CXXXIX.—*Preparation and Resolution of* dl-cis-2 : 5-*Dimethylpiperazine.*

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ON reducing 2 : 5-dimethylpyrazine, $N\leqslant\begin{matrix}CMe{:}CH\\CH{\cdot}CMe\end{matrix}\geqslant N$, with sodium and alcohol, Stoehr (*J. pr. Chem.*, 1893, **47**, 494; 1897, **55**, 49) obtained two products which he described as the α- and β-2 : 5-

dimethylpiperazines; the α-compound constituted the main product and only small quantities of the β-isomeride were formed. Pope and Read identified Stoehr's α-2 : 5-dimethylpiperazine as the *trans*-isomeride (J., 1912, **101**, 2325), but did not separate the β-compound from the reduction product of the pyrazine; they secured, however, a quantity of residues left during the manufacture of lycetol, the tartrate of the α-base, and separated therefrom a substance which corresponded closely in properties with Stoehr's β-base. The study of the latter product (J., 1914, **105**, 219) conclusively proved it to be the *cis*-2 : 6-dimethylpiperazine, which Pope and Read hence supposed to be Stoehr's β-2 : 5-dimethylpiperazine. This supposition is now shown to be erroneous.

The confusion arose from the close similarity in physical properties between the *dl-cis*-2 : 5-dimethylpiperazine, m. p. 114—115°, and the *cis*-2 : 6-dimethylpiperazine, m. p. 110—111°; the 1 : 4-dibenzoyl derivatives melt at 145—146° and 147—148°, respectively, but mixtures of the two melt at about 120—130°.

The present paper describes the repetition of Stoehr's preparation of his β-2 : 5-dimethylpiperazine and the resolution of this compound into its *d*- and *l*-components. The resolution was effected by Pope and Read's method of condensation with *d*-hydroxymethylenecamphor, and Stoehr's β-compound is thus proved to be the *dl-cis*-2 : 5-dimethylpiperazine.

EXPERIMENTAL.

*iso*Nitrosoacetone (270 g.) was prepared from ethyl acetoacetate (700 g.) by the method of Ceresole (*Ber.*, 1882, **15**, 1326) and then reduced by the method of Gabriel and Pinkus (*Ber.*, 1893, **26**, 2206) to 2 : 5-dimethylpyrazine, each 50 g. yielding about 12 g. of the base. The 2 : 5-dimethylpyrazine (10 g.) was then reduced as described by Stoehr and the mixture of α- and β-dimethylpiperazine hydrochlorides (about 8 g.) isolated; the operation was repeated until about 160 g. of the salt had been obtained. The dried and powdered hydrochloride was repeatedly extracted with boiling absolute alcohol, in which the α- or *trans*-compound is very sparingly soluble; the alcoholic extract on evaporation yielded about 8 g. of crude *dl-cis*-dimethylpiperazine. The reduction product of the pyrazine thus contains about 95% of the *trans*-compound and only about 5% of the *cis*-isomeride.

dl-1 : 4-*Dibenzoyl*-cis-2 : 5-*dimethylpiperazine*.—This compound, prepared by the Schotten-Baumann reaction from the hydrochloride, crystallises from alcohol in colourless prisms, m. p. 145—146°; Stoehr gives 147—148° for his β-compound. Analysis failed to reveal the presence of a molecule of water of crystallis-

ation indicated by Stoehr (Found: C, 74·4; H, 6·8; N, 8·7. Calc. for $C_{20}H_{22}O_2N_2$, C, 74·5; H, 6·8; N, 8·7%); the identity in composition between the α- and β-compounds may be associated with the close similarity in crystalline form previously noted (J., 1914, **105**, 223). As remarked above, the compound depresses the melting point, namely, 145—146°, of Pope and Read's 1 : 4-dibenzoyl-*cis*-2 : 6-dimethylpiperazine.

The p-*Toluenesulphonyl Derivatives.*—In view of the similarity in melting point between the *cis*-2 : 5- and *cis*-2 : 6-isomerides just noted, it was thought desirable to prepare other acidic derivatives. The 1 : 4-*di*-p-*toluenesulphonyldimethylpiperazines* were made by warming the hydrochlorides of the base with *p*-toluenesulphonyl chloride and caustic soda solution.

1 : 4-*Di*-p-*toluenesulphonyl*-cis-2 : 5-*dimethylpiperazine* crystallises from alcohol in minute, colourless prisms, m. p. 146—147°, the melting point being the same as that of the corresponding benzoyl derivative (Found: C, 56·9; H, 6·15. $C_{20}H_{16}O_4N_2S_2$ requires C, 56·8; H, 6·2%).

1 : 4-*Di*-p-*toluenesulphonyl*-trans-2 : 5-*dimethylpiperazine* is almost insoluble in the usual solvents and after washing with alcohol melted at 225°; it is remarkable that this melting point is also identical with that of the benzoyl derivative (Found: C, 56·9; H, 6·2%).

1 : 4-Di-*p*-toluenesulphonyl-*cis*-2 : 6-dimethylpiperazine is very soluble in alcohol and acetone, but less soluble in light petroleum; it crystallises from the latter, to which a little alcohol has been added, in needles, m. p. 89—90° (Found: C, 56·8; H, 6·2%). The marked difference in physical properties between these three isomerides is further confirmation of the separate identity of the three parent bases.

Resolution of cis-2 : 5-*Dimethylpiperazine.*—The hydrochloride of the racemic base was boiled in alcoholic solution with caustic potash (2 mols.) and *d*-hydroxymethylenecamphor (2 mols.) for ½ hour; the gummy deposit obtained on pouring into water crystallised on treatment with light petroleum and then melted at 167—170°. On fractional crystallisation from light petroleum containing a little alcohol d-cis-2 : 5-*dimethylpiperazine*-d-*bismethylenecamphor*, $C_8H_{14}<\begin{matrix}C{:}CH\cdot N{-}CH_2{-}\!-\!CHMe\ OC\\ |\qquad\qquad\qquad\qquad\quad|\\ CO\quad CHMe{-}CH_2\cdot N\cdot CH{=}\!=\!C\end{matrix}>C_8H_{14}$, was obtained in colourless needles, m. p. 210°. 0·1016 G. made up to 20 c.c. with alcohol gave α_{5461} + 7·6° in a 2-dcm. tube; whence $[\alpha]^{20°}_{5461}$ = + 747°. The more soluble fraction after several crystallisations melted at 176—177°; this product represents l-cis-2 : 5-*dimethylpiperazine*-d-*bismethylenecamphor* which still contained some stereo-

isomeride and gave $[\alpha]_{5461}^{20°}$ + 635° in alcoholic solution (Found : C, 76·8; H, 9·6. $C_{28}H_{42}O_2N_2$ requires C, 76·7; H, 9·6%).

The *d*- and *l*-dimethylpiperazines were separated from the above derivatives by treatment with bromine by the method of Read and Pope and isolated as the hydrobromides; neither salt showed measurable rotatory power in alcoholic solution. In many analogous cases, however, the specific rotation of a base is a small fraction of that of the benzoyl derivative; the *d*- and *l*-hydrobromides were therefore benzoylated in the hope that optical activity might be detected.

d- *and* l-1 : 4-*Dibenzoyl*-cis-2 : 5-*dimethylpiperazine*.—The *d*-isomeride was obtained pure by crystallisation from acetone and forms colourless prisms, m. p. 164—165° (Found : C, 75·1; H, 6·7. $C_{20}H_{22}O_2N_2$ requires C, 74·5; H, 6·8%). 0·0985 G. made up to 20 c.c. with alcohol gave α_{5461} + 2·44° in a 2-dcm. tube; whence $[\alpha]_{5461}$ = + 247°.

The *l*-isomeride was not separable in a pure state from the material available, and the best specimen obtained melted at 140—142° and gave $[\alpha]_{5461}$ — 146° in alcoholic solution.

In order to make sure that these compounds had not been confused with the benzoyl ester of hydroxymethylenecamphor, which has nearly the same carbon and hydrogen content, the latter substance was prepared; it melts at 119—120° (Bishop, Claisen, and Sinclair, *Annalen*, 1894, **281**, 374). 0·0820 G. made up to 20 c.c. with alcohol gave α_{5461} + 1·44° in a 2-dcm. tube, whence $[\alpha]_{5461}^{20°}$ = + 175°. Further to ensure that no confusion has occurred, the *trans*-2 : 5-dimethylpiperazine-*d*-methylenecamphor of Pope and Read (J., 1912, **101**, 2334) was again recovered from the various fractions and converted into its benzoyl derivative. In no case was an optically active benzoyl derivative obtained.

Summary.

Stoehr's β-2 : 5-dimethylpiperazine has been identified as the *cis*-isomeride by resolving it into optically active components. It is not identical with the *cis*-2 : 6-dimethylpiperazine of Pope and Read, although the similarity in physical properties between the two bases and their corresponding derivatives is such as to suggest identity.

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