−)-3-Dimethylamino-1 : 1-diphenylbutyl cyanide (VIII), the precursor of " (−)-Methadone " (VII) gave, on cleavage with sodamide, the (+)-aminobutane (VI) which, from the foregoing work, must be related to the (−)-amino-alcohol (V). Thus the analgesically active isomers " (−)-Methadone " (VII) and the (−)-sulphone (IV) are both related to D-(−)-alanine. Ethyl β-dimethylaminobutyrate, derived from L-(+)-alanine, upon reaction with thienyl-lithium, gave (−)-3-dimethylamino-1 : 1-di-2′-thienylbutan-1-ol which was dehydrated by dry hydrogen chloride to yield (−)-3-dimethylamino-1 : 1-di-2′-thienylbut-1-ene (III*a*), the analgesically active (+)-isomer therefore being related to D-(−)-alanine. Reductive ethylation of β-aminobutyric acid hydrochloride, derived from D-(−)alanine, was carried out by Bowman's method (*J.*, 1950, 1346), and esterification of the product gave ethyl β-diethylaminobutyrate (II*b*). This ester, on reaction with thienyl-lithium followed by dehydration of

the resulting 3-diethylamino-1 : 1-di-2′-thienylbutan-1-ol, gave analgesically active (+)-3-diethylamino-1 : 1-di-2′-thienylbut-1-ene (III*b*) which is thus related to D-(−)-alanine.

The significance of these configurational relations in connection with the stereochemical requirements of analgesics has been discussed elsewhere (Beckett and Casy, *J. Pharm. Pharmacol.*, 1954, **6**, 986).

Experimental

Microanalyses were by Mr. G. S. Crouch, School of Pharmacy, University of London.

Equiv. wts. of the bases were determined by titration with 0·02N-perchloric acid in glacial acetic acid with crystal-violet as indicator. Titration of the hydriodide was carried out in the same solvent in the presence of mercuric acetate by Pifer and Wollish's method (*J. Amer. Pharm. Assoc., Sci. Ed.*, 1951, **40**, 609).

N-*Phthaloyl*-L-*alanine*.—(+)-Benzoyl-L-alanine, prepared by resolution by Pope and Gibson's method (*J.*, 1912, **101**, 939), was hydrolysed with hydrochloric acid to L-(+)-alanine hydrochloride, $[\alpha]_D^{21}$ +9·5° (*c* 13·0 in H_2O). The hydrochloride (9·2 g.) in water was neutralised with N-sodium hydroxide, and the mixture evaporated to dryness. The product was heated with phthalic anhydride (11·9 g.) for 15 min. at 170—180° and the resultant oil, which solidified on cooling, crystallised from water to give colourless needles of *N*-phthaloyl-L-alanine (13·4 g.), m. p. 149—150°, $[\alpha]_D^{20}$ −23·6° (*c* 1·8 in EtOH) {Fischer, *loc. cit.*, gives m. p. 150—151° (corr.), $[\alpha]_D^{20}$ −17·8° ± 0·2° (*c* 8·13 in EtOH), and Balenović *et al.*, *loc. cit.*, give m. p. 150—151°, $[\alpha]_D^{20}$ −18·3° ± 0·7° (*c* 2·6 in EtOH)}.

N-*Phthaloyl*-D-*alanine*.—This was prepared in the same way from D-(−)-alanine hydrochloride ($[\alpha]_D^{21}$ −9·9° ± 0·2° (*c* 13·0 in H_2O) {Bowman and Stroud, *loc. cit.*, give $[\alpha]_D^{18}$ −9·13° (*c* 13·1 in H_2O)} derived from (−)-benzoyl-D-alanine (see Pope and Gibson, *loc. cit.*), and had m. p. 149—150°, $[\alpha]_D^{20}$ +23·4° ± 0·5° (*c* 1·8 in EtOH).

1-*Diazo*-3-*phthalimidobutan*-2-*one*.—*N*-Phthaloylalanine (10 g.) and redistilled thionyl chloride (10 c.c.) were heated for 1 hr. at 60° and the excess of thionyl chloride removed under reduced pressure. The crude *N*-phthaloylalanyl chloride (10·5 g.), after being kept overnight in a vacuum-desiccator, was dissolved in benzene (50 c.c.) and added dropwise to a stirred, ice-cooled solution of diazomethane in ether (250 c.c.; prepared from methyl *N*-nitroso-2-methylamino*iso*butyl ketone, 30 g.). The mixture was stirred for 1 hr. at room temperature, then left for 2 hr., and the solvent and excess of diazomethane were removed by distillation. The residue crystallised from ethyl acetate–light petroleum (b. p. 40—60°) to give the diazo-ketone (9 g.), m. p. 107—108° (Balenović, *Experientia*, 1947, **3**, 369, gives m. p. 111°).

The (−)-isomer, prepared in the same way from (−)-*N*-phthaloyl-L-alanine, was obtained as an orange-coloured oil, $[\alpha]_D^{24}$ −88·5° ± 1° (*c* 0·5 in ethyl acetate) {Balenović *et al.*, *loc. cit.*, give m. p. 88°, $[\alpha]_D^{18}$ −69·3° ± 1° (*c* 0·48 in ethyl acetate)}.

The (+)-isomer, prepared from (+)-*N*-phthaloyl-D-alanine, was obtained as an orange-coloured oil, $[\alpha]_D^{17}$ +86·7° ± 0·3°.

Rearrangement of 1-*Diazo*-3-*phthalimidobutan*-2-*one*.—(a) *Methyl* β-*phthalimidobutyrate*. A 7% solution (4 c.c.) of silver benzoate in triethylamine was added dropwise during 2 hr. to a stirred solution of the diazo-ketone (2 g.) in methanol (50 c.c.). The mixture was refluxed for a few minutes with charcoal, filtered, and evaporated to dryness, to give a pale yellow oil which rapidly solidified. The solid was extracted several times with hot light petroleum (b. p. 40—60°), the combined extracts were evaporated to dryness, and the residual solid (1·9 g.) crystallised from ethanol to give colourless plates of *methyl* β-*phthalimidobutyrate*, m. p. 61° (Found : C, 63·6; H, 5·3; N, 5·8. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7%).

The (−)-isomer, prepared in the same way from the (+)-diazo-ketone, was obtained as a yellow liquid, b. p. 140—144°/0·7 mm., $[\alpha]_D^{23}$ −33·1° ± 0·5° (*c* 0·5 in C_6H_6) {*idem*, *loc. cit.*, give m. p. 38°, $[\alpha]_D^{16}$ +26·3° ± 1° (*c* 0·26 in C_6H_6) for the (+)-isomer}.

(b) β-*Phthalimidobutyramide*. A mixture of the diazo-ketone (1 g.), methanol saturated with ammonia (20 c.c.), and a saturated solution of silver nitrate in 80% (aqueous) methanol (2·5 c.c.) was gently warmed. When evolution of gas ceased, the mixture was refluxed for 30 min. and the solvent and excess of ammonia were removed under reduced pressure. The residue was refluxed with a slight excess of alcoholic hydrochloric acid (and charcoal), and the mixture filtered and concentrated to give, on cooling, feathery crystals of β-*phthalimidobutyramide* (0·4 g.), m. p. 188—189° (Found : C, 61·7; H, 4·85; N, 12·3. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2; N, 12·1%).

The (+)-isomer prepared in the same way from the (−)-diazo-ketone had m. p. 200°, $[\alpha]_D^{19}$ +46·1° (*c* 0·5 in EtOH).

β-*Phthalimidobutyric Acid and its Derivatives.*—β-Aminobutyric acid (2 g.), m. p. 190—191° (Fischer and Grah, *Annalen*, 1911, **383**, 365, give m. p. 188—189°), prepared by hydrolysis of ethyl β-aminobutyrate, was heated with phthalic anhydride (3·45 g.) for 15 min. at 180—185°. The product solidified on cooling and crystallised from water, to give colourless needles of β-*phthalimidobutyric acid* (3·5 g.), m. p. 122—123° (Found: C, 60·1; H, 4·7; N, 5·9. $C_{12}H_{11}O_4N,\frac{1}{2}H_2O$ requires C, 59·5; H, 5·0; N, 5·8%). The methyl ester, prepared by using diazomethane, had m. p. 61°, alone or mixed with a specimen derived from the diazo-ketone. The amide, prepared by the action of ammonia on the acid chloride, had m. p. 188°, alone or mixed with a specimen derived from the diazo-ketone.

3-*Dimethylamino*-1 : 1-*diphenylbutan*-1-*ol* (V).—A mixture of methyl β-phthalimidobutyrate (6·5 g.), glacial acetic acid (16 c.c.), and concentrated hydrochloric acid (20 c.c.) was refluxed for 7 hr., then left overnight, and the phthalic acid was filtered off. The filtrate was evaporated to dryness under reduced pressure to give crude β-aminobutyric acid hydrochloride, which was dissolved in water (115 c.c.), and shaken with hydrogen at room temperature and pressure in the presence of aqueous formaldehyde (8·4 c.c.) and 5% palladised charcoal (6 g.). After 48 hr. the absorption of hydrogen ceased, the mixture was filtered, and the filtrate evaporated on a steam-bath to remove the excess of formaldehyde and then to dryness under reduced pressure. The residual crude β-dimethylaminobutyric acid hydrochloride (3·5 g.) was treated with ethanolic N-hydrochloric acid (60 c.c.) and next morning the mixture was evaporated to dryness under reduced pressure. This procedure was repeated twice. The residue was made just alkaline with concentrated aqueous sodium hydroxide, ether was added, and the mixture made into a slurry with anhydrous potassium carbonate. The solution was decanted and dried (K_2CO_3), the ether evaporated off, and the residue distilled to give ethyl β-dimethylaminobutyrate (II*a*) (2·1 g.), b. p. 66°/16 mm., n_D^{19} 1·4260 (Found: equiv., 159. Calc. for $C_8H_{17}O_2N$: equiv., 159). It gave a methiodide, m. p. 129—130° (Breckpot, *Bull. Soc. chim. Belg.*, 1923, **32**, 412, gives m. p. 127—128°). The ester (1·5 g.) was treated with phenylmagnesium bromide according to Kjaer and Petersen's method (*Acta Chem. Scand.*, 1951, **5**, 1145), to give colourless plates of 3-dimethylamino-1 : 1-diphenylbutan-1-ol (V) (1 g.), m. p. 121—122° (*idem, loc. cit.*, give m. p. 123°).

The (−)-isomer, prepared in the same way using ethyl β-dimethylaminobutyrate derived from (−)-methyl β-phthalimidobutyrate, had m. p. 148—149°, $[\alpha]_D^{17}$ −46·8° ± 0·8° (*c* 1·0 in 0·08N-HCl) {Archer and Auerbach, *loc. cit.*, give m. p. 150·6—152·2° (corr.), $[\alpha]_D^{24}$ −41·1° (*c* 2·3 in aq. HCl) for material obtained by hydrolysis of (−)-dimethylamino-1 : 1-diphenylbutyl ethyl sulphone (IV)}.

Resolution of 3-*Dimethylamino*-1 : 1-*diphenylbutan*-1-*ol* (V).—The amino-alcohol (2·7 g.) and (+)-tartaric acid (1·5 g.) were dissolved in a hot mixture of acetone (17·5 c.c.) and 96% ethanol (17·5 c.c.). The crystals which were formed on cooling were recrystallised twice from the same solvent, to give the (+)-amino-alcohol (+)-tartrate (0·65 g.), m. p. 186—188°, $[\alpha]_D^{24}$ +40·0° ± 0·5° (*c* 0·9 in H_2O). The base was liberated with dilute aqueous ammonia and crystallised from ethanol to give the (+)-amino-alcohol, m. p. 149—150°, $[\alpha]_D^{24}$ +47·0° (*c* 0·8 in 0·08N-HCl).

(−)-3-*Dimethylamino*-1 : 1-*diphenylbut*-1-*ene*.—This, prepared from the (+)-amino-alcohol by Archer and Auerbach's method (*loc. cit.*), had $[\alpha]_D^{19}$ −170° (*c* 1·0 in EtOH), and gave a picrate, yellow needles (from ethanol), m. p. 165—167° {*idem, loc. cit.*, give $[\alpha]_D^{25}$ +149° (*c* 1·0 in EtOH) for the (+)-isomer and m. p. 164·5° for its picrate}.

(−)-3-*Dimethylamino*-1 : 1-*diphenylbutane* (VI).—The (−)-amino-butene hydrochloride (0·4 g.) in ethanol (10 c.c.) and 5% palladised charcoal (0·5 g.) were shaken with hydrogen at room temperature and pressure. After 4 hr., when absorption had ceased, the mixture was filtered and evaporated to dryness, and the base, which was liberated with dilute aqueous ammonia, was extracted with ether. After drying (Na_2SO_4) the ether was removed to give the (−)-amino-butane (0·35 g.) as a pale yellow oil which formed a hydrochloride, colourless needles (from ether–ethanol), m. p. 180—182°, $[\alpha]_D^{20}$ −42·7° (*c* 0·8 in H_2O) {Eddy, May, and Mosettig, *J. Org. Chem.*, 1952, **17**, 321, give m. p. 180—182°, $[\alpha]_D^{20}$ −43·3° (*c* 1·04 in H_2O) for material derived from "(+)-Methadone"}, and a picrate, yellow plates (from ethanol), m. p. 132° [see below for the picrate of the corresponding (+)-amino-butane].

Cleavage of (−)-3-*Dimethylamino*-1 : 1-*diphenylbutyl Cyanide* (VIII).—The (−)-amino-cyanide was cleaved by the method of Klenk, Suter, and Archer (*J. Amer. Chem. Soc.*, 1948, **70**, 3846) to give (+)-3-dimethylamino-1 : 1-diphenylbutane (VI) as a pale yellow oil. The latter gave a hydrochloride, m. p. 183—184°, from acetone, $[\alpha]_D^{19}$ +52·7° (*c* 1·0 in H_2O) {Eddy *et al.*, *loc. cit.*, give m. p. 179—181°, [α] +43·1° (*c* 0·53 in H_2O)}, and a *picrate*, yellow plates (from

ethanol), m. p. 132° (Found : C, 59·65; H, 5·4; N, 11·5. $C_{24}H_{26}O_7N_4$ requires C, 59·75; H, 5·4; N, 11·6%).

(−)-3-*Dimethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene Hydrobromide*.—(−)-3-*Dimethylamino*-1 : 1-*di*-2′-*thienylbutan*-1-*ol* was prepared from ethyl β-dimethylaminobutyrate (II*a*) [derived from (+)-β-phthalimidobutyramide] by reaction with thienyl-lithium according to Adamson's method (*loc. cit.*). It had m. p. 96—97°, $[\alpha]_D^{18}$ −56·5° ± 0·3° (*c* 0·9 in EtOH) (Found : C, 59·6; H, 6·5; N, 5·1; S, 22·9. $C_{14}H_{19}ONS_2$ requires C, 59·8; H, 6·8; N, 5·0; S, 22·8%). Dry hydrogen chloride was passed for 10 min. through a solution of the amino-alcohol (0·23 g.) in chloroform (2 c.c.), the solvent removed under reduced pressure, and the residue in water stirred with charcoal for a few minutes at 60°. The mixture was filtered, and the base liberated with dilute aqueous ammonia, and extracted with ether. After drying (Na_2SO_4), the solvent was removed to give the (−)-amino-butene (III*a*) (0·18 g.) as a yellow oil. It gave a *hydrobromide*, pale buff plates (from ether–ethanol), m. p. 163—164°, $[\alpha]_D^{22}$ −104° ± 1° (*c* 0·4 in H_2O) (Found : C, 49·1; H, 5·2; N, 3·95; S, 18·4. $C_{14}H_{18}NS_2Br$ requires C, 48·8; H, 5·2; N, 4·1; S, 18·6%).

3-*Diethylamino*-1 : 1-*di*-2′-*thienylbut*-1-*ene Hydriodide*.—β-Aminobutyric acid (I) (2 g.), in water (80 c.c.), was shaken with hydrogen at room temperature and pressure in the presence of acetaldehyde (3·5 g.) and 5% palladised charcoal (4 g.). After 24 hr. the absorption of hydrogen ceased, and the mixture was filtered and evaporated to dryness under reduced pressure. The residual crude β-diethylaminobutyric acid (2·8 g.) was esterified by the method described above for β-dimethylaminobutyric acid, to give ethyl β-diethylaminobutyrate (II*b*) (2·2 g.), b. p. 98—100°/20 mm., n_D^{19} 1·4292 (Found : equiv., 188. Calc. for $C_{10}H_{21}O_2N$: equiv., 187). It gave a *styphnate*, yellow needles (from ethanol), m. p. 67·5—68·5° (Found : C, 44·65; H, 5·55; N, 13·1. $C_{16}H_{24}O_{10}N_4$ requires C, 44·4; H, 5·6; N, 13·0%). The amino-ester, on reaction with thienyl-lithium, gave 3-diethylamino-1 : 1-di-2′-thienylbutan-1-ol, m. p. 74—75° (*idem*, *loc. cit.*, gives m. p. 75—76°). The amino-alcohol was converted into the amino-butene (III*b*) by the method described above for the corresponding dimethylamino-compound. It gave a *hydriodide*, colourless plates (from ether–ethanol), m. p. 147—148° (Found : C, 46·3; H, 5·1. $C_{16}H_{22}NS_2I$ requires C, 45·8; H, 5·25%).

The (+)-*hydriodide*, prepared in the same way by using ethyl β-diethylaminobutyrate derived from (−)-methyl β-phthalimidobutyrate, had m. p. 139—140°, $[\alpha]_D^{20}$ +109° ± 2° (*c* 0·9 in EtOH) (Found : C, 45·4; H, 5·0; N, 3·2; S, 15·5%; equiv., 417. $C_{16}H_{22}NS_2I$ requires C, 45·8; H, 5·25; N, 3·3; S, 15·3%; equiv., 419).

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