## 89. *The Stereochemical Relationships of Some Optically Active Amines and Amino-acids. Part I. The Configuration of Valine.*

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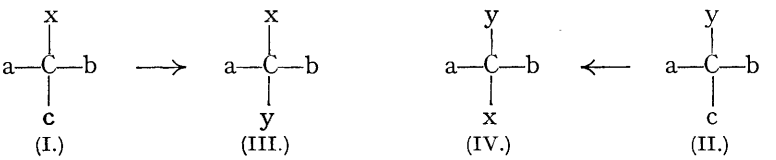
The method introduced by Clough (J., 1918, **113**, 526 : for further references, see Freudenberg, " Stereochemie," 1932, p. 693) of correlating the stereochemical configurations of similarly constituted, optically active compounds from observations on the alterations in their rotatory power, accompanying the introduction of similar substituents, has been employed by Karrer and van der S. Veer (*Helv. Chim. Acta*, 1932, **15**, 746) to determine the configuration of valine. The naturally occurring, dextrorotatory amino-acid and its ethyl ester, on conversion into the benzoyl, benzenesulphonyl, and other acyl derivatives, showed optical displacements of a similar sign and magnitude to those which accompany the introduction of the same substituents into (+)-alanine (Karrer, Escher, and Widmer, *Helv. Chim. Acta*, 1926, **9**, 301; Freudenberg and Rhino, *Ber.*, 1924, **57**, 1547), and the conclusion was therefore drawn that both acids belong to the same steric series. Since, in the opinion of the present authors, the results obtained by the method of optical displacements are not so trustworthy as those furnished by purely chemical methods, the present investigation was undertaken with the object of determining the relative configurations of valine and alanine by means of chemical transformations.

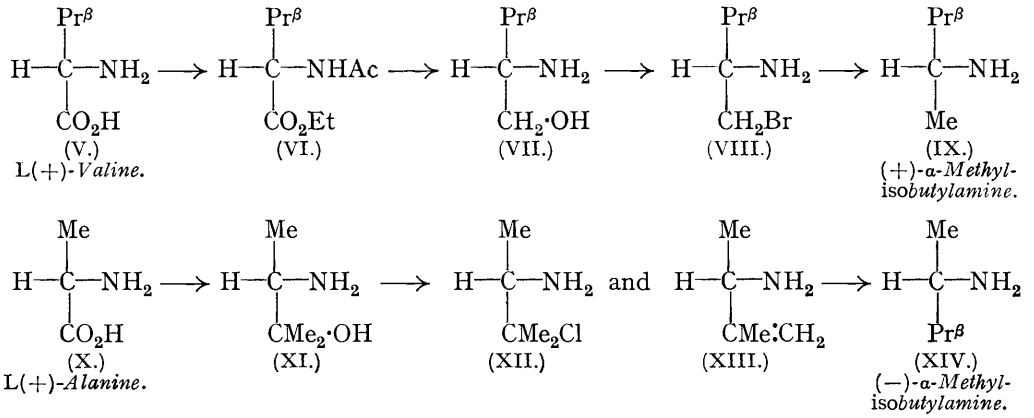



The method employed depends on the following principle : if two optically active compounds, Cabcx and Cabcy, having the same stereochemical configurations (I) and (II),

are each converted into Cabxy by transformation of a common group c into y and x respectively, the two compounds (III) and (IV) produced will have opposite configurations, provided that the reactions used in effecting the transformations do not involve, at any stage, a Walden inversion owing to the rupture of the group c from the asymmetric atom.

In order to apply this principle to the determination of the relative configurations of valine and alanine, it is necessary to convert the carboxyl group in the first-named acid into the methyl group, and the carboxyl of alanine must be transformed into the *iso*propyl group. If the two α-methyl*iso*butylamines (IX) and (XIV) produced have opposite signs of rotation, the original amino-acids (V) and (X) must have the same stereochemical configuration.

The reactions employed to effect the transformations are shown in the scheme :




The α-methyl*iso*butylamine obtained from (+)-alanine gave a lævorotatory hydrochloride, and that from (+)-valine furnished a dextrorotatory hydrochloride : the *p*-nitrobenzoyl derivatives of the two amines also showed opposite signs of rotation. From these results it is definitely established that the naturally occurring, dextrorotatory valine has the same stereochemical configuration as (+)-alanine. Roger's modification (*Helv. Chim. Acta*, **1929**, **12**, 1060) of Freudenberg's method of denoting both the configuration and the sign of rotation being adopted, the amino-acid will be designated *L*(+)-valine.

*Conversion of* L(+)-*Valine into* (+)-α-*Methyl*iso*butylamine.*—The formyl derivative of *L*(+)-valine (V), when boiled with alcoholic hydrogen chloride, underwent simultaneous hydrolysis and esterification, yielding valine ester hydrochloride, which, on acetylation, gave *ethyl* L(—)-α-*acetamido*iso*valerate* (VI), $[\alpha]_{5461}$ — 20·1°. The acetylation was accompanied by slight racemisation, since the valine hydrochloride obtained from the ester by hydrolysis had a rotatory power, $[\alpha]_D$ + 27·1°, somewhat lower than that of the optically pure hydrochloride, $[\alpha]_D$ + 28·8°. On reduction with sodium and alcohol, the acetyl ester yielded L(+)-*valinol* (VII), the main portion of which (A), after isolation in the form of its *hydrochloride*, had $[\alpha]_{5461}$ + 1·2°. Since the optically pure hydrochloride obtained by the resolution of inactive valinol had $[\alpha]_{5461}$ + 16·4°, the reduction of the ester was accompanied by profound racemisation. In view of this small rotation and also of the fact that we propose to utilise the active valinols as reference compounds for correlating the configuration of other amino-acids, it became necessary to establish beyond doubt that the optical activity of the reduction product was actually due to the amino-alcohol and not to some impurity, whose presence would not be revealed by analysis ; and this was ultimately accomplished by a comparison of its benzoyl derivatives with those of the fully active valinol.

The resolution of inactive valinol was readily effected by crystallisation of its hydrogen (+)-tartrate from alcohol, and the hydrochlorides of both the *D*(—)- and the *L*(+)-amino-alcohol were obtained in a pure condition. On benzoylation in the presence of aqueous sodium hydroxide, *L*(+)-valinol gave a lævorotatory ON-*dibenzoyl* derivative (XV),

$[\alpha]_{5461}$ — 20·1°, which was converted, by heating with an excess of benzoyl chloride in the presence of pyridine, into a dextrorotatory *tribenzoyl* derivative (XVI), $[\alpha]_{5461}$ + 133·1°.

(XV.) $Pr^{\beta}\cdot CH(NHBz)\cdot CH_2\cdot OBz$ $\qquad$ $Pr^{\beta}\cdot CH(NBz_2)\cdot CH_2\cdot OBz$ (XVI.)

The successive conversion of *L*( + )-valinol into its di- and tri-benzoyl derivatives is, in each case, accompanied by a reversal in the sign of the rotation. A similar behaviour was shown by the feebly active valinol, obtained by the reduction of *L*( — )-acetamido*iso*-valerate, the dibenzoyl derivative being lævorotatory, $[\alpha]_{5461}$ — 1·3°, and the tribenzoyl derivative dextrorotatory, $[\alpha]_{5461}$ + 3·3°. From these results there can be no doubt that the activity shown by the reduction product of the ester is due to the presence of *L*( + )-valinol hydrochloride. Further confirmation was furnished later by the isolation, from the mother-liquors from which the feebly active hydrochloride had been removed, of a very small amount of *L*(+)-valinol hydrochloride (B) having a rotatory power, $[\alpha]_{5461}$ + 14·5°, almost equal to that of the fully active compound, and showing the same alternation in the sign of the rotation on conversion into its di- and tri-benzoyl derivatives. The comparison of the rotations of these derivatives is facilitated by the table given below, in which the values for the specific rotations (for λ 5461) have been collected :

| Derivative. | *L*-Valinol from resolution. | *L*-Valinol from reduction. A. | B. |
|---|---|---|---|
| Hydrochloride | + 16·4° | + 1·2° | + 14·5° |
| Dibenzoyl | — 20·1 | — 1·3 | — 18·1 |
| Tribenzoyl | + 133·1 | + 3·3 | + 117·0 |

The reduction of *L*(+)-valinol (VII) to α-methyl*iso*butylamine (IX) was accomplished by heating the hydrochloride with hydrogen bromide in acetic acid solution, and reducing the resulting *α-bromomethyl*iso*butylamine hydrobromide* (as VIII) catalytically in the presence of palladised charcoal. The (+)-*α-methyl*iso*butylamine hydrochloride* obtained had only a small rotation, $[\alpha]_{5461}$ + 3·5°, but gave a strongly active *p*-nitrobenzoyl derivative, $[\alpha]_{5461}$ — 55·8°.

*D*(—)-Valinol was reduced in a similar manner, and the resulting (—)-*α-methyl*iso*butyl-amine* furnished a *hydrochloride*, having $[\alpha]_{5461}$ — 3·4°, and a p-*nitrobenzoyl* derivative with $[\alpha]_{5461}$ + 55·8°. In view of this identity in the magnitude of the rotations of the two isomerides, it would appear that the reduction of the active valinols is not attended with any racemisation.

The inactive valinol required for the resolution was prepared partly from inactive valine by conversion into ethyl α-acetamido*iso*valerate, followed by reduction with sodium and butyl alcohol, and partly by the method illustrated in the following scheme :

$$CHMe_2\cdot CH_2\cdot NO_2 \longrightarrow CHMe_2\cdot CH(NO_2)\cdot CH_2\cdot OH \longrightarrow CHMe_2\cdot CH(NH_2)\cdot CH_2\cdot OH$$
(XVII.) (XVIII.)

α-Nitro*iso*butane (XVII), prepared from *iso*butyl iodide and silver nitrite, was condensed with formaldehyde by Shaw's method (*Rec. trav. chim.*, 1898, **17**, 50), and the resulting β-*nitro*iso*amyl alcohol* (XVIII) reduced with iron and hydrochloric acid. Although the reduction of the nitro-alcohol to valinol proceeded very smoothly, this method of preparation possessed no advantages over the alternative method on account of the poor yields in the earlier stages of the synthesis.

*Conversion of* L(+)-*Alanine into* (—)-α-*Methyl*iso*butylamine.*—*L*(+)-Alanine (X) was esterified, and the ethyl ester hydrochloride treated with methylmagnesium iodide. The (+)-β-*hydroxy-α-methyl*iso*butylamine hydrochloride* (XI) produced had a rotatory power, $[\alpha]_{5461}$ + 5·6°, somewhat less than that of the fully active amino-alcohol, $[\alpha]_{5461}$ + 6·1°, prepared by the resolution of the inactive compound, but gave a N-*benzoyl* derivative having the full activity. The resolution of the inactive alcohol was effected by the crystallisation of the *hydrogen* (+)-*tartrate* from alcohol, the *hydrochloride* of the (+)-*amino-alcohol* being readily isolated in a pure condition. The *hydrochloride* of (—)-β-*hydroxy-α-methyl*iso*butylamine* could not be obtained entirely free from the stereoisomeric form,

but the N-*benzoyl* derivative was prepared in an optically pure condition by crystallisation from light petroleum. The reduction of (+)-β-hydroxy-α-methyl*iso*butylamine (XI) to (−)-α-methyl*iso*butylamine (XIV) at first presented some difficulty. The method, successfully employed in the case of the valinols, failed when applied to the isomeric amino-alcohol. Heating with hydrobromic acid under various conditions caused profound decomposition, the greater part of the nitrogen being eliminated in the form of ammonia, and the small amount of α-methyl*iso*butylamine, isolated from the product after catalytic reduction, was completely inactive. The conversion of the (+)-amino-alcohol into (−)-α-methyl*iso*-butylamine was ultimately accomplished by treatment of the hydrochloride with phosphorus pentachloride in chloroform solution, followed by catalytic reduction in the presence of palladised charcoal. The action of phosphorus pentachloride results in the formation of a mixture of the *chloro-amine* (XII) and the unsaturated *amine* (XIII), both of which readily undergo reduction. Some racemisation takes place during the interaction with phosphorus pentachloride, for the rotatory power of the (−)-α-*methyl*iso*butylamine hydrochloride* varied in different experiments from $[\alpha]_{5461}$ − 1·35° to − 2·65°, and was always lower than that of the corresponding hydrochloride (± 3·5°) obtained by the reduction of the active valinols. The rotation of the p-*nitrobenzoyl* derivative varied from $[\alpha]_{5461}$ + 44·1° to + 47·4°, but could be raised by repeated crystallisation to a value (+ 53·8°) almost equal to that of the fully active compound.

In view of the fact that the optically active forms of benzoylalanine may be readily obtained by the method of resolution described by Pope and Gibson (J., 1912, **101**, 939), experiments were undertaken, during the earlier part of this investigation, in the hope of utilising the benzoyl derivatives in place of the free amino-acids for effecting similar transformations to those described above. It was found that inactive benzoylalanine could be smoothly converted, by direct esterification at the ordinary temperature, into its methyl ester, which furnished the *N*-benzoyl derivative of β-hydroxy-α-methyl*iso*butylamine in excellent yield, when treated with methylmagnesium iodide. Attempts to reduce this benzoyl derivative under various conditions were unsuccessful. Moreover, the benzoyl derivative could not be hydrolysed without undergoing extensive decomposition, and further experiments in this direction were therefore abandoned.

## Experimental.

All temperatures are corrected.

*Preparation of Inactive Valinol.*—This amino-alcohol has been prepared by Karrer, Gisler, Horlacher, Locher, Mäder, and Thomann (*Helv. Chim. Acta*, 1922, **5**, 478) from valine ethyl ester by reduction with sodium and ethyl alcohol. A much better yield is obtained by reducing the acetyl derivative of the ester in butyl-alcoholic solution and isolating the amino-alcohol by steam distillation. The acetyl ester was more conveniently prepared by the following procedure than by that of Karrer, Miyamichi, Storm, and Widmer (*ibid.*, 1925, **8**, 205).

Valine (50 g.) was esterified with alcohol (300 c.c.) and hydrogen chloride in the usual manner and, after removal of the excess of alcohol under reduced pressure, the residual valine ester hydrochloride was heated for 1 hour on the steam-bath with anhydrous sodium acetate (50 g.) and acetic anhydride (200 g.). The acetic anhydride was distilled under diminished pressure, and the residue extracted with chloroform: distillation of the chloroform extract gave ethyl α-acet-amido*iso*valerate as a viscid oil (59 g.), b. p. 157—158°/21 mm., having a faint garlic odour (Found: N, 7·8. Calc.: N, 7·5%).

The reduction to valinol was effected by rapidly adding sodium (19 g.) to a boiling solution of the ester (12 g.) in butyl alcohol (160 c.c.), which had been dehydrated by distillation over magnesium butyloxide (Lund and Bjerrum, *Ber.*, 1931, **64**, 210). After 1 hour's boiling, water was added, and the mixture distilled in steam until the distillate was no longer alkaline. Valinol is only slowly volatile in steam and the vapours have a pronounced odour resembling that of crude acetamide. The distillate was acidified with hydrochloric acid, the aqueous layer separated and evaporated, the residue warmed with butyl alcohol, and the solution filtered from a small amount of ammonium chloride. On the addition of ether to the butyl-alcoholic solution, valinol hydrochloride separated; it crystallised from acetone in small, lustrous, hygroscopic plates (4 g.), m. p. 118—119° (Karrer *et al.*, *loc. cit.*, give 114°) (Found: N, 10·0; Cl, 25·6. Calc.: N, 10·0; Cl, 25·4%).

Valinol was also prepared as follows: α-nitro*iso*butane was condensed with formaldehyde as described by Shaw (*loc. cit.*), and the resulting β-nitro*iso*amyl alcohol (14 g., b. p. 98°/7 mm.) reduced by heating on the steam-bath with iron powder (17 g.) and alcohol (100 c.c.) whilst hydrochloric acid (90 c.c. of 5*N*) was gradually added. After 12 hours the alcohol was removed by distillation, and the valinol liberated by the addition of sodium hydroxide, distilled in steam, and isolated as its hydrochloride in the manner described previously (yield, 90%) (Found: N, 10·0%).

The N-*monobenzoyl* derivative of valinol was prepared by shaking a solution of the hydrochloride (1 g.) and potassium carbonate (5 g.) in water (20 c.c.) with benzoyl chloride (1·2 g.) dissolved in ether (5 c.c.). The dried ethereal extract gave a gummy residue, which crystallised from light petroleum in colourless needles (0·6 g.), m. p. 81—82° (Found: N, 6·6. $C_{12}H_{17}O_2N$ requires N, 6·8%). The *dibenzoyl* derivative, prepared in a similar manner with an excess of benzoyl chloride (3 mols.) and aqueous sodium hydroxide, separated from aqueous methyl alcohol in long stout prisms, m. p. 114° [Found: C, 73·2; H, 6·9; N, 4·6; *M* (Rast), 334. $C_{19}H_{21}O_3N$ requires C, 73·2; H, 6·8; N, 4·5%; *M*, 311]. *Tribenzoyl* derivative: benzoyl chloride (1 c.c.) was gradually added to dibenzoylvalinol (0·15 g.) dissolved in pyridine (5 c.c.), and the mixture heated for 1 hour on the steam-bath. After 24 hours at room temperature, the mixture was boiled with water; the resulting brown resin crystallised from aqueous alcohol in small lustrous plates (0·15 g.), m. p. 135° [Found: C, 75·3; H, 6·0; N, 3·6: *M* (Rast), 428. $C_{26}H_{25}O_4N$ requires C, 75·2; H, 6·1; N, 3·4%; *M*, 415].

*Reduction of Inactive Valinol to α-Methyl*iso*butylamine.*—A solution of valinol hydrochloride (3 g.) in glacial acetic acid (12 c.c.) was saturated with hydrogen bromide at − 15° and heated in a sealed tube for 10 hours at 130—140°. The solid obtained by evaporation under reduced pressure was dissolved in alcohol, and the solution filtered from ammonium bromide. On the addition of ether, *α-bromomethyl*iso*butylamine hydrobromide* (2·7 g.) separated. It still contained a little ammonium bromide, from which it was freed by solution in warm butyl alcohol and reprecipitation with ether; slender lustrous needles, m. p. 211—212° (decomp.) with previous darkening at 203° (Found: Br, 64·4. $C_5H_{13}NBr_2$ requires Br, 64·7%).

The catalytic reduction of the preceding bromo-compound was carried out by shaking the hydrobromide (1 g.), dissolved in aqueous acetic acid (30 c.c. of 7·5%) containing sodium acetate (1 g.), with palladised charcoal (4 g. containing 10% of the metal) in hydrogen at room temperature and pressure. Reduction was complete in 80 minutes, almost the theoretical amount of hydrogen being absorbed (reduction proceeded very slowly and was incomplete if the sodium acetate was omitted). After filtration from the catalyst, the solution was made alkaline with sodium hydroxide and distilled. Neutralisation of the distillate with hydrochloric acid, followed by evaporation, gave a solid, which was crystallised from acetone, a small amount of ammonium chloride being removed by filtration; α-methyl*iso*butylamine hydrochloride separated in long lustrous needles (0·4 g.), m. p. 203° (Found: Cl, 28·8. Calc.: Cl, 28·7%). The p-*nitrobenzoyl* derivative was prepared by shaking a solution of the hydrochloride (0·25 g.) and sodium carbonate (0·45 g.) in water (10 c.c.) for 20 minutes with *p*-nitrobenzoyl chloride (0·45 g.) dissolved in benzene (10 c.c.). The residue from the dried benzene extract crystallised from *cyclo*hexane in very slender, felted needles (0·42 g.), m. p. 115° (Found: C, 61·1; H, 6·9; N, 11·8. $C_{12}H_{16}O_3N_2$ requires C, 61·0; H, 6·8; N, 11·9%).

For purposes of comparison α-methyl*iso*butylamine was prepared by the reduction of methyl *iso*propyl ketoxime, which was obtained by gradually adding aqueous potassium hydroxide (11·5 g. in 20 c.c.) to a mechanically stirred mixture of methyl *iso*propyl ketone (17 g.) and hydroxylamine hydrochloride (15 g.), dissolved in water (20 c.c.). After 2 hours, the oxime (12·5 g.) was collected in ether, distilled (b. p. 158—160°; compare Nageli, *Ber.*, 1883, **16**, 2984), and reduced in boiling amyl-alcoholic solution (300 c.c.) with sodium (25 g.). The resulting amine was isolated by distillation in steam and converted into its hydrochloride (11·5 g.) (Found: N, 11·2. Calc.: N, 11·3%), which had m. p. (and mixed m. p.) 203°, and gave a *p*-nitrobenzoyl derivative, m. p. (and mixed m. p.) 115°. The hydrochloride has been described by Trasciatti (*Gazzetta*, 1899, **29**, 92), who prepared the amine by reducing α-methyl α-cyano*iso*propyl ketoxime with sodium and alcohol.

*Resolution of Valinol.*—Freshly precipitated silver oxide (from 25 g. of the nitrate) was shaken with valinol hydrochloride (14·2 g.) dissolved in water (300 c.c.), for 20 minutes. On the addition of (+)-tartaric acid (16 g.) to the filtered solution, a slight precipitate of silver tartrate was produced, which was decomposed by passing hydrogen sulphide through the hot liquid. The gummy residue, obtained after removal of the silver sulphide and evaporation of the solution under diminished pressure, was dissolved in alcohol (100 c.c.) and kept in the ice-chest over-night.

The crop which separated was crystallised from alcohol and consisted of D(−)-*valinol hydrogen* (+)-*tartrate*, long prismatic needles (7·1 g.), m. p. 116°, containing $1H_2O$; it had $[\alpha]_{5461}^{20°}$ + 10·2°, $[\alpha]_{5780}^{20°}$ + 9·5° in water ($c$ = 4·92, $l$ = 2), this value remaining unchanged on further crystallisation (Found : loss on drying in a vacuum at 100°, 6·7; N, 5·0. $C_9H_{19}O_7N,H_2O$ requires $H_2O$, 6·6; N, 5·2%). The *hydrochloride*, prepared by addition of aqueous sodium hydroxide to the tartrate, distillation in steam, neutralisation of the distillate with hydrochloric acid, and evaporation, crystallised from acetone in small lustrous plates, m. p. 113°, and gave $[\alpha]_{5461}^{20°}$ − 16·5°, $[\alpha]_{5780}^{20°}$ − 14·7° ($l$ = 2, $c$ = 6·22) in water (Found : N, 9·9; Cl, 25·4. $C_5H_{13}ON,HCl$ requires N, 10·0; Cl, 25·4%).

The first alcoholic filtrate from the preceding tartrate was diluted with acetone (800 c.c.) and kept at room temperature for 24 hours. After decantation from the gummy solid which separated, the solution was evaporated, and the amino-alcohol isolated from the residual tartrate in the form of its hydrochloride, in the same manner as described for the enantiomorph. The crude product was freed from ammonium chloride by solution in warm butyl alcohol, followed by precipitation with ether, and crystallised from acetone. L(+)-*Valinol hydrochloride* had m. p. 112—114°, $[\alpha]_{5461}^{20°}$ + 16·4°, $[\alpha]_{5780}^{20°}$ + 14·7° ($c$ = 6·32, $l$ = 2) in water (Found : N, 9·9; Cl, 25·3%).

*Benzoyl Derivatives of* D(−)- *and* L(+)-*Valinols*.—These were prepared in the same manner as described above for the inactive compounds. The *dibenzoyl* derivative of D(−)-*valinol* crystallised from aqueous alcohol in slender needles, m. p. 117°, and had $[\alpha]_{5461}^{21°}$ + 20·2° ($c$ = 3·97, $l$ = 1) in pyridine (Found : C, 73·4; H, 6·7; N, 4·6. $C_{19}H_{21}O_3N$ requires C, 73·3; H, 6·8; N, 4·5%); and the *tribenzoyl* derivative in long needles, m. p. 119°, $[\alpha]_{5461}^{20°}$ − 133·8°, $[\alpha]_{5780}$ − 119·2° ($c$ = 4·536, $l$ = 1) in pyridine (Found : C, 75·2; H, 6·0; N, 3·6. $C_{26}H_{25}O_4N$ requires C, 75·2; H, 6·1; N, 3·4%). The *dibenzoyl* derivative of L(+)-*valinol* had m. p. 117° and gave $[\alpha]_{5461}^{20°}$ − 20·1°, $[\alpha]_{5780}^{20°}$ − 17·5° ($c$ = 4·60, $l$ = 1) in pyridine (Found : N, 4·6%); the *tribenzoyl* derivative had m. p. 119°, and $[\alpha]_{5461}^{19°}$ + 133·1° ($c$ = 4·629, $l$ = 1) in pyridine (Found : N, 3·5%).

*Conversion of* L(+)-*Valine into* L(+)-*Valinol Hydrochloride*.—*L*(−)-Formylvaline was prepared by the resolution of the inactive compound and had $[\alpha]_{5461}^{20°}$ − 19·9°, $[\alpha]_{5780}^{20°}$ − 17·7° ($c$ = 3·646, $l$ = 4) in water : Fischer (*Ber.*, 1906, **39**, 2320) gives $[\alpha]_{D}^{20°}$ − 16·9°. The formyl derivative (14·7 g.) was hydrolysed and esterified in one operation by heating with alcohol (300 c.c.) saturated with hydrogen chloride. After 2 hours, the excess of alcohol was distilled under reduced pressure, and the residual ester hydrochloride acetylated by heating on the steam-bath for 1 hour with sodium acetate (40 g.) and acetic anhydride (70 c.c.). *Ethyl* L(−)-α-*acetamido*iso-*valerate* was isolated, as described for the inactive isomeride, as a colourless viscid liquid (15 g.), b. p. 158°/21 mm., which crystallised in elongated flat plates when kept for several weeks in the ice-chest (Found : N, 7·5. $C_9H_{17}O_3N$ requires N, 7·5%). It gave in the homogeneous condition $n_D^{18°}$ 1·4517; $d_4^{18°}$ 1·028; $[R_L]_D$ 49·08 (calc., 49·24); $\alpha_{5461}^{18°}$ − 10·31°; $\alpha_{5780}^{18°}$ − 9·15°; $[\alpha]_{5461}^{18°}$ − 20·1°; $[\alpha]_{5780}^{18°}$ − 17·8° ($l$ = 0·5). A portion of the ester was hydrolysed by boiling for 2·5 hours with 10 times its weight of hydrobromic acid (12%). The resulting *L*(+)-valine was isolated in a similar manner to that described by Fischer (*loc. cit.*) for the hydrolysis of the formyl derivative, and gave $[\alpha]_{5461}^{21°}$ + 32·77°, $[\alpha]_{5780}^{21°}$ + 28·56° ($l$ = 2, $c$ = 4·754) in hydrochloric acid (20%). The value for $[\alpha]_{D}^{21°}$ + 27·1°, calculated from these results, is only slightly lower than that given by Fischer for the optically pure amino-acid, *viz.*, $[\alpha]_{D}^{20°}$ + 28·8°, under the same conditions, and hence the conversion of the *L*(−)-formyl derivative into *L*(−)-acetylvaline ethyl ester is not accompanied by any appreciable racemisation.

The reduction of the ester (22 g.) was carried out with sodium (39 g.) and ethyl alcohol (1 l.), dried by distillation from magnesium ethoxide. After being boiled for 30 minutes, the mixture was treated with water, the greater part of the alkali neutralised with hydrochloric acid, and the base steam-distilled and isolated as the hydrochloride in the usual manner. The crude product was decolorised with charcoal in hot butyl alcohol, precipitated by the addition of ether, and crystallised from acetone. The L(+)-*valinol hydrochloride* (3·7 g.) thus obtained had m. p. 116—117°, $[\alpha]_{5461}^{18°}$ + 1·2° ($c$ = 12·3, $l$ = 2) in aqueous solution (Found : N, 10·1; Cl, 25·7%); the *dibenzoyl* derivative, m. p. 114—116° (Found : C, 73·6; H, 6·9; N, 4·5%) had $[\alpha]_{5461}^{21°}$ − 1·3° ($c$ = 7·46, $l$ = 2) in pyridine, and the *tribenzoyl* derivative, m. p. 136° (Found : C, 75·4; H, 5·8; N, 3·4%), $[\alpha]_{5461}^{21°}$ + 3·3° ($c$ = 10·4, $l$ = 1) in the same solvent. The mother-liquors from which the preceding hydrochloride had been separated gave, on evaporation, a pale yellow syrup, which solidified to a brittle resin (0·4 g.) when kept for several weeks in a vacuum over sulphuric acid. This could not be crystallised and contained calcium chloride derived from the charcoal used in decolorising the crude hydrochloride. The volatile base was therefore liberated by steam distillation with aqueous sodium hydroxide and reconverted into the hydro-

chloride. On crystallisation from acetone, a small amount of *L*(+)-valinol hydrochloride (0·13 g.) was obtained having a rotation, $[\alpha]_{5461}^{17°}$ + 14·5° (*c* = 2·96, *l* = 1 in water), only slightly lower than that of the optically pure hydrochloride (m. p. and mixed m. p. 113°. Found: N, 10·2%). It showed the characteristic changes in rotation when converted into its *benzoyl* derivatives; the *dibenzoyl* derivative, m. p. 115—116°, had $[\alpha]_{5461}^{21°}$ − 18·1° (*c* = 3·15, *l* = 1) in pyridine (Found: N, 4·9%), the *tribenzoyl* derivative, m. p. 120°, $[\alpha]_{5461}^{20°}$ + 117° (*c* = 1·034, *l* = 1) in the same solvent (Found: N, 3·6%).

*Reduction of the Active Valinols to α-Methyl*iso*butylamine.*—*L*(+)-Valinol hydrochloride (0·5 g.) having $[\alpha]_{5461}^{20°}$ +16·4° was dissolved in glacial acetic acid (10 c.c.) and the solution, after saturation with hydrogen bromide at − 10°, was heated in a sealed tube at 100° for 7 hours. The crude α-bromomethyl*iso*butylamine hydrobromide obtained by evaporating the solution under reduced pressure was dissolved in water (40 c.c.) containing sodium acetate (2 g.) and reduced catalytically in the presence of palladised charcoal (2 g. containing 15% of the metal); the theoretical amount of hydrogen was absorbed in 15 minutes. The filtered solution was basified with sodium hydroxide and distilled. Neutralisation of the distillate with hydrochloric acid, followed by evaporation, yielded (+)-α-*methyl*iso*butylamine hydrochloride*, which crystallised from acetone in lustrous slender needles (0·23 g.), m. p. 205° (previous sintering at 192°), $[\alpha]_{5461}^{17°}$ + 3·5° (*c* = 6·54, *l* = 1) in water (Found: N, 11·3; Cl, 28·8. $C_5H_{13}N$,HCl requires N, 11·3; Cl, 28·7%); the p-*nitrobenzoyl* derivative, prepared as described previously for the inactive isomeride, crystallised from *cyclo*hexane in voluminous, faintly yellow, filamentous needles, m. p. 112°, $[\alpha]_{5461}^{15°}$ − 55·8°, $[\alpha]_{5780}^{15°}$ − 48·9° (*c* = 4·871, *l* = 1) in pyridine (Found: C, 61·3; H, 6·8; N, 11·9. $C_{12}H_{16}O_3N_2$ requires C, 61·0; H, 6·8; N, 11·9%).

The conversion of *D*(−)-valinol into α-bromo*iso*butylamine was carried under somewhat milder conditions than those employed for the *L*(+)-isomeride: the hydrochloride (0·5 g.) was heated with glacial acetic acid (10 c.c.), saturated with hydrogen bromide at − 8°, for only 5 hours at 70—75°, but under these conditions the replacement of the hydroxyl group was incomplete. The product from the catalytic reduction consisted of a mixture of unchanged valinol hydrochloride and (−)-α-*methyl*iso*butylamine hydrochloride*. The last-named compound was separated by crystallisation from acetone and had $[\alpha]_{5461}^{21°}$ − 3·4° (*c* = 3·55, *l* = 1) in water (Found: Cl, 28·5%); the p-*nitrobenzoyl* derivative, m. p. 112·5°, gave $[\alpha]_{5461}^{18°}$ + 55·8° (*c* = 3·664, *l* = 1) in pyridine (Found: C, 61·1; H, 6·6; N, 11·9%).

*Conversion of* L(+)-*Alanine into* (+)-β-*Hydroxy*-α-*methyl*iso*butylamine.*—Benzoylalanine was resolved by the method of Pope and Gibson (*loc. cit.*) and furnished *L*(+)-alanine, which had $[\alpha]_{5461}^{20°}$ + 11·1° (*c* = 8·87, *l* = 2) in water, and was esterified in the usual manner. *L*(+)-Alanine ethyl ester hydrochloride (10·3 g.) was added in portions, during 15 minutes, to a solution of methylmagnesium iodide prepared from methyl iodide (57 g.; 6 mols.) in ether (400 c.c.), the mixture being mechanically stirred and heated to boiling for 3 hours. After decomposition with water (150 c.c.), the ethereal solution was decanted, and volatile bases were then removed from the residual sludge of magnesium hydroxide by the addition of sodium hydroxide and distillation in steam. The crude product, obtained by neutralising the distillate with hydrochloric acid, followed by evaporation, was freed from ammonium chloride by solution in hot butyl alcohol and precipitation with ether. (+)-β-*Hydroxy*-α-*methyl*iso*butylamine hydrochloride* crystallised from acetone in long prismatic needles, m. p. 136°, and gave $[\alpha]_{5461}^{21°}$ + 5·6° (*c* = 4·14, *l* = 2) in water (Found: N, 9·9; Cl, 25·8. $C_5H_{13}ON$,HCl requires N, 10·0; Cl, 25·4%). Although the hydrochloride had a rotation somewhat lower than that of the optically pure compound obtained by the resolution of the inactive alcohol, on benzoylation in the presence of aqueous sodium hydroxide in the usual manner it yielded a N-*monobenzoyl* derivative, which crystallised from benzene–light petroleum in voluminous clusters of long needles, m. p. 116° (Found: C, 69·9; H, 8·4; N, 6·8. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·3; N, 6·8%), and had the full activity $[\alpha]_{5461}^{20°}$ − 17·2° (*c* = 5·20, *l* = 1) in pyridine and $[\alpha]_{5461}^{21°}$ + 8·1° (*c* = 4·81, *l* = 1) in alcohol.

*Preparation and Reduction of Inactive* β-*Hydroxy*-α-*methyl*iso*butylamine.*—The amino-alcohol was prepared by the interaction of inactive alanine ethyl ester hydrochloride (1 mol.) and methylmagnesium iodide (6 mols.) in ethereal solution, and isolated as the hydrochloride in a similar manner to that described above for the (+)-isomeride. The best yields (60—66%) were obtained by heating the reaction mixture for only 30 minutes after the addition of the ester hydrochloride, and also by filtering the aqueous solution from the magnesium hydroxide before the amino-alcohol was distilled in steam (if the magnesium hydroxide is not removed, the crude hydrochloride contains a considerable amount of ammonium chloride). β-*Hydroxy*-α-*methyl*iso*butylamine hydrochloride* crystallised from aqueous acetone in small hard prisms containing

water of crystallisation (Found : loss on drying at 80° in a vacuum, 11·5. Found for the dried material : N, 8·7; Cl, 25·5. $C_5H_{13}ON,HCl,H_2O$ requires loss 11·4%. $C_5H_{13}ON,HCl$ requires N, 8·9; Cl, 25·4%) : the anhydrous salt had m. p. 117°. The N-*monobenzoyl* derivative crystallised in long slender needles, m. p. 96° (Found : C, 69·7; H, 8·6; N, 6·6. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·3; N, 6·7%).

The reduction of β-hydroxy-α-methyl*iso*butylamine was effected by treating the hydrochloride with phosphorus pentachloride in chloroform solution, followed by catalytic reduction in a similar manner to that described below in the case of the active isomerides; the resulting α-methyl*iso*butylamine hydrochloride was identical with that obtained by the reduction of valinol (m. p. and mixed m. p. 203°) (Found : N, 11·5; Cl, 28·6%).

*Resolution of* β-*Hydroxy-*α-*methyl*iso*butylamine.*—(+)-Tartaric acid (13 g.) was dissolved in an aqueous solution (1300 c.c.) of the inactive amino-alcohol, prepared by distilling the hydrochloride (12 g.) with a slight excess of sodium hydroxide. The gummy residue obtained by evaporating the solution under reduced pressure was dissolved in alcohol (150 c.c.) and filtered from a small amount of ammonium hydrogen tartrate which separated. On the addition of acetone (400 c.c.), the solution deposited (over-night in the ice-chest) (+)-β-*hydroxy-*α-*methyl*iso*butylamine* (+)-*tartrate*, which was obtained in a pure condition by crystallisation from alcohol (200 c.c. of 96%). It formed long hard prisms (8 g.), containing water of crystallisation, which was removed by heating at 50° in a vacuum. The anhydrous salt had m. p. 166—167° (sintering at 161°), $[\alpha]_{5461}^{18°}$ + 22·2° ($c$ = 5·15, $l$ = 2) in water (Found : C, 43·0; H, 7·7; N, 5·6. $C_9H_{19}O_7N$ requires C, 42·7; H, 7·6; N, 5·5%). The *hydrochloride* was prepared from the tartrate by steam distillation with aqueous sodium hydroxide, followed by neutralisation and evaporation of the distillate. It had m. p. 140°, $[\alpha]_{5461}^{19°}$ + 6·1°, $[\alpha]_{5780}^{19°}$ + 5·4° ($c$ = 4·21, $l$ = 2) in water (Found : N, 10·3; Cl, 25·4%). The N-*monobenzoyl* derivative, m. p. 116°, gave $[\alpha]_{5461}^{21°}$ + 8·3° ($c$ = 5·01, $l$ = 1) in alcohol and $[\alpha]_{5461}^{21°}$ − 16·8° ($c$ = 4·96, $l$ = 1) in pyridine (Found : C, 69·7; H, 8·3; N, 6·7%).

(−)-β-*Hydroxy-*α-*methyl*iso*butylamine hydrogen* (+)-*tartrate* was isolated from the first alcoholic mother-liquor from the crystallisation of the preceding tartrate by addition of acetone (800 c.c.), filtration from a further small crop which separated over-night, and concentration of the solution to 250 c.c. It formed voluminous aggregates of slender felted needles, which on recrystallisation from acetone–alcohol had $[\alpha]_{5461}^{16°}$ + 15·6 ($c$ = 4·84, $l$ = 2) in water (Found : loss on drying at 100° in a vacuum, 6·6; N, 5·2. $C_9H_9O_7N,H_2O$ requires loss, 6·6; N, 5·2%) : the anhydrous salt had m. p. 122° (decomp.). Although the rotation remained unaltered on further crystallisation, the tartrate was not quite optically pure, since the *hydrochloride*, m. p. 138—139° (Found : Cl, 25·4%), prepared from it by distillation in the usual manner, had, after several crystallisations from alcohol–di*iso*propyl ether, a somewhat lower rotation, $[\alpha]_{5461}^{20°}$ − 5·5° ($c$ = 5·06, $l$ = 2), in water than that of the (+)-isomeride. The *N*-monobenzoyl derivative crystallised from benzene–light petroleum in long needles, m. p. 116·5°, and had $[\alpha]_{5461}^{21°}$ + 17·7°, $[\alpha]_{6780}^{21°}$ + 15·2° ($c$ = 4·99, $l$ = 1) in pyridine, and $[\alpha]_{5461}^{19°}$ − 8·0° ($c$ = 4·85, $l$ = 1) in alcohol.

*Reduction of* (+)- *and* (−)-β-*Hydroxy-*α-*methyl*iso*butylamines.*—Phosphorus pentachloride (3·5 g.) was added in portions during 10 minutes to the (+)-amino-alcohol hydrochloride (2·5 g. having $[\alpha]_{5461}^{19°}$ + 6·1°), suspended in chloroform (25 c.c.), and the solution then heated under reflux for a further 10 minutes. After removal of the chloroform and phosphorus oxychloride under reduced pressure, the crystalline residue was dissolved in methyl alcohol (20 c.c.) and catalytically reduced at the ordinary temperature and pressure in the presence of palladised charcoal (2 g. containing 30% of the metal). After filtration from the catalyst, the solution was basified with sodium hydroxide, distilled, and the (−)-α-methyl*iso*butylamine isolated from the distillate as the *hydrochloride* (1·2 g.), which after crystallisation from acetone had m. p. 201—204° (sintering at 195°), $[\alpha]_{5461}^{20°}$ − 1·65 ($c$ = 4·96, $l$ = 2) in water (Found : N, 11·3; Cl, 28·5), and gave a p-*nitrobenzoyl* derivative, m. p. 107—108° (Found : C, 60·7; H, 6·7; N, 11·6%), having a lower rotation, $[\alpha]_{5461}^{17°}$ + 44·1 ($c$ = 4·817, $l$ = 1), in pyridine than that of the *p*-nitrobenzoyl derivatives obtained by the reduction of the active valinols. In a second experiment in which the (+)-amino-alcohol hydrochloride (2·8 g.) was gradually added, with cooling, to the pentachloride (4·2 g.) in chloroform (15 c.c.), and the mixture then shaken for 30 minutes at room temperature, the intermediate product was isolated by evaporating the solution under diminished pressure, dissolving the residue in alcohol, and precipitating the product with ether. From the analytical results, and also from its behaviour on reduction, it appears to consist of a mixture of the chloro-amine (XII) and the unsaturated amine (XIII). After catalytic reduction in dilute hydrochloric solution, it gave (−)-α-methyl*iso*butylamine hydrochloride, having $[\alpha]_{5461}^{20°}$ − 2·1° ($c$ = 4·72, $l$ = 2) in water : this yielded a p-*nitrobenzoyl*

derivative, the rotation of which was raised from $[\alpha]_{5461}^{20°}$ + 47·4° to + 53·8° ($c$ = 4·72, $l$ = 2, in pyridine) after four crystallisations from benzene–light petroleum.

The reduction of (—)-β-hydroxy-α-methyl*iso*butylamine hydrochloride, having $[\alpha]_{5461}^{20°}$ — 4·6°, was carried out in a similar manner : the resulting (+)-α-*methyl*iso*butylamine hydrochloride* had $[\alpha]_{5461}^{17°}$ + 2·4° ($c$ = 5·18, $l$ = 1) in water (Found : C, 48·6; H, 11·4. $C_5H_{13}N$,HCl requires C, 48·6; H, 11·4%), and gave a p-*nitrobenzoyl* derivative, m. p. 112°, $[\alpha]_{5461}^{17°}$ — 43·5° ($c$ = 4·835, $l$ = 1) in pyridine (Found : C, 61·1; H, 7·1; N, 11·9%).

*Experiments with Benzoylalanine.*—The methyl ester of inactive benzoylalanine, which has been prepared from the acid chloride by Max (*Annalen*, 1909, **369**, 276), was obtained in excellent yield by saturating a solution of the acid (20 g.) in methyl alcohol (200 c.c.) with hydrogen chloride and allowing the solution to remain for 24 hours at the ordinary temperature. After removal of the excess of alcohol under reduced pressure, the residue was triturated with cold aqueous sodium carbonate and crystallised from aqueous alcohol; slender needles m. p. 81°. When heated for 8 hours with methylmagnesium iodide (6 mols.) in ethereal solution, it furnished the *N*-benzoyl derivative of β-hydroxy-α-methyl*iso*butylamine (m. p. and mixed m. p. 96°. Found : N, 6·6%) in 80% yield. Hydrolysis, accompanied by elimination of ammonia, occurred when the benzoyl derivative was heated under reflux with alcoholic potassium hydroxide (60 c.c. of 0·5*N*) for 14 hours : the amino-alcohol was isolated as the hydrochloride in the usual manner, the yield being only 8%. Attempts to convert the amino-alcohol into *N*-benzoyl-α-methyl*iso*butylamine under various conditions, by treatment with hydrobromic acid, thionyl chloride, and phosphorus pentachloride, followed by reduction both catalytically and otherwise, were unsuccessful.

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