

600. *Configurational Studies in Synthetic Analgesics. Part III.\**  
*The Configuration of (–)-Phenadoxone.*

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The configuration of (–)-phenadoxone has been shown to be identical with that of (–)-methadone by a study of molecular rotations in various solvents. The inapplicability of Freudenberg's displacement rule and Leithe's rule to certain systems is demonstrated.

It has been found that nearly all the analgesic activity of (±)-phenadoxone (6-morpholino-4 : 4-diphenylheptan-3-one) resides in the (–)-isomer.† In an attempt to correlate the configuration of this isomer with that of (–)-methadone to provide further information concerning the stereoselectivity of "analgesic receptor sites," certain isomers were prepared.

Attempts to resolve (±)-3-morpholino-1 : 1-diphenylbutyl cyanide (IIa) by means of (+)-tartaric acid and (+)-dibenzoyltartaric acid were unsuccessful; crystallisation of an equimolar mixture of the cyanide (IIa) and (+)-tartaric acid from aqueous ethanol yielded the free base, probably owing to its very weakly basic nature [ $pK_a' 6.09$ ; cf. 3-dimethylamino-1 : 1-diphenylbutyl cyanide (Ia),  $pK_a' 8.31$ <sup>4</sup>]. Resolution was achieved by use of (+)-camphor-10-sulphonic acid. The (+)-cyanide (IIa) with ethylmagnesium bromide gave the (+)-ketone (IIb) [(+)-phenadoxone], and on hydrolysis with aqueous sulphuric acid gave the (+)-amide (IIc). Cleavage of the cyanide group with sodamide gave (+)-3-morpholino-1 : 1-diphenylbutane (IIId). The preparation of the 3-dimethylamino-compounds (Ia, b, d, f, and g) and (III) has been reported elsewhere.<sup>1,5,6</sup> The (–)-amide (Ic) was prepared in the same way as the corresponding 3-morpholino-compound (IIc), and the ester (Ie) by a modification of the method of Gardner *et al.*<sup>7</sup>

\* The papers cited in refs. 1 and 2 are regarded as Parts I and II.

† "(–)-Phenadoxone" is 64 times as active as the (+)-isomer by the electric grid assay<sup>3</sup> and 15 times as active by the radiant heat method<sup>3</sup> (Elks, personal communication).

<sup>1</sup> Beckett and Casy, *J.*, 1955, 900.

<sup>2</sup> Beckett and Harper, *J.*, 1957, 858.

<sup>3</sup> Basil, Edge, and Somers, *Brit. J. Pharmacol.*, 1950, **5**, 125.

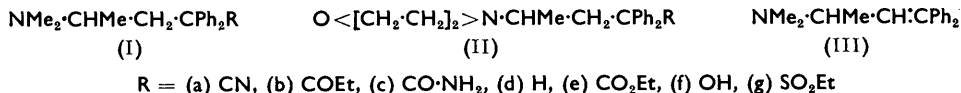
<sup>4</sup> Beckett, *J. Pharm. Pharmacol.*, 1956, **8**, 848.

<sup>5</sup> Larsen, Tullar, Elpern, and Buck, *J. Amer. Chem. Soc.*, 1948, **70**, 4194.

<sup>6</sup> Tullar, Wetterau, and Archer, *ibid.*, p. 3959.

<sup>7</sup> Gardner, Easton, and Stevens, *ibid.*, p. 2906.

Quasi-racemate formation was investigated in this series. Although the (+)- and the (-)-cyanide (Ia) formed a racemate the temperature-composition diagrams of mixtures of (+)-(Ia) and (+)-(IIa), and of (-)-(Ia) and (+)-(IIa) showed no significant difference and could not therefore be used for the assignment of configuration.



In Table 1, the molecular rotations of various isomers of the methadone type (I) and the phenadoxone type (II) are recorded (variations due to concentrations are much less than those due to change of solvent). The configurational identity of compounds within series (I) has already been established;<sup>1</sup> the configurational identity of those of the phenadoxone series (II) follows since their preparation from the (+)-amino-cyanide (IIa) has not involved the asymmetric centre.

TABLE 1. *Molecular rotations at 19° ± 1° (c in parentheses).*

R	Methadone series (I) in:				Direction of displacement	Phenadoxone series (II) in:				Direction of displacement
	C <sub>6</sub> H <sub>12</sub>	C <sub>6</sub> H <sub>6</sub>	EtOH	H <sub>2</sub> O <sup>a</sup>		C <sub>6</sub> H <sub>12</sub>	C <sub>6</sub> H <sub>6</sub>	EtOH	H <sub>2</sub> O <sup>a</sup>	
COEt ...	-106° (1.2)	-74.2° (1.3)	-80.4° (1.5)	-386° <sup>b</sup> (1.5)	→	+247° (0.8)	+179° (0.8)	+245° (0.8)	+345° (0.8)	→
CN .....	-181 (0.9)	-165 (0.8)	-142 (0.8)	+16.7° <sup>b</sup> (5.0)	→	+183 (1.0)	+154 (1.0)	+211 (1.0)	-4.8 (1.0)	→
H .....	-168 (4.8)	-127 (4.7)	+30.4 (3.4)	+153 (1.0)	→	+145 (1.0)	+123 (1.0)	+54.6 (1.0)	-96.6 (1.0)	→
CO·NH <sub>2</sub>	-497 (0.5)	-536 (0.9)	-332 (0.9)	-249 (0.9)	→	+420 (0.9)	+491 (0.9)	+431 (0.9)	+256 (0.9)	→
CO <sub>2</sub> Et ...	-278 (2.0)	-240 (1.8)	-163 (1.8)	-135 (1.0)	→	—	—	—	—	—
SO <sub>2</sub> Et ...	—	+41.4 <sup>c, d</sup> (2.0)	0 <sup>d</sup> (2.0)	-109 <sup>d</sup> (5.0)	→	—	—	—	—	—
OH .....	+99.0 (0.8)	+87.7 (1.9)	-73.5 (0.8)	-121 (1.0)	→	—	—	—	—	—
(III) ...	+321 (1.0)	+309 (1.0)	+427 (1.0)	+614 (0.9)	→	—	—	—	—	—

<sup>a</sup> Hydrochloride. <sup>b</sup> See ref. 5. <sup>c</sup> In acetone. <sup>d</sup> See ref. 6.

Freudenberg's displacement rule<sup>8</sup> states that if two similarly constituted asymmetric molecules are chemically altered in the same way, the change in molecular rotation will be in the same direction in each case (and usually of the same order of magnitude). The pairs (Ia, IIa, etc.) satisfy the requirement of structural similarity and study of  $\Delta[M]$  values (see Table 2) for the base hydrochlorides in water shows a consistent series

TABLE 2. *Molecular rotation differences relative to compounds (Ib) and (IIb).*

R	Methadone series (I) in:				Phenadoxone series (II) in:			
	C <sub>6</sub> H <sub>12</sub>	C <sub>6</sub> H <sub>6</sub>	EtOH	H <sub>2</sub> O <sup>a</sup>	C <sub>6</sub> H <sub>12</sub>	C <sub>6</sub> H <sub>6</sub>	EtOH	H <sub>2</sub> O <sup>a</sup>
CN .....	-75°	-91°	-62°	+403°	-64°	-25°	-34°	-350°
H .....	-62	-53	+110	+539	-102	-56	-190	-442
CO·NH <sub>2</sub> .....	-391	-462	-252	+37	+173	+312	+186	-89

<sup>a</sup> Hydrochloride.

of oppositely directed values. Assignment of non-identical configurations to (-)-methadone (Ib) and (+)-phenadoxone (IIb) on this evidence alone is not justified however, as  $\Delta[M]$  values of the bases are not similarly related in other solvents.

Leithe<sup>9</sup> presented evidence that the molecular rotations of bases possessing analogous

<sup>8</sup> Freudenberg, *Ber.*, 1933, **66**, 177.

<sup>9</sup> Leithe, *Oesterr. Chem. Ztg.*, 1932, **35**, 133; *Ber.*, 1934, **67**, 1261.

asymmetric centres and of like configuration are displaced in the same direction when examined in a series of solvents of increasing polarity. The configuration of certain molecules has been assigned on the basis of this method, but the present authors have questioned the validity of such assignments<sup>10</sup> (see also Bentley and Cardwell<sup>11</sup>). In Table I, the compounds of the methadone series differ only in their substituent on the carbon atom  $\beta$  to the asymmetric centre; the direction of molecular-rotational change brought about by increase in the polarity of the solvent is not similar for all these compounds. Opposite effects occur even for compounds of not too dissimilar group types, e.g., ketone and amide, ketone and ester. Since rotations are usually measured for few or even only one wavelength it is not unexpected that the above rules have only limited application. It is possible that the correlation of changes in the magnitude and position of rotational "maxima" and "minima"<sup>12</sup> upon group displacement or changes in the polarity of the solvent might be a more reliable criterion.

Despite the above limitations, it seems reasonable to use dependence of molecular rotation on polarity of solvent (using one wavelength) in relating configurations of compounds of type (I) and (II) in which only the basic group is altered, provided a number of corresponding members of each series are available, configurational identity within each series is established, and a consistency of patterns observed. Table I shows that the molecular rotation of (–)-methadone (Ib) is displaced towards increasing laevorotation and that of (+)-phenadoxone (IIb) towards increasing dextrorotation as the polarity of the solvent increases, while the cyanides (Ia and IIa), the amides (Ic and IIc), and the hydrocarbon pairs (Id and IIId) also show opposite trends. Certain  $[M]$  values are anomalous, e.g., that of the cyanide (IIa) in ethanol and a number of  $[M]$  values measured in cyclohexane. For the ketone (Ib), the amide (Ic), and the olefin (III), the  $[M]$  values in the latter solvent are contrary to the general trend. It is significant, however, that similar anomalies occur in the  $[M]$  values in cyclohexane of the ketone and amide of the phenadoxone series. Unlike configurations are therefore assigned to the members of each pair in the (I) and (II) series.

It follows that the configuration of (–)-phenadoxone, the analgesically active isomer, is identical with that of (–)-methadone and hence<sup>1</sup> also with that of (–)-3-dimethylamino-1:1-diphenylbutyl ethyl sulphone, (+)-dimethylthiambutene and (+)-diethylthiambutene. Each of these isomers is the more analgesically active member of an enantiomorphous pair and the present finding further supports the proposed stereochemical requirements of analgesics discussed elsewhere.<sup>13</sup>

#### 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 Oracet blue B as indicator.<sup>14</sup> Titration of hydrochlorides was carried out in the same solvent in the presence of mercuric acetate by Pifer and Wollish's method.<sup>15</sup>

*Resolution of 3-Morpholino-1:1-diphenylbutyl Cyanide (IIa).*—The amino-cyanide (24 g.) and (+)-camphor-10-sulphonic acid (17.4 g.) were dissolved in warm acetone (120 c.c.) and kept overnight in a refrigerator. The crystals formed were recrystallised twice from acetone, to give the (+)-amino-cyanide (+)-camphor-10-sulphonate (3.2 g.), m. p. 106–108.5°,  $[\alpha]_D^{22} + 23.1^\circ \pm 0.5^\circ$  (c 3.0 in EtOH). The base was liberated with dilute aqueous ammonia and crystallised from ethanol, to give the (+)-amino-cyanide m. p. 109–110°,  $[\alpha]_D^{20} + 65.7^\circ \pm 0.3^\circ$  (c 1.0 in EtOH),  $[\alpha]_D^{20} + 48.1^\circ \pm 0.5^\circ$  (c 0.97 in benzene),  $[\alpha]_D^{20} + 57.2^\circ \pm 0.6^\circ$  (c 0.96 in cyclohexane),  $[\alpha]_D^{19} - 1.5^\circ \pm 0.8^\circ$  (c 1.0 in 0.04N-HCl).

(+)-6-Morpholino-4:4-diphenylheptan-3-one Hydrochloride.—The (+)-amino-cyanide (IIa)

<sup>10</sup> Beckett and Casy, *Nature*, 1954, **173**, 1231.

<sup>11</sup> Bentley and Cardwell, *J.*, 1955, 3252.

<sup>12</sup> Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362 (and refs. there cited).

<sup>13</sup> Beckett and Casy, *J. Pharm. Pharmacol.*, 1954, **6**, 986.

<sup>14</sup> Beckett and Tinley, "Titrations in Non-Aqueous Solvents," The British Drug Houses Ltd., Poole.

<sup>15</sup> Pifer and Wollish, *J. Amer. Pharm. Assoc., Sci. Ed.*, 1951, **40**, 609.

(0.5 g.) in dry toluene (5 c.c.) was added to ethylmagnesium bromide in ether (5 c.c.) prepared from magnesium (0.1 g.) and ethyl bromide (0.62 g.). The ether was distilled off, and the mixture refluxed for 5 hr. and then added to ice and concentrated hydrochloric acid (2.5 c.c.). The solid which separated was heated with 2*N*-hydrochloric acid (10 c.c.) on a water-bath for 30 min., and the free base liberated with dilute aqueous ammonia and extracted with ether. After drying ( $\text{Na}_2\text{SO}_4$ ), the ether was removed, to give the (+)-amino-ketone (IIb) which formed a *hydrochloride*, needles (from ether-ethanol), m. p. 240° (decomp.),  $[\alpha]_{\text{D}}^{20} + 78.0^\circ \pm 0.7^\circ$  (*c* 0.9 in  $\text{H}_2\text{O}$ ) (Found: C, 70.8; H, 7.3%; equiv., 396.  $\text{C}_{23}\text{H}_{30}\text{O}_2\text{NCl}$  requires C, 71.1; H, 7.7%; equiv., 388). The free base from the (-)-amino-ketone hydrochloride, m. p. 247°,  $[\alpha]_{\text{D}}^{20} - 88.8^\circ \pm 0.4^\circ$  (*c* 0.76 in  $\text{H}_2\text{O}$ ), had  $[\alpha]_{\text{D}}^{20} - 69.7^\circ \pm 0.5^\circ$  (*c* 0.76 in EtOH),  $[\alpha]_{\text{D}}^{20} - 50.9^\circ$  (*c* 0.84 in benzene) and  $[\alpha]_{\text{D}}^{20} - 70.4^\circ$  (*c* 0.8 in cyclohexane).

*γ*-Morpholino- $\alpha$ -diphenylvaleramide (IIc).—A mixture of the amino-cyanide (IIa), concentrated sulphuric acid (9 c.c.), and water (0.9 c.c.) was heated on a steam-bath for 3 hr., poured on ice, and made alkaline with dilute aqueous ammonia. The solid which separated was crystallised from aqueous ethanol, to give needles of the *amino-amide* (IIc) (4.5 g.), m. p. 143—144° (decomp.) (Found: C, 74.3; H, 7.5; N, 8.0%; equiv., 337.  $\text{C}_{21}\text{H}_{26}\text{O}_2\text{N}_2$  requires C, 74.6; H, 7.7; N, 8.3%; equiv., 338).

The (+)-*amino-amide*, prepared in the same way, had m. p. 78—82°,  $[\alpha]_{\text{D}}^{18} + 121^\circ \pm 2^\circ$  (*c* 0.89 in EtOH),  $[\alpha]_{\text{D}}^{18} + 138^\circ \pm 2^\circ$  (*c* 0.86 in benzene),  $[\alpha]_{\text{D}}^{18} + 118^\circ \pm 2^\circ$  (*c* 0.87 in cyclohexane),  $[\alpha]_{\text{D}}^{18} + 71.9^\circ$  (*c* 0.86 in 0.04*N*-HCl) (Found: C, 72.4; H, 7.9; N, 7.7%; equiv., 351.  $\text{C}_{21}\text{H}_{26}\text{O}_2\text{N}_2 \cdot \frac{1}{2}\text{H}_2\text{O}$  requires C, 72.6; H, 7.8; N, 8.05%; equiv., 347).

(+)-3-Morpholino-1:1-diphenylbutane.—A mixture of the (+)-amino-cyanide (IIa) (2 g.), sodamide (2 g.), and dry toluene (20 c.c.) was refluxed for 24 hr., filtered, and evaporated, to give the (+)-amino-butane (1.4 g.) as a pale yellow oil. It formed a *picrate*, yellow needles (from ethanol-acetone), m. p. 176—177° (Found: C, 59.4; H, 5.4%; equiv., 518.  $\text{C}_{26}\text{H}_{28}\text{O}_8\text{N}_4$  requires C, 59.55; H, 5.3%; equiv., 524). The free base had  $[\alpha]_{\text{D}}^{18} + 18.5^\circ \pm 1^\circ$  (*c* 1.0 in EtOH),  $[\alpha]_{\text{D}}^{18} + 41.6^\circ \pm 1^\circ$  (*c* 1.0 in benzene),  $[\alpha]_{\text{D}}^{18} + 49.0^\circ \pm 1^\circ$  (*c* 1.0 in cyclohexane) and  $[\alpha]_{\text{D}}^{18} - 29.1^\circ \pm 0.5^\circ$  (*c* 1.0 in 0.04*N*-HCl).

3-Dimethylamino-1:1-diphenylbutyl cyanide (Ia) was resolved by the method of Larsen *et al.*<sup>5</sup> and the (+)-isomer converted into the amino-ketone (Ib) with ethylmagnesium bromide as described above. It had m. p. 100—101°,  $[\alpha]_{\text{D}}^{20} + 27.5^\circ \pm 0.5^\circ$  (*c* 1.2 in EtOH),  $[\alpha]_{\text{D}}^{20} + 24.0^\circ$  (*c* 1.3 in benzene),  $[\alpha]_{\text{D}}^{20} + 34.4^\circ \pm 0.4^\circ$  (*c* 1.2 in cyclohexane) {Larsen *et al.*<sup>5</sup> give m. p. 100—101°,  $[\alpha]_{\text{D}}^{25} + 26^\circ$  (*c* 1.5 in EtOH)}.

*γ*-Dimethylamino- $\alpha$ -diphenylvaleramide (Ic), prepared from the (-)-amino-cyanide (Ia) as described above for the amide (IIc), formed needles (from aqueous ethanol), m. p. 134.5—135.5°,  $[\alpha]_{\text{D}}^{20} - 112^\circ$  (*c* 0.87 in EtOH),  $[\alpha]_{\text{D}}^{20} - 181^\circ \pm 1^\circ$  (*c* 0.9 in benzene),  $[\alpha]_{\text{D}}^{20} - 168^\circ \pm 1^\circ$  (*c* 0.5 in cyclohexane),  $[\alpha]_{\text{D}}^{20} - 84.1^\circ \pm 0.5^\circ$  (*c* 0.9 in 0.04*N*-HCl) (Found: C, 77.6; H, 8.3; N, 9.5%; equiv., 294.  $\text{C}_{19}\text{H}_{24}\text{ON}_2$  requires C, 77.0; H, 8.1; N, 9.5%; equiv., 296).

*Ethyl γ*-Dimethylamino- $\alpha$ -diphenylvalerate (Ie).—The (-)-amino-cyanide (Ia) was hydrolysed by the method of Gardner *et al.*<sup>7</sup> to (-)-4-dimethylamino-2:2-diphenylpentanoic acid hydrogen sulphate. A mixture of the (-)-salt (1.3 g.) and redistilled thionyl chloride (2 c.c.) was heated at  $>60^\circ$  for 30 min. The excess of thionyl chloride was distilled off under reduced pressure and the residue shaken with benzene until it solidified. The solid was washed with benzene, then refluxed with ethanol (20 c.c.) for 2 hr., and poured into water. The free base was liberated with dilute aqueous ammonia and extracted with ether. After drying ( $\text{Na}_2\text{SO}_4$ ), the ether was removed, to give the oily (-)-amino-ester (Ie) that gave a hydrochloride (from ether-acetone), m. p. 169—170°,  $[\alpha]_{\text{D}}^{21} - 37.3 \pm 0.4^\circ$  (*c* 1.1 in  $\text{H}_2\text{O}$ ) {Pohland *et al.*<sup>16</sup> give m. p. 172—173°,  $[\alpha]_{\text{D}}^{25} - 38^\circ$  (*c* 0.2 in  $\text{H}_2\text{O}$ )}. The free base had  $[\alpha]_{\text{D}}^{20} - 50^\circ$  (*c* 1.8 in EtOH),  $[\alpha]_{\text{D}}^{20} - 73.8^\circ$  (*c* 1.8 in benzene),  $[\alpha]_{\text{D}}^{20} - 85.5^\circ \pm 0.5^\circ$  (*c* 2.0 in cyclohexane).

We are indebted to Glaxo Laboratories for making available ( $\pm$ )-3-morpholino-1:1-diphenylbutyl cyanide and a sample of (-)-phenadoxone.