162. *Configurational Studies in Synthetic Analgesics: the Synthesis of (−)-Methadone from* D-(−)-*Alanine.*

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(−)-Methadone nitrile has been synthesised from D-(−)-alanine by a series of reactions not involving the asymmetric centre. This evidence, with previous work,[1] proves that the Wolff rearrangement involving (−)-1-diazo-3-phthalimidobutan-2-one proceeds with complete retention of configuration.

In synthetic analgesics possessing one asymmetric carbon atom, nearly all the analgesic activity exhibited by the racemic mixture resides in one of the isomers. Beckett and Casy [1] proved that a number of analgesically active isomers including (−)-methadone [(−)-6-dimethylamino-4 : 4-diphenylheptan-3-one] possess identical configurations related to D-(−)-alanine. The key reaction in the stereochemical correlations was the conversion of alanine into β-aminobutyric acid by an Arndt–Eistert reaction, by a modification of the method of Balenović, Cerar, and Fuks.[2] Lane and his co-workers [3] found that the Wolff rearrangement involving migration of an asymmetric group proceeded with retention

[1] Beckett and Casy, *J.*, 1955, 900.
[2] Balenović, Cerar, and Fuks, *J.*, 1952, 3316.
[3] Lane, Willenz, Weissberger, and Wallis, *J. Org. Chem.*, 1940, **5**, 276; Lane and Wallis, *ibid.*, 1941, **6**, 443; Lane and Wallis, *J. Amer. Chem. Soc.*, 1941, **63**, 1674.

of configuration in compounds of the type $CRR'R''\cdot CO\cdot CHN_2$, while those containing an enolisable hydrogen atom were completely racemised. Sax and Bergmann [4] found some racemisation in the rearrangement of a diazo-ketone of the type $CHRR'\cdot CO\cdot CHN_2$. Wiberg and Hutton, however, report that the rearrangement of benzylmethyldiazoacetone proceeded with retention of configuration, while the rearrangement of *sec.*-butyl diazomethyl ketone gave the expected products with $97 \pm 3\%$ retention of configuration. Beckett and Casy [1] demonstrated the optical purity of the intermediates in their series of reactions by the numerical identity of the rotations of some of their products and the isomers obtained by the resolution of the corresponding racemic mixtures. Consequently by implication, the Wolff rearrangement in this series proceeded without racemisation and, although complete inversion in the reaction seems highly improbable, its absence hitherto has not been established unequivocally.

(−)-Methadone nitrile was related to D-(−)-alanine by reactions outlined in the annexed scheme, preliminary work being carried out with racemic material. The participation of the intermediate ethyleneimonium ion with consequent formation of two isomeric products in the usual methadone synthesis, precluded its application in the present investigation.[6]

$$\underset{(I)}{Me\cdot CH(NH\cdot CHO)\cdot CO_2H} \longrightarrow \underset{(II)}{Me\cdot CH(NHMe)\cdot CH_2\cdot OH} \longrightarrow \underset{(III)}{Me\cdot CH(NMe\cdot CHO)\cdot CH_2\cdot OH} \longrightarrow$$

$$\underset{(IV)}{Me\cdot CH(NMe\cdot CHO)\cdot CH_2Cl} \longrightarrow \underset{(V)}{Me\cdot CH(NMe\cdot CHO)\cdot CH_2\cdot CPh_2\cdot CN} \longrightarrow \underset{(VI)}{Me\cdot CH(NMe_2)CH_2\cdot CPh_2\cdot CN}$$

Alanine was converted into *N*-formylalanine (I) by the method of Biilman, K. A. Jensen, and H. B. Jensen.[7] Karrer, Portmann, and Suter [8] have shown that amino-acids may be reduced with lithium aluminium hydride without loss of optical activity. *N*-Formylalanine was reduced to the alcohol (II) by extracting the former with tetrahydrofuran into a suspension of lithium aluminium hydride in tetrahydrofuran; Vogl and Pohn's procedure [9] for the reduction of amino-acids gave only poor yields of the desired amino-alcohol. The alcohol (II) and formamide at 150—160° gave 2-(*N*-methylformamido)propan-1-ol (III), converted by thionyl chloride in pyridine into the chloride (IV) which with diphenylacetonitrile in the presence of sodamide and sodium iodide gave the cyanide (V); this was reduced by *s*-trioxan in hot 98—100% formic acid to the nitrile (VI). The last stages of this synthesis are analogous to those used by Sletzinger, Chamberlin, and Tishler [10] for the preparation of *iso*methadone nitrile.

Methadone nitrile prepared by this route from D-(−)-alanine hydrochloride was lævorotatory and had an optical purity of approximately 72%. (−)-Methadone nitrile has therefore the same configuration as D-(−)-alanine; this evidence and work reported previously [1] prove that the Wolff rearrangement of (−)-1-diazo-3-phthalimidobutan-2-one proceeds with complete retention of configuration when Beckett and Casy's method [1] is adopted.

Experimental

Microanalyses were by G. S. Crouch, School of Pharmacy, University of London. Equiv. wts. of bases and picrates were determined by titration with 0·02N-perchloric acid in glacial acetic acid with crystal-violet as indicator.[11]

D-(+)-N-*Formylalanine*.—(−)-Benzoyl-D-alanine [12] was hydrolysed with hydrochloric acid

[4] Sax and Bergmann, *J. Amer. Chem. Soc.*, 1955, **77**, 1910.
[5] Wiberg and Hutton, *ibid.*, 1956, **78**, 1640.
[6] Schultz, Robb, and Sprague, *ibid.*, 1947, **69**, 188; Walton, Ofner, and Thorpe, *J.*, 1949, 648; Ofner, *J.*, 1951, 1800.
[7] Biilman, K. A. Jensen, and H. B. Jensen, *Bull. Soc. chim. France*, 1934, **1**, 1667.
[8] Karrer, Portmann, and Suter, *Helv. Chim. Acta*, 1948, **31**, 1617.
[9] Vogl and Pohn, *Monatsh.*, 1952, **83**, 541.
[10] Sletzinger, Chamberlin, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 5619.
[11] Beckett and Tinley, "Titration in Non-Aqueous Solvents," B.D.H. Ltd., Poole, England.
[12] Pope and Gibson, *J.*, 1912, **101**, 939.

to D-(−)-alanine hydrochloride, $[\alpha]_D^{21}$ −9·5° ± 0·2° (*c* 13·3 in H_2O) {Bowman and Stroud [13] give $[\alpha]_D^{18}$ −9·13° (*c* 13·1 in H_2O)}. This (39 g.) in water was neutralised with ammonia, and the mixture evaporated to dryness. The product was dried, powdered, and formylated by the method of Biilman *et al.*[7] After cooling, the inorganic material was filtered off, and the filtrate evaporated under reduced pressure to give an impure solid (33 g.). A small portion crystallised from water had $[\alpha]_D^{23\cdot5}$ +46·4° (*c* 0·55 in H_2O).

2-Methylaminopropan-1-ol (II).—*N*-Formylalanine [7] (37 g.; m. p. 147—148°), in a Soxhlet thimble, was extracted with tetrahydrofuran into a suspension of lithium aluminium hydride (37 g.) in tetrahydrofuran (600 c.c.) by refluxing the solvent at 100—110° for 120 hr. After cooling, the excess of hydride was decomposed with damp ether, and the ether solution separated. The inorganic residue was extracted with 1 : 1 ether–tetrahydrofuran (3 × 500 c.c.) and then by refluxing with ethanol (3 × 500 c.c.; 30 min.). After being dried (Na_2SO_4), the combined ethanolic extracts were evaporated under reduced pressure, the residue was dissolved in the minimum quantity of ethanol, and an equal volume of dry ether was added. After 24 hr. at 0°, the inorganic deposit was filtered off, and the filtrate added to the ether extracts. Removal of the solvent gave a liquid which on distillation gave *2-methylaminopropan-1-ol* (19·5 g.), b. p. 85—86°/28 mm., n_D^{20} 1·4418 (Found: equiv., 90·0. $C_4H_{11}ON$ requires equiv., 89·1). It gave a *picrate* as needles (from ethanol), m. p. 104—105° (Found: C, 37·3; H, 4·5; N, 17·3%; equiv., 317. $C_{10}H_{14}O_8N_4$ requires C, 37·7; H, 4·4; N, 17·6%; equiv., 318).

The (−)-isomer (6 g.), prepared in the same way from crude D-(+)-*N*-formylalanine (30 g.), had b. p. 83—86°/29 mm., $[\alpha]_D^{22}$ −29·26° (*c* 1·28 in EtOH) (Found: equiv., 92). The *picrate* (from ethanol) had m. p. 105—105·5° (Found: C, 37·8; H, 4·3; N, 17·6%).

2-(N-Methylformamido)propan-1-ol (III).—The foregoing alcohol (8·7 g.) and formamide (4·5 g.) were heated with stirring at 150—160° for 6 hr., then distilled under reduced pressure, to give 2-(*N*-methylformamido)propan-1-ol (10·6 g.), b. p. 114—116°/0·2 mm. Its *hydrogen 3-nitrophthalate* crystallised from 30% aqueous ethanol in needles, m. p. 158—160° (Found: C, 50·4; H, 4·3; N, 9·0%; equiv., 309. $C_{13}H_{14}O_7N_2$ requires C, 50·3; H, 4·5; N, 9·0%; equiv., 310).

The (−)-*alcohol*, prepared in the same way, had b. p. 113—115°/0·2 mm., and solidified to plates, m. p. 48·5—49·5°, $[\alpha]_D^{20\cdot5}$ −29·09° ± 0·3° (*c* 1·3 in EtOH) (Found: C, 49·9; H, 9·5; N, 11·4. $C_5H_{11}O_2N$ requires C, 51·2; H, 9·5; N, 11·9%).

2-(N-Methylformamido)propyl Chloride (IV).—Thionyl chloride (31 g.) in dry chloroform (15 c.c.) was added during 1 hr. to 2-(methylformamido)propan-1-ol (22 g.) in chloroform (88 c.c.) and pyridine (19·5 g.); the mixture was heated with stirring at 75° for 15 hr., cooled, and washed with saturated sodium chloride solution (3 × 10 c.c.), and the combined aqueous washings were extracted with chloroform (3 × 15 c.c.). The original chloroform solution and the extracts were combined, washed with saturated sodium hydrogen carbonate solution (14 c.c.) and water (10 c.c.), dried (Na_2SO_4), filtered, evaporated, and distilled, to yield a product (18·7 g.), b. p. 85—86°/1 mm., n_D^{20} 1·4849, which was acidic to Universal Indicator (Found: sap. val., 136; Cl^- after saponification, 25·6. $C_5H_{10}ONCl$ requires sap. val., 135·5; Cl^-, 26·1%). This product, even when kept in a refrigerator quickly became yellowish-green and a small amount of solid separated. Repeated preparation and fractional distillation failed to give material of satisfactory elementary analysis, although consistently good results were obtained for the sap. val. and the Cl^- of freshly distilled material.

The (−)-isomer prepared similarly had b. p. 84—85°/1·4 mm., $[\alpha]_D^{20\cdot5}$ −17·3° ± 0·2° (*c* 1·5 in $CHCl_3$) (Found: sap. val., 136).

Condensation of 2-(N-Methylformamido)propyl Chloride with Diphenylacetonitrile.—Dry nitrogen was passed over a stirred solution of diphenylacetonitrile (21 g.) in dry xylene (44 c.c.), and a slurry of sodamide (4·4 g.) in dry xylene (38 c.c.) added. The mixture was heated at 105—110° for 2 hr. On cooling to 30°, sodium iodide (0·3 g.) was added, followed during 15 min. by a solution of freshly distilled 2-(methylformamido)propyl chloride (7·4 g.) in xylene (15 c.c.). The temperature was increased to 110° during 20 min., and kept thereat for 4 hr. On cooling, the mixture was washed with water, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to a brown oil (23 g.). A solution of this in dry ether (100 c.c.) was allowed to evaporate slowly, giving successive crops of crude diphenylacetonitrile. Evaporation of the combined mother-liquors gave a reddish-brown oil (16 g.) which was chromatographed in light petroleum (b. p. 80—100°) (150 c.c.)–benzene (75 c.c.) on alumina (Peter Spence, Type

[13] Bowman and Stroud, *J.*, 1950, 1342.

" O "; 105 × 2·5 cm.) (42 × 100-c.c. fractions; flow rate 3 c.c. per min.). The concentration of benzene in the solvent was gradually increased and finally 1 : 19 ethanol–benzene was used. From the first 36 fractions diphenylacetonitrile (9·8 g.) was obtained. Fractions 37—41 (6·3 g.) consisted of a reddish-brown oil of which 5·4 g. was stored in ether at 0° for 8 days; there separated crystals of diphenylacetamide (0·09 g.), m. p. 169—170° (from toluene) (Found : C, 79·4; H, 6·3; N, 6·7. Calc. for $C_{14}H_{13}ON$: C, 79·6; H, 6·1; N, 6·6%) (Hellerman, Cohn, and Hoen [14] give m. p. 167·5—168·5°). Further proof of identity was obtained from the infrared spectrum.

The ethereal mother-liquor, on evaporation, gave 3-(N-*methylformamido*)-1 : 1-*diphenylbutyl cyanide* as an oil (Found : C, 78·5; H, 6·8; N, 9·0. $C_{19}H_{20}ON_2$ requires C, 78·1; H, 6·9; N, 9·6%).

The (−)-isomer prepared in the same way was an oil, $[\alpha]_D^{20}$ −9·1° (*c* 1·0 in $CHCl_3$), $[\alpha]_D^{20}$ −10·5° (*c* 1·0 in C_6H_6). The optical rotation determined on various chromatographic fractions of the oil showed some variation, indicating that the product was not completely pure.

3-*Dimethylamino*-1 : 1-*diphenylbutyl Cyanide*.—3-(Methylformamido)-1 : 1-diphenylbutyl cyanide (1 g.), 98—100% formic acid (2 c.c.), and *s*-trioxan (0·8 g.) were refluxed at 120—125° for 168 hr. After cooling, the mixture was poured into water (6 c.c.), and the solution acidified with dilute hydrochloric acid. Extraction with ether gave a non-basic oil (0·27 g.) (not investigated). The aqueous solution was made alkaline with ammonia and extracted with ether, and the ethereal extracts were dried (Na_2SO_4), filtered, and evaporated to a solid (0·5 g.) which, crystallised from ethanol, gave 3-dimethylamino-1 : 1-diphenylbutyl cyanide (VI), m. p. and mixed m. p. 90—91°. The picrate crystallised from ethanol in cubes, and on recrystallisation from acetone–ethanol had m. p. 148·5—149, undepressed on admixture with authentic picrate of m. p. 149—150° (Found : C, 59·1; H, 5·1; N, 13·2. Calc. for $C_{25}H_{25}O_7N_5$: C, 59·2; H, 5·0; N, 13·8%) (Schultz, Robb, and Sprague [15] give m. p. 145—146°). The infrared spectra of the new and the authentic sample were identical.

The (−)-3-dimethylamino-1 : 1-diphenylbutyl cyanide [derived from D-(−)-alanine hydrochloride] prepared in the same way had m. p. 99·5—100°, $[\alpha]_D^{23}$ −35·3° (*c* 0·82 in EtOH), and a mixed m. p. of 100° with optically pure (−)-3-dimethylamino-1 : 1-diphenylbutyl cyanide, m. p. 100°, $[\alpha]_D^{18}$ −49° (*c* 1·3 in EtOH). The infrared spectrum was identical with that of an authentic sample of methadone nitrile.

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[14] Hellerman, Cohn, and Hoen, *J. Amer. Chem. Soc.*, 1928, **50**, 1725.
[15] Schultz, Robb, and Sprague, *ibid.*, 1947, **69**, 2456.