*iso*Thiocyanates XXVII *. The Absolute Configuration of Optically Active 2-Butylamine and 2-Butyl *iso*Thiocyanate

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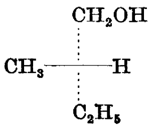
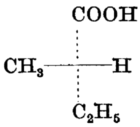
The isolation from natural sources of 2-butyl *iso*thiocyanate was effected by Hofmann[1] in 1874. Gadamer[2] later established the glycosidic origin and dextrorotatory character of the mustard oil and accomplished its synthesis from (+)-2-butylamine. The configuration of the latter, relative to glyceraldehyde, can be inferred from the kinetically controlled interconversions of 2-butylamine, 2-butyl halides and 2-butanol established by the Ingold school[3]. Various authors have correlated 2-butanol with glyceraldehyde through lactic acid as a key intermediate (*cf.* Ref.[4]).

In the course of current investigations in this laboratory, it became of interest to correlate optically active 2-butylamine, and hence 2-butyl *iso*thiocyanate, with glyceraldehyde through transformations not involving inversions at the asymmetric centre. This has been achieved in the following way:



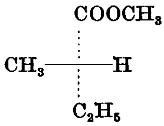
$$\begin{array}{ccc} & \mathrm{CH_2OH} & \\ \mathrm{CH_3} & - & \mathrm{H} \\ & \mathrm{C_2H_5} & \end{array}$$

(—)
I



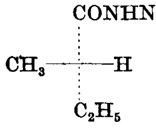
$$\begin{array}{ccc} & \mathrm{COOH} & \\ \mathrm{CH_3} & - & \mathrm{H} \\ & \mathrm{C_2H_5} & \end{array}$$

(+)
II



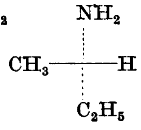
$$\begin{array}{ccc} & \mathrm{COOCH_3} & \\ \mathrm{CH_3} & - & \mathrm{H} \\ & \mathrm{C_2H_5} & \end{array}$$

(+)
III



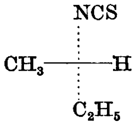
$$\begin{array}{ccc} & \mathrm{CONHNH_2} & \\ \mathrm{CH_3} & - & \mathrm{H} \\ & \mathrm{C_2H_5} & \end{array}$$

(+)
IV



$$\begin{array}{ccc} & \mathrm{NH_2} & \\ \mathrm{CH_3} & - & \mathrm{H} \\ & \mathrm{C_2H_5} & \end{array}$$

(+)
V



$$\begin{array}{ccc} & \mathrm{NCS} & \\ \mathrm{CH_3} & - & \mathrm{H} \\ & \mathrm{C_2H_5} & \end{array}$$

(+)
VI

(−)-2-Methylbutanol ('active amyl alcohol') (I) was oxidized to (+)-2-methylbutyric acid (II), and the latter further converted into (+)-methyl 2-methylbutyrate (III) and (+)-2-methylbutyric acid hydrazide (IV). Curtius rearrangement of the corresponding azide, followed by acid hydrolysis of the intermediate urethan, ultimately furnished *dextrorotatory* 2-butylamine (V), characterized as its hydrochloride and benzoyl derivative. Since Jones and Wallis[5] first demonstrated the Curtius rearrangement to take place without racemization, evidence has become abundant that this intramolecular displacement reaction proceeds with full retention of configuration (*cf. e. g.* Ref.[6]).

The above symbols (I)−(VI), represent the absolute configurations on following grounds: (I) has been configuratively related with (−)-glyceraldehyde through a rather circumstantial series of transformations, recently summarized by Crombie and Harper[7]. The assignment has been verified by Freudenberg's ingenious application[8] of dihydroshikimic acid for determining the configuration of (+)-3-methylhexane, which has been correlated with (I) many years ago[9]. The X-ray evidence of Bijvoet *et al.*[10] finally renders established relationship with glyceraldehyde equal to knowledge of the absolute configuration.

Correlation of (I) with C-3 in natural *iso*leucine has been achieved in various ways (*cf. e. g.* Ref.[11]). Hence, natural *iso*leucine and (+)-2-butyl *iso*thiocyanate (VI) belong to the same configurational series. The direct determination of the absolute configuration of the former by means of X-ray crystallography[12] provides an independent confirmation of the above assignments, which may prove useful also for the purpose of establishing the correlation of (+)-2-butyl *iso*thiocyanate with its glucosidic progenitor (glucocochlearin) as suggested by Ettlinger and Lundeen[13].

Experimental. Melting points are uncorrected. Rotations are measured in a 1 dm tube.

(+)-2-Methylbutyric acid (II). An optically active acid, produced by oxidation of essentially pure (—)-2-methylbutanol, served as a starting material for the following syntheses. The acid had the rotation value: $[\alpha]_D^{21}$ +19.6° (neat), D_4^{21} 0.937, somewhat higher than most literature values.

(+)-Methyl 2-methylbutyrate (III). Esterification of the above acid (65 g) with methanol

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(600 ml), and a few drops of sulphuric acid, afforded the methyl ester (44 g) as a colourless liquid, b. p. 115°, n_D^{25} 1.3916, D_4^{22} 0.888, $[\alpha]_D^{22}$ +23.6° (neat), $[\alpha]_D^{21}$ +26.0° (c 1.8, MeOH).

Guye[14] reported the value $[\alpha]_D^{22}$ +22.03° for the ester, corrected to supposedly optically pure condition, while von Doering and Aschner[15] listed the value $[\alpha]_D^{27}$ +21.1° (c 1.7, MeOH) for a specimen prepared from 2-methylbutyric acid, having $[\alpha]_D^{27}$ +17.75° (neat) and claimed to be 98 % optically pure. The enantiomeric ester, deriving from an acid with $[\alpha]_D^{17}$ —17.35°, was reported by Prelog and Zalán[16] with the rotation value $[\alpha]_D^{15}$ —19.42° (neat).

(+)-2-Methylbutyric acid hydrazide (IV). The methyl ester (30 g) was slowly added to a large excess of boiling 90 % hydrazine hydrate, and the mixture was refluxed for 2 h. On removal of hydrazine *in vacuo*, the crude hydrazide separated (29 g). Three sublimations afforded an analytical specimen as thin, colourless needles, m. p. 96°. $[\alpha]_D^{22}$ +41.3° (c 2.6, H_2O). (Found: C 51.80; H 10.54; N 24.24. Calc. for $C_5H_{12}N_2O$: C 51.68; H 10.43; N 24.21).

(+)-2-Butylamine (V). To a stirred solution of the hydrazide (28 g) in 1 N HCl (400 ml), covered with ether and cooled to 0°, was added a concentrated aqueous solution of $NaNO_2$ (22 g). The ether phase was separated, combined with two additional ether extracts, and briefly dried over Na_2SO_4. Anhydrous ethanol (*ca.* 300 ml) was added and the solution was refluxed for 2 h, when the N_2-evolution had completely ceased. A small fraction of the oily urethan, remaining upon removal of the solvents, was refluxed with 20 % HCl for 10 h, when removal of water and acid resulted in separation of the crystalline amine hydrochloride. This was covered with ether and strong alkali was slowly added to liberate the amine. Ether was removed from the carefully dried extract by distillation through a 3-feet helix-packed column, and (+)-2-butylamine distilled as a colourless liquid, b. p. 62.5°, n_D^{25} 1.3853. The rotation value, $[\alpha]_D^{22}$ +6.1° (neat), was measured on a fore-run probably still containing traces of water. Literature values are: $[\alpha]_D^{15.5}$ +6.42° (neat)[2b], $[\alpha]_D^{20}$ +7.44° (neat)[17], and $[\alpha]_D$ +7.4° (c *ca.* 25, H_2O)[18].

The hydrochloride separated from acetone in colourless, hygroscopic needles, m. p. 152—153° (closed tube), $[\alpha]_D^{19}$ —1.05° (c 13.3, H_2O) (Found: N 12.47; Cl 32.50. Calc. for $C_4H_{12}ClN$: N 12.78; Cl 32.34). Literature values: $[\alpha]_D^{20}$ —2.05° (c 7.3, H_2O)[2b], $[\alpha]_D^{20}$ —1.13° (c 14.0, H_2O)[17] and, for the enantiomorphous salt, $[\alpha]_D^{20}$ +0.90° (c. 3.7, H_2O)[19].

(+)-N-(2-Methylbutyl)-benzamide. Benzoylation of the above amine, performed under customary Schotten-Baumann conditions, furnished the benzamide, separating from 50 % ethanol in colourless needles, m. p. 97°, $[\alpha]_D^{21}$ +34.9° (c 1.1, EtOH) (Found: C 74.60; H 8.40; N 7.82. Calc. for $C_{11}H_{15}NO$: C 74.56; H; 8.54 N 7.91.) Previously reported data: m. p. 92°, $[\alpha]_D^{21}$ +30.7 (c 1, EtOH)[19], m. p. 92.0—92.5°, $[\alpha]_D^{25}$ +30.74° (c 4, EtOH)[20].

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