

## ABSOLUTE CONFIGURATIONS OF SOME HETEROCYCLIC ACIDS\*

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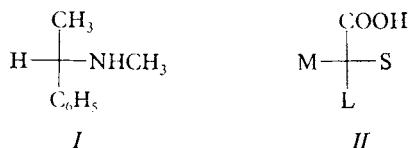
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Employing the method of asymmetric transformation, the absolute configurations of heterocyclic acids *III*, *IV*, *Va*, and *VIIa* have been determined. The acids *Va* and *VIIa* were chemically correlated with alcohols of known absolute configurations.

The method of asymmetric transformation, based on acylation of an optically active amine of known configuration with an excess of a racemic acid (or excess of a racemic amine with an optically active acid), was worked out to determine the absolute configurations of compounds with an amino group attached to the chirality centre<sup>1-5</sup>, and acids with the chirality centre at the  $\alpha$  position to the carbonyl group<sup>6-9</sup>. In the present paper it was used to determine the absolute configurations of some heterocyclic acids.

Analysis of the preferred transition states has shown that if (*S*)-(-)-1-phenyl-1-methylaminoethane (*I*) is used for the reaction, the absolute configuration of the isolated acid corresponds to formula *II*. The same applies *vice versa*, to the reaction between an optically active acid and a racemic amine. In the heterocyclic acids studied, the grouping containing the hetero atom appears to be a bulkier substituent (*L*) than that having a skeleton of carbon atoms only (*M*).



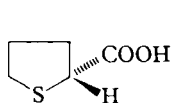
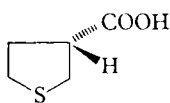
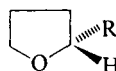
The asymmetric transformations were accomplished with the racemic acids *III*, *IV*, *Va*, and *VIIa* (50% molar excess) by reaction with (*S*)-(-)-1-phenyl-1-methylami-

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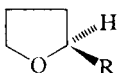
noethane in the presence of dicyclohexylcarbodiimide. The acids *Va* and *VIIa* were also used in the alternative way of the transformation, in which their optically active forms reacted with a 0.5 molar excess of the racemic amine *I*.

In agreement with the literature<sup>10,11</sup>, reactions of the racemic acids *III* and *IV* with the amine *I* afforded acids of absolute configuration (*R*)-(–). Reactions of the acids *Va*, *VIIa* with the amine *I* gave dextrorotatory acids of absolute configuration *R*. The same conclusion can be drawn from the asymmetric transformation in the alternative way; reactions of the dextrorotatory acids *Va*, *VIIa* with the racemic amine *I* led in either case to the laevorotatory amine of absolute configuration *I*.

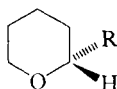
The absolute configurations of the acids *Va*, *VIIa* have not yet been known. Since the corresponding hydroxy derivatives *Vc*, *VIIc* were reported<sup>12,13</sup> to have an absolute configuration of (*R*)-(–), we reduced the corresponding methyl esters with lithium aluminium hydride. The laevorotatory enantiomer of acid *VIa* afforded a dextrorotatory alcohol *VIc*, the dextrorotatory acid *VIIa* gave a laevorotatory alcohol *VIIc*, which corroborates the (*R*)-(+)- configuration of the two acids, deduced from the asymmetric transformation.

*III**IV*

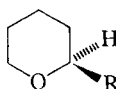
*Va*, R = COOH  
*Vb*, R = COOCH<sub>3</sub>  
*Vc*, R = CH<sub>2</sub>OH



*VIa*, R = COOH  
*VIb*, R = COOCH<sub>3</sub>  
*VIc*, R = CH<sub>2</sub>OH



*VIIa*, R = COOH  
*VIIb*, R = COOCH<sub>3</sub>  
*VIIc*, R = CH<sub>2</sub>OH

*VIIIa*, R = COOH

## EXPERIMENTAL

The melting points were not corrected. The analytical samples were dried for 8 h *in vacuo* (oil pump). The optical rotation of the compounds was measured with an accuracy of  $\pm 0.02^\circ$ .

*Starting compounds:* Thiolane-2-carboxylic acid<sup>14</sup> (*III*), b.p. 110–112°C/0.05 kPa, m.p. 51°C; thiolane-3-carboxylic acid<sup>15</sup> (*IV*), b.p. 85–89°C/0.04 kPa, m.p. 54–56°C (light petroleum); tetrahydrofuran-2-carboxylic acid<sup>16</sup> (*VIa*), b.p. 126–130°C/1.8 kPa; tetrahydropyran-2-carboxylic acid<sup>17</sup> (*VIIIa*), b.p. 128–130°C/1.6 kPa.

(S)-(-)-Tetrahydrofuran-2-carboxylic Acid (*VIa*)

To a solution of 68.2 g of quinine in boiling ethanol, 24.5 g of racemic tetrahydrofuran-2-carboxylic acid in ethanol was added. The separated crystals were recrystallized three times from ethanol; yield 13 g of the quinine salt, m.p. 142–145°C,  $[\alpha]_{\text{D}}^{20} - 128.6^\circ$  (c 4.5, water). After an addition of sulphuric acid and ten-fold extraction into ether there was obtained 1.5 g of *VIa*, b.p. 128°C/2.7 kPa,  $[\alpha]_{\text{D}}^{20} - 12.6^\circ$  (c 7.7, water). For  $\text{C}_5\text{H}_8\text{O}_3$  (116.1) calculated: 51.72% C, 6.94% H; found: 51.80% C, 7.02% H.

(S)-(+)-Methyl Tetrahydrofuran-2-carboxylate (*VIb*)

An ethereal solution of 1.5 g of *VIa*, b.p. 128°C/2.7 kPa,  $[\alpha]_{\text{D}}^{20} - 12.6^\circ$  (c 7.7, water), was mixed with an ethereal solution of diazomethane; yield 0.9 g of *VIb*, b.p. 69–70°C/2.4 kPa,  $(\alpha)_{\text{D}}^{20} + 9.2^\circ$  (subst.). For  $\text{C}_6\text{H}_{10}\text{O}_3$  (130.1) calculated: 55.37% C, 7.74% H; found: 55.38% C, 7.80% H.

(S)-(+)-2-Hydroxymethyltetrahydrofuran (*VIc*)

To a suspension of 0.3 g of lithium aluminium hydride in 15 ml of ether, a solution of 0.82 g of *VIb* in 20 ml of ether was added dropwise and the mixture was stirred for 4 h at room temperature. After adding successively 0.3 ml of water, 0.3 ml of 15% sodium hydroxide and 0.9 ml of water the precipitate was filtered off, washed with ether, and the ethereal solution was dried with magnesium sulphate; b.p. 62°C/2.4 kPa,  $(\alpha)_{\text{D}}^{20} + 1.08$  (subst.), a single product by gas chromatography (5% Carbowax). For  $\text{C}_5\text{H}_{10}\text{O}_2$  (102.1) calculated: 58.79% C, 9.87% H; found: 58.42% C, 10.11% H.

(S)-(-)-Tetrahydropyran-2-carboxylic Acid (*VIIIa*)

Hot ethanolic solutions of 23.4 g of racemic tetrahydropyran-2-carboxylic acid<sup>17</sup> and 58.3 g of (-)-quinine were mixed. The crystals that separated after cooling and an addition of ether were purified by a three-fold recrystallization from ethanol; yield 3.9 g of the salt, m.p. 180–189°C  $[\alpha]_{\text{D}}^{20} - 134^\circ$  (c 4.8, ethanol). The salt was suspended in water and sulphuric acid was added. The released acid *VIIIa* was taken into ether in a continuous extraction apparatus and distilled; yield 0.9 g, b.p. 143°C/3.3 kPa,  $(\alpha)_{\text{D}}^{20} - 175^\circ$  (subst). For  $\text{C}_6\text{H}_{10}\text{O}_3$  (130.1) calculated: 55.37% C, 7.75% H; found: 55.26% C, 7.68% H.

(R)-(+)-Methyl Tetrahydropyran-2-carboxylate (*VIIb*)

The acid released from a mother liquor of the quinine salt, b.p. 122–123°C/2 kPa,  $[\alpha]_{\text{D}}^{20} + 7.1^\circ$  (subst.) was mixed with an ethereal solution of diazomethane. The ester boiled at 80°C/1.9 kPa,  $[\alpha]_{\text{D}}^{20} + 4.4^\circ$  (subst.). For  $\text{C}_7\text{H}_{12}\text{O}_3$  (144.1) calculated: 58.32% C, 8.39% H; found: 58.48% C, 8.25% H.

(R)-(-)-2-Hydroxymethyltetrahydropyran (*VIIc*)

To 0.31 g of lithium aluminium hydride suspended in 20 ml of ether, 1.2 g of *VIIb* in 20 ml of ether was added dropwise. After stirring for 5 h at room temperature the mixture was decomposed by adding water and 10% sulphuric acid and the product was taken into ether. B.p. 83°C/2 kPa,  $[\alpha]_{\text{D}}^{20} - 9.8^\circ$  (c 1.0, water), single by gas chromatography (5% Carbowax). <sup>1</sup>H NMR spectrum (in  $\text{C}^2\text{HCl}_3$ )  $\delta$  ppm 1.53 m, 6 H; 2.95, s, 1 H; 3.45 m, 4 H; 4.02, m, 1 H. For  $\text{C}_6\text{H}_{12}\text{O}_2$  (116.1) calculated: 62.04% C, 10.41% H; found: 62.20% C, 10.54% H.

## Asymmetric Transformation

To a solution of racemic *III* (1.98 g) in 5 ml of tetrahydrofuran, 2.04 g of N,N-dicyclohexylcarbodiimide in 3 ml of tetrahydrofuran was added and the mixture was stirred for 1 h. After cooling to  $-30^{\circ}\text{C}$ , 1.35 g of *I* (*S*)-(-)-1-phenyl-1-methylaminomethane<sup>8</sup>, b.p.  $77-78^{\circ}\text{C}/2\text{ kPa}$ ,  $[\alpha]_{\text{D}}^{20} -64.5^{\circ}$  (*c* 3.6, ethanol) in 5 ml of tetrahydrofuran was added. The mixture was left standing for 24 h at room temperature and worked up in the usual way; yield 0.38 g of (*R*)-(-)-acid *III*,  $[\alpha]_{\text{D}}^{20} -14.2^{\circ}$  (*c* 13, ethanol). Analogously obtained were:

(*R*)-(-)-Acid *IV*, 0.1 g, b.p.  $73-75^{\circ}\text{C}/0.07\text{ kPa}$ , m.p.  $54-56^{\circ}\text{C}$ ,  $[\alpha]_{\text{D}}^{20} -1.33^{\circ}$  (*c* 7.0, ethanol), from 1.32 g of racemic *IV*, 1.36 g of N,N'-dicyclohexylcarbodiimide and 0.9 g of (-)-amine *I*.

(*R*)-(+)-Acid *Va*, 0.300 g,  $[\alpha]_{\text{D}}^{20} +2^{\circ}$  (*c* 11, water), from 2.32 g of racemic *Va*, 4.12 g of N,N'-dicyclohexylcarbodiimide and 1.8 g (-)-amine *I*.

(*S*)-(-)-Amine *I*, 2.4 g, b.p.  $71-72^{\circ}\text{C}/2.4\text{ kPa}$ ,  $[\alpha]_{\text{D}}^{20} -0.29^{\circ}$  (subst.), from 2.9 g of (*R*)-(+)-acid *Va*,  $[\alpha]_{\text{D}}^{20} +4.8^{\circ}$  (*c* 5.5, water), 5.15 g of N,N'-dicyclohexylcarbodiimide and 5.06 g of racemic amine *I*.

(*R*)-(+)-Acid *VIIa*, 0.115 g,  $[\alpha]_{\text{D}}^{20} +2.2^{\circ}$  (*c* 4.6, ethanol), from 1.1 g of racemic *VIIa*, 1.73 g of N,N'-dicyclohexylcarbodiimide and 0.75 g of (-)-amine *I*.

(*S*)-(-)-Amine *I*, b.p.  $67-69^{\circ}\text{C}/2.4\text{ kPa}$ ,  $[\alpha]_{\text{D}}^{20} -0.73^{\circ}$  (subst.), from (*R*)-(+)-acid *VIIa*,  $[\alpha]_{\text{D}}^{20} +8^{\circ}$  (subst.), 1.11 g of N,N'-dicyclohexylcarbodiimide and 1.01 g of racemic amine *I*.

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