*The Absolute Configuration of (−)-N, N-Dimethyl-1, 2-diphenylethylamine and its Analgesic Activity**

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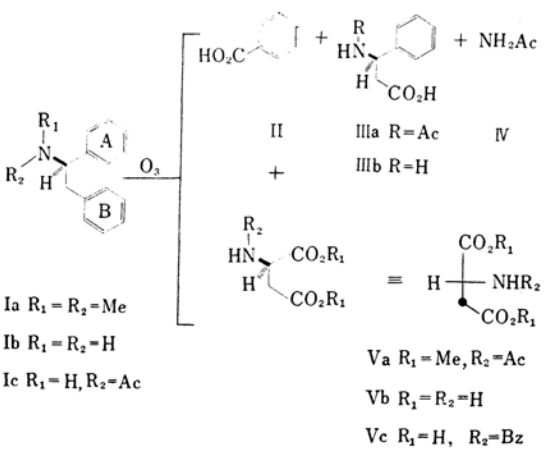
The (−)-antipode of *N*, *N*-dimethyl-1, 2-diphenylethylamine (Ia) derived from (−)-1, 2-diphenylethylamine (Ib) has been found to possess 1/2∼1/3 the analgesic activity of morphine, whereas the (+)-enantiomer shows negligible activity[1]. This is but one of numerous instances[2,3] in which only one optical active antipode of a compound is physiological efficacious. In this paper, the determination of the absolute configuration of the (−) analgesic Ia is reported.

Acetylation of (−)-1, 2-diphenylethylamine (Ib) gave (+)-*N*-acetyl-1, 2-diphenylethylamine (Ic), which was exhaustively ozonized; the reaction mixture was oxidized with peracetic acid. Upon working up the reaction mixture,



benzoic acid II and (+)-2-acetylamino-2-phenylpropionic acid (IIIa) were isolated and identified, IIIa being then further hydrolyzed to (+)-2-amino-2-phenylpropionic acid (IIIb).

Treatment of the mother liquor of II and IIIa with diazomethane, followed by distillation in vacuo, afforded acetamide IV and dimethyl *N*-acetylaspartate (Va), which was then hydrolyzed with diluted sulfuric acid. The reaction mixture, freed from sulfate ions, was subjected to paper chromatography (methanol: conc. aq. ammonia=3:1). Only a single spot of aspartic acid (R_f 0.24), and no spot corresponding to phenylalanine (R_f 0.63) nor to glycine (R_f 0.46), was detected. This indicates that the carbon atom to which the phenyl and acetamino groups are attached is vulnerable to oxidation and that the B ring is oxidized preferentially to the A ring, probably for steric reasons. The sulfate-free filtrate was concentrated to afford D-aspartic acid (Vb) (decomp. p. 320°C, $[\alpha]_D^{20}$ −23.2° (*c* 1.9 in 1 N hydrochloric acid)), the infrared absorption spectrum of which was superimposable on that of natural L-aspartic acid (decomp. p. 320°C, $[\alpha]_D^{21}$ +23.4° (*c* 2.2 in 1 N hydrochloric acid)).

The identity was further checked by preparing benzoyl-D-aspartic acid (Vc), which gave a racemic compound (with one mole of water of crystallization; m. p., 162∼165°C, after drying at 115°C) with enantiometric benzoyl-L-aspartic acid.

These findings established the (R)-configuration of analgesic active (−)-*N*, *N*-dimethyl-1, 2-diphenylethylamine (Ia)[4]. Inspection of a molecular model of Ia reveals a close stereochemical resemblance with natural (−)-morphine (VI)[5,6].

Since the A and B rings of morphine are almost perpendicular to each other, Ia might be expected to take an analogous eclipsed conformation VII, rather than the energetically favorable conformation VIII, in approaching some reactive surface in the nervous system. A recent observation[7] seems to support this assumption. Neither of the enantiomers of 9-dimethylamino-9, 10-dihydrophenanthrene (IX), in spite of their close resemblance to Ia, show any pronounced analgesic activity.

The reason for this may lie in the fact that

* For a preliminary account of this work, see M. Nakazaki, *Chem. & Ind.*, **1962**, 1577.

1) K. Ogiu, H. Fujimura and Y. Yamakawa, *J. Pharm. Chem. Soc. Japan*, **80**, 283 (1960).

2) H. Brockmann, "Das Biologische Verhalten Stereoisomerer Verbindungen", in K. Freudenberg, "Stereochemie", Franz Deuticke, Leipzig and Wien (1933), p. 920.

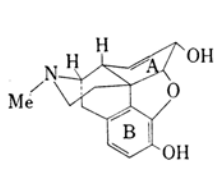
3) A. H. Beckett, "Stereochemical Factors in Biological Activity", in E. Jucker, "Progress in Drug Research", Vol. 1, Birkhauser Verlag, Basel and Stuttgart (1959).

4) This correlation also established the (R)-configuration of IIIa and IIIb.

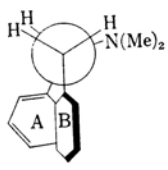
5) K. Kalvoda, P. Buchschacher and O. Jeger, *Helv. Chim. Acta*, **38**, 477 (1955).

6) K. Goto and I. Yamamoto (*Proc. Japan Acad.*, **33**, 477 (1957)) prepared (+)-morphine and showed its analgesic inactivity.

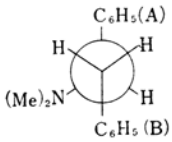
7) M. Hori, Y. Abe, Y. Yamakawa and H. Fujimura, *Ann. Proc. Gifu Pharm. College*, **8**, 65 (1958).



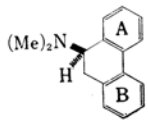
VI



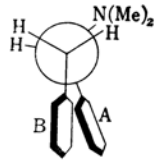
VII



VIII



IX



X

IX can not have a conformation in which the A and B rings are perpendicular to each other due to the linkage between two benzene nuclei (projection formula X).

Experimental

(+)-Tartarate of (—)-1, 2-Diphenylethylamine.—The (+)-tartarate of (−)-Ib was recrystallized from diluted acetic acid to give crystals; m. p., 229~230°C (decomp.), $[\alpha]_D^{19}$ −55.3° (*c* 0.92 in water)[8].

(—)-1, 2-Diphenylethylamine (Ib).—Into a solution of 10 g. of sodium hydroxide in 100 cc. of water was added 25 g. of (+)-tartarate of (−)-1, 2-diphenylethylamine; the milky emulsion was then extracted with ether. After being washed with a saturated sodium chloride solution and dried over potassium hydroxide pellets, the solvent was removed to afford a pale yellow oil, which distilled at 122~124°C/3 mmHg and weighed 18.1 g. $[\alpha]_D^{19}$ −51.2° (*c* 3.7 in ethanol).

(+)-*N*-Acetyl-1, 2-diphenylethylamine (Ic).—To a solution of 16 g. of Ib in 30 cc. of ether, 10 g. of acetic anhydride in 35 cc. of ether was added. After the crystals which had precipitated were filtered (19 g.) and washed with ether, these were recrystallized from ethanol to give Ic (m. p., 166~167°C), which weighed 16.4 g. $[\alpha]_D^{18}$ +35.7° (*c* 1.5 in acetic acid).

Found: C, 80.5; H, 7.4. Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16%.

Exhaustive Ozonolysis of (+)-*N*-Acetyl-1, 2-diphenylethylamine (Ic).—A stream of ozone (about 2%) was passed into a solution of 10 g. of Ic in 90 cc. of acetic acid at 19°C for 39 hr., during which time 8.5 cc. of water was added twice. After 10 cc. of 30% hydrogen peroxide had been added, the reaction mixture was allowed to stand for 24 hr. at room temperature. The solution was then warmed on a water bath for 2 hr., and the excess hydrogen peroxide was destroyed by heating the solution with a small amount of palladium on a carbon catalyst.

To remove the acetic acid, 20 cc. of water was added, and the aqueous solution was concentrated at reduced pressure. This process was repeated three times. When the viscous pale yellow residue was dissolved in 20 cc. of water and kept at room temperature, 0.2 g. of leaflets precipitated; these were recrystallized from water to give crystals (m. p., 120~121°C). Their identity with benzoic acid was established by mixed melting point determination with an authentic specimen. When the filtrate from benzoic acid was again concentrated, 0.3 g. of prismatic crystals precipitated; these were identified as (+)-2-acetylamino-2-phenylpropionic acid (IIIa) (vide infra). The filtrate was concentrated again at reduced pressure. The viscous yellow residue (7.5 g.) was dried in a vacuum desiccator over concentrated sulfuric acid overnight to give a glassy solid (7.0 g.), which was then dissolved in 40 cc. of methanol and treated with 140 cc. of an ether solution of diazomethane prepared from 14 g. of nitrosomethylurea. After being kept at room temperature for 3 hr., the excess diazomethane was destroyed with 10 drops of acetic acid, and a small amount of fluffy material was removed by filtration. Removal of the solvent gave a viscous dark red liquid (6 g.) which was distilled at 0.01 mmHg to give 0.1 g. of a sublimate on the wall of the receiver. This sublimate was collected and recrystallized from benzene to give crystals (m. p., 75~78°C) which were identified as acetamid by mixed melting point determination with an authentic specimen.

The main fraction consisted of a viscous yellow oil[9] (b. p., 100~125°C/0.01 mmHg), which weighed 3.5 g. This oil (1.30 g.) was refluxed with 15 cc. of 2.07 N sulfuric acid for 3 hr. and the sulfate ion was removed by adding 82.5 cc. of 0.38 N barium hydroxide (pH 3.4). The barium sulfate was removed by centrifuging and washed with water twice. The filtrate and washings were then combined and filtered through a layer of a Hyflo super cell. The clear solution was concentrated to give 0.199 g. of crystals; further concentration of the mother liquor gave the second crops, 0.27 g. The combined crystals were recrystallized from water to afford 0.405 g. of crystals, which decomposed at 320°C (in a sealed capillary). $[\alpha]_D^{20}$ −23.2° (*c* 1.9 in 1 N hydrochloric acid). Their infrared absorption spectrum in Nujol was found to be superimposable on that of authentic natural L-aspartic acid, $[\alpha]_D^{21}$ +23.4° (*c* 2.2 in 1 N hydrochloric acid).

Found: C, 36.1; H, 5.5; N, 10.5. Calcd. for $C_4H_7O_4N$: C, 36.09; H, 5.30; N, 10.52%.

Benzoyl-D-aspartic Acid (Vc).—The above-mentioned D-aspartic acid (0.198 g.) obtained from Ic was dissolved in 3.3 cc. of water and benzoylated with 1.1 g. of sodium hydrogen carbonate and 0.6 g. of benzoyl chloride, according to Fischer's procedure[10], to give 0.160 g. of needles after recrystallization from water (m. p., 178~179°C, $[\alpha]_D^{18}$

8) R. Söderquist (*J. prakt. Chem.*, (2) **101**, 297 (1921)) reported the following physical constants: (−)-Ib, b. p., 159°C/9 mmHg, $[\alpha]_D^{15}$ −11.80°; (+)-tartarate, m. p., 220~221°C, $[\alpha]_D^{20}$ −43°; the acetyl derivative of (+)-amine prepared by resolution via the (−)-malate, m. p., 168.5°C, $[\alpha]_D^{20}$ −15° (*c* 0.66 in ethanol).

9) E. Hardegger and H. Braunschweiger (*Helv. Chim. Acta*, **41**, 1125 (1961)) obtained dimethyl *N*-acetyl-L-aspartate (b. p., 160~169°C, high vacuum; m. p., 60~61°C, $[\alpha]_D$ −13.4°,) by the exhaustive ozonolysis of *N*-acetyl-L-tryptophane.

$-26.9°$ (*c* 1.49 in 0.1 N potassium hydroxide)). Their infrared absorption spectrum (in Nujol) was found identical with that of benzoyl-L-aspartic acid (m. p., 180~181°C, $[\alpha]_D^{19}$ $+27.7°$ (*c* 2.2 in 0.1 N potassium hydroxide)) prepared from natural L-aspartic acid.

Found: C, 55.5; H, 4.9; N, 6.1. Calcd. for $C_{11}H_{11}O_5N$: C, 55.69; H, 4.67; N, 5.91%.

Racemic Benzoyl-aspartic Acid. — A mixture of the same amount (49 mg.) of benzoyl-D-aspartic acid obtained from the ozonolysis of Ic and authentic benzoyl-L-aspartic acid was recrystallized from water to give the racemic compound with one mole of water of recrystallization[10].

Found: C, 52.0; H, 5.0; N, 5.5. Calcd. for $C_{11}H_{13}O_6N$: C, 51.76; H, 5.13; N, 5.49%.

Anhydride obtained by drying at 115°C for 1 hr. at reduced pressure melted at 162~163°C[10].

(+)-2-Acetylamino-2-phenylpropionic Acid (IIIa). —The prismatic crystals obtained from the reaction mixture of ozonolysis of Ic (vide supra) was recrystallized from water to give prisms (m. p., 193~195°C, $[\alpha]_D^{21}$ $+75.0°$ (*c* 1.48 in 0.1 N potassium hydroxide), $[\alpha]_D^{21}$ $+116.2°$ (*c* 0.28 in ethanol)) whose infrared absorption spectrum was found to be superimposable on that of racemic 2-acetylamino-2-phenylpropionic acid (m. p. 162~165°C), prepared according to Posner's procedure[11] and recrystallized from diluted aqueous dimethylformamide[11].

Found: C, 63.7; H, 6.6; N, 7.0. Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76%.

(+)-2-Amino-2-phenylpropionic Acid (IIIb). — A mixture of 0.23 g. of IIIa and 4.2 cc. of 10% hydrochloric acid was refluxed for 2 hr. After 10.90 cc. of 0.1 N potassium hydroxide had been added, the solution was concentrated at reduced pressure to precipitate crystals which were recrystallized from 4 cc. of water to afford 0.09 g. of crystals (m. p., 221°C, $[\alpha]_D^{20}$ $+9.5°$ (*c* 1.07 in water))[12]. The crystals' infrared absorption spectrum (in Nujol) showed almost the same pattern as racemic 2-amino-2-phenylpropionic acid[13] (decomp. p., 221°C), but a slight discrepancy was observed.

Found: C, 65.3; H, 6.8; N, 8.7. Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48%.

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10) E. Fischer (*Ber.*, 32, 2451 (1899)) reported for benzoyl-L-aspartic acid: m. p., 180~181°. $[\alpha]_D^{18}$ $-26.9°$ (*c* 9.56 in the presence of 2 mol. of potassium hydroxide), and for racemic benzoyl-aspartic acid (without water of crystallization): m. p., 161~162°C.

11) T. Posner (*Ber.*, 38, 2320 (1905)): m. p., 161~162°C from ethanol or acetic aicd.

12) E. Fischer, H. Scheibler and R. Groh (*Ber.*, 43, 2020 (1910)) resolved racemic 2-formylamino-2-phenylpropionic acid with the aid of its quinine and quinidine salts: (+)-formyl compound (m. p., 142~143°C, $[\alpha]_D^{20}$ $+115.2°$ (*c* 8.2 in ethanol)) gave (+)-2-amino-2-phenylpropionic acid, m. p., 224~235°C (decomp.), $[\alpha]_D^{20}$ $+6.9°$ (*c* 1.09 in water). They did not prepare the optical active acetyl derivative.

13) Prepared according to the procedure of R. E. Steiger, "Organic Syntheses", Coll. Vol. III (1955), P. 91.