LXIV.—*The Resolution of* dl-*Alanine and the Formation of* trans-2 : 5-*Dimethylpiperazine.*

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THE α-2 : 5-dimethylpiperazine of Stoehr (*J. pr. Chem.*, 1893, **47**, 494; 1897, **55**, 49) was identified by Pope and Read (J., 1912, **101**, 2327; 1914, **105**, 219) as the *trans*-isomeride; the same compound was obtained by Hoyer (*Z. physiol. Chem.*, 1902, **34**, 347) by the reduction of lactimide, $NH<^{CO\cdot CHMe}_{CHMe\cdot CO}>NH$. The latter compound would therefore appear to be internally compensated or *trans*-3 : 6-diketo-2 : 5-dimethylpiperazine produced by anhydride formation from a molecule each of *d*- and *l*-alanine; this conclusion, as will be shown later, is not necessarily correct. The two optically active alanines, on the other hand, yield optically active anhydrides (E. Fischer, *Ber.*, 1906, **39**, 453) which are necessarily the *d*- and *l-cis*-3 : 6-diketo-2 : 5-dimethylpiperazines. It might be expected that on reduction the latter substances would yield the *d*- and *l-cis*-2 : 5-dimethylpiperazines; the racemic compound of these two isomerides should be represented by the β-2 : 5-dimethylpiperazine of Stoehr (*loc. cit.*), but Pope and Read were unable to separate such a compound from the material which they examined.

It thus seemed desirable to reduce the anhydride of one of the optically active alanine anhydrides or *cis*-3 : 6-diketo-2 : 5-dimethylpiperazines for the purpose of isolating and further characterising the *d*- and *l-cis*-2 : 5-dimethylpiperazines which were presumably associated in Stoehr's β-compound. A certain quantity of *d*-alanine was prepared by the hydrolysis of silk as described by Fischer (*Ber.*, 1906, **39**, 462), but the process, although satisfactory, is tedious. The preparation was hastened by preparing *dl*-alanine from acetaldehyde, potassium cyanide and ammonium chloride by the method of Zelinsky and Stadnikov (*Ber.*, 1908, **41**, 2061) and resolving this into its optically active components.

Fischer (*Ber.*, 1899, **32**, 2459) resolved benzoyl-*dl*-alanine by crystallisation with cinchonine, and Gibson and Pope (J., 1912, **101**, 939) improved this method by the alternate use of strychnine and brucine; the hydrolysis to *d*- and *l*-alanine proceeds, however, only with difficulty. Gibson and Simonsen (J., 1915, **107**, 798) resolved *dl-p*-toluenesulphonylalanine by crystallisation with strychnine and brucine, and Colombano and Sanna (*Atti R. Accad. Lincei*, 1913, **22**, ii, 292) resolved *dl*-alanine by crystallising its ethyl ester with *d*-bromocamphorsulphonic acid.

None of these methods proved satisfactory for preparing the

optically active alanines in quantity and we therefore devised a new one. It was found that *d*-hydroxymethylenecamphor and *d*-chloromethylenecamphor do not condense with *dl*-alanine, but that condensation occurs readily with the ethyl ester of alanine; the method of resolution by means of *d*-hydroxymethylenecamphor described by Pope and Read (J., 1914, **105**, 219) is therefore applicable and the condensation products can be hydrolysed by concentrated hydrochloric acid, yielding the optically active alanines. This method of resolving *dl*-alanine seems to be the most convenient yet described; by its aid *l*-alanine has been separated in quantity from the racemic compound.

Several methods for converting the *d*- and *l*-alanines into the *d*- and *l-cis*-3 : 6-diketo-2 : 5-dimethylpiperazines, or the optically active lactimides, were studied. Hoyer's method of heating alanine in dry hydrogen chloride at 180—200°, boiling the product with lead hydroxide, and removing the metal by hydrogen sulphide gave poor yields. One method described by Fischer (*Ber.*, 1906, **39**, 467), in which the ethyl ester of alanylalanine, prepared from alanine ethyl ester and alanyl chloride, is treated with gaseous ammonia, also gives poor yields. Fischer's second method (*Ber.*, 1906, **39**, 543), in which the ethyl ester of alanine is preserved for several weeks, is satisfactory and gives a yield of about 70%.

When the optically active lactimides, which have necessarily the *cis*-configuration, were reduced with sodium and alcohol, the chief product, and indeed the only one which could be isolated, was the potentially optically inactive *trans*-2 : 5-dimethylpiperazine identified by Pope and Read. It thus seems clear that the lactimide undergoes enolisation during reduction in accordance with the scheme

$$\mathrm{NH}\!<\!\begin{matrix}\mathrm{CO\cdot CHMe}\\ \mathrm{CHMe\cdot CO}\end{matrix}\!>\!\mathrm{NH} \longrightarrow \mathrm{NH}\!<\!\begin{matrix}\mathrm{C(OH){:}CMe}\\ \mathrm{CMe{:}C(OH)}\end{matrix}\!>\!\mathrm{NH}$$

$$\longrightarrow \mathrm{NH}\!<\!\begin{matrix}\mathrm{CH_2\cdot CHMe}\\ \mathrm{CHMe\cdot CH_2}\end{matrix}\!>\!\mathrm{NH},$$

and that the original *cis*-compound thus becomes converted into the *trans*-2 : 5-dimethylpiperazine accompanied by little, if any, of the *cis*-isomeride. No evidence is thus obtainable as to whether inactive lactimide is the racemic or *cis*-compound or the internally compensated or *trans*-compound.

EXPERIMENTAL.

dl-Alanine, prepared by Zelinsky and Stadinov's method, was converted into its ethyl ester, which was then heated for 2 hours on the water-bath with an equimolecular quantity of *d*-hydroxymethylenecamphor. On pouring into water, extracting with light

petroleum, and evaporating the petroleum solution after drying with potassium carbonate, an oil was obtained which readily crystallised; the crystalline product was repeatedly crystallised from light petroleum until its melting point became constant at 108—109°. The substance thus obtained in long, white needles is the d-*methylene-camphor*-l-*alanine ethyl* ester, $C_8H_{14}<\begin{matrix}C{:}CH\cdot NH\cdot CHMe\cdot CO_2Et\\ CO\end{matrix}$ (Found : C, 68·9; H, 8·9. $C_{16}H_{25}O_3N$ requires C, 68·8; H, 9·0%). The substance is so soluble in most organic solvents that it can only be conveniently crystallised from light petroleum. 0·1008 Gram, made up to 20 c.c. with absolute alcohol, gave $\alpha_{\text{Hg green}} = +2{\cdot}58°$ in a 2-dcm. tube at 20°; whence $[\alpha]_{\text{Hg green}} = +256°$.

This compound, when treated by the bromine method of Pope and Read, yielded only resinous products from which alanine could not be separated; it is, however, hydrolysed by distillation in steam after admixture with concentrated hydrochloric acid. Hydroxymethylenecamphor distils away and *l*-alanine hydrochloride remains behind; the hydrochloric acid is removed with the aid of lead hydroxide, the excess of the latter by hydrogen sulphide, and the *l*-alanine then separated by crystallisation from the residual aqueous solution. 1·8761 Gram, made up to 20 c.c. with 1·25*N*-hydrochloric acid solution, gave $\alpha_{\text{Hg green}} = -3{\cdot}22°$ in a 2-dcm. tube at 20°; whence $[\alpha]_{\text{Hg green}} = -12{\cdot}2°$; this value is numerically identical with that given by *d*-alanine prepared from silk, but is, of course, of opposite sign. This simple type of method will be further studied in its applications to the resolution of racemic aminocarboxylic acids.

Reduction of l-*Lactimide.*—*l*-Alanine was converted into its ethyl ester and preserved for several weeks until solidification had apparently become complete; after crystallisation from alcohol a 70% yield of *l*-lactimide was obtained. The product melted at 272° and showed $[\alpha]_D^{20^\circ} = +29{\cdot}1°$ in a 2% alcoholic solution. The *l*-lactimide (6 g.) was treated with absolute alcohol (300 c.c.), and sodium (32 g.) gradually added with constant shaking. After removal of the alcohol, the reduction product was benzoylated; the only separable product was the optically inactive dibenzoyl-*trans*-2 : 5-dimethylpiperazine (0·8 g.) of Pope and Read. The identity of the product was confirmed by mixed melting-point determinations with a sample of the latter substance; each, and the mixtures, melted at 227—228°.

No better yields were obtained by reducing the *l*-lactimide in amyl-alcoholic solution and it is noteworthy that Gaurilov (*Bull. Soc. chim.*, 1925, **37**, 1651) obtained only a 15% yield of piperazine by this mode of reducing 2 : 5-diketopiperazine. The lactimide

could not be reduced by colloidal palladium or platinum, by calcium or calcium hydride and alcohol, or by aluminium amalgam in aqueous-alcoholic solution.

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