171. *The Epimeric* (±)-1 : 3-*Diaminocyclohexanes.*

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cis- and *trans*-1 : 3-Diamino*cyclo*hexane have been prepared by Schmidt reactions on the corresponding dicarboxylic acids. Contrary to the claim of Skita and Rössler [1] no inversion of configuration occurs in the Curtius reaction of the *trans*-dicarboxylic acid. Evidence in support of the configurations is given.

Merling [2] prepared a 1 : 3-diamino*cyclo*hexane, b. p. 193°/752 mm., d^{15} 0·956 (diacetyl derivative, m. p. 256°), by sodium–alcohol reduction of dihydroresorcinol dioxime, and a similar product is described by Kötz and Grethe.[3] The methods of preparation used by these and other authors are known to give epimeric mixtures, and in an attempt to distinguish the geometrical isomers Skita and Rössler [1] applied the Curtius reaction to the epimeric methyl hexahydro*iso*phthalates. Two dihydrazides were obtained but unexpectedly [4] each apparently yielded the same diethylurethane and diamine, b. p. 198° (picrate, m. p. 265°); the authors suggested that a Walden inversion had occurred during the conversion of one isomeric diazide (neither was isolated) into the diurethane. This diamine was identified with that of Merling,[2] and an attempt to prepare the other epimer by hydrogenation of *m*-nitroaniline afforded a picrate, m. p. 254°, from which a diamine, b. p. 202°, tentatively assigned the *trans*-configuration, was obtained.

No inversion was detected in the preparation of the epimeric 3-amino*cyclo*hexanecarboxylic acid by the Schmidt reaction,[5] and we now report the production of two discrete diamines in approx. 45% yield, isolated by an improved technique, when an excess of hydrazoic acid is allowed to remain in prolonged contact with the hexahydro*iso*phthalic acids. The characteristics of the epimeric 1 : 3-diamino*cyclo*hexanes so obtained from the corresponding hexahydro*iso*phthalic acids are given in the Table.

	cis	*trans*
B. p.	197—198°/760 mm. 46—48°/0·1 mm.	197—198°/760 mm. 46—48°/0·1 mm.
d_4^{20}	0·9515	0·9652
n_D^{20}	1·4911	1·4957
Diacetyl derivative, m. p.	263°	220—221°
Di-*p*-nitrobenzoyl derivative, m. p.	329—330°	240—241°
Dipicrate, m. p. (corr.)	275°	269°
Dihydrochloride, m. p.	>360°	330°

In view of these results it appeared highly improbable that inversion should have occurred under the milder conditions of the Curtius reaction. We therefore repeated the Curtius reaction, following as closely as possible the conditions specified by Skita and Rössler.[1] The dihydrazides closely resembled the two different entities described by these authors. The diazides were converted directly into their respective diethyl- and dibenzylurethanes. The diethylurethanes both had m. p. 146—147°, but on admixture this was depressed by some 30°, thus proving that although very similar they are different compounds. Moreover, the dibenzylurethanes proved to be quite different. To avoid possible inversion during hydrolysis of the diethylurethanes, the diamines were prepared by hydrogenolysis of the dibenzylurethanes, easily and in good yield by the use of W7 Raney nickel catalyst, and were identified as the epimers expected if no inversion had taken place. On hydrolysis of the *trans*-diethylurethane as described by Skita and Rössler, only the *trans*-diamine was obtained.

We therefore conclude that the Curtius reaction proceeds with the same stereochemical specificity as the Schmidt reaction in this case. The identity of the b. p.s of the diamines and of the m. p.s of the diethylurethanes is misleading. Moreover, the picrates could

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[1] Skita and Rössler, *Ber.*, 1939, **72**, 461.

[2] Merling, *Annalen*, 1894, **278**, 36.

[3] *J. prakt. Chem.*, 1909, **80**, 503.

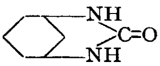
[4] Cf. Wallis and Lane, "Organic Reactions," Wiley, 1946, Vol. III, p. 272.

[5] Hewgill and Jefferies, *J.*, 1955, 2767.

be satisfactorily crystallised only from water : the use of aqueous ethanol failed to reveal the differences in crystalline form and gave a *cis*-picrate with practically the same m. p. as the *trans*-epimer.

To obtain some idea of the relative stability of the epimeric diamines and, if possible, to render them more accessible other methods of preparation were examined. The platinum-catalysed reduction of dihydroresorcinol dioxime, though very slow, gave a good yield of an epimeric mixture of diamines. Both the picrates and the acetyl derivatives of this mixture were easily separated into the pure epimers by fractional crystallisation, giving a *cis* : *trans* ratio of 6 : 1 and 8 : 1 respectively. Although Skita and Berendt,[6] and Skita and Rössler,[1] prepared the diamine by platinum-catalysed reduction of *m*-nitroaniline, this was found by us to yield mainly polymers, which were not identified. However, platinum-catalysed hydrogenation of *NN'*-diacetyl-*m*-phenylenediamine afforded a mixture of the epimeric hexahydro-compounds in fair yield.

Further evidence for the configurations assigned involved attempts to prepare the cyclic urea, 2 : 4-diaza*bicyclo*[3 : 3 : 1]nonan-3-one (I) which was finally isolated in small yield from the prolonged reaction between the *cis*-diamine and diethyl carbonate at a high temperature and pressure. Under the same conditions the *trans*-diamine afforded only polymeric material. It is apparent that ring closure of *cis*-1 : 3-disubstituted *cyclo*hexanes proceeds readily only at elevated temperatures, a condition conducive to the formation of the energetically less favourable diaxial conformation. This conjecture receives additional support from the failure of the *cis*-diamine to condense with carbonyl chloride under standard conditions. Reaction with ethyl chloroformate afforded the diethylurethane. It is known that phthalic anhydride reacts with hydrazoic acid to give some benziminazolone,[7] but hexahydro*iso*phthalic anhydride with hydrazoic acid gave only a mixture of the *cis*-diamine and amino-acid.



(I)

It will be seen from the Table that the values of the physical constants (except the b. p.) of the *trans*-diamine are higher than those of the *cis*-epimer. In addition, all the derivatives of the *cis*-diamine, except the diethylurethane, have higher m. p.s and lower solubilities than their corresponding *trans*-epimers. These results are in accord with the reversal of the Auwers–Skita rule for 1 : 3-disubstituted *cyclo*hexanes ;[8] although this reversal indicates the diequatorial structure for the *cis*-diamine, some degree of stabilisation of the diaxial structure would result from intramolecular hydrogen bonding, which has been shown to exist in *cis*-*cyclo*hexane-1 : 3-diol.[9] The existence of the diaxial form in aqueous solution appears to be precluded by the similarity of the pK_{a_1} values for the *cis*- (10·36) and *trans*-diamine (10·30). The somewhat larger difference between the pK_{a_2} values (*cis* 8·54, *trans* 8·29) is in agreement with the greater separation, and therefore stabilisation, of the charges possible for the diprotonated amine in the diequatorial conformation.

EXPERIMENTAL

cis- and *trans*-Hexahydro*iso*phthalic acid, and solutions of hydrazoic acid, were prepared as described previously.[5]

cis-1 : 3-*Diamino*cyclo*hexane*.—A 7·7% solution of hydrazoic acid in chloroform (130 ml.) was added dropwise (3 hr.) to a stirred mixture, at 40°, of chloroform (100 ml.) and a solution of *cis*-hexahydro*iso*phthalic acid (15 g.) in concentrated sulphuric acid (45 ml.). Stirring was continued at 50° for a further 4 hr., evolution of nitrogen having then practically ceased. Evaporation of the chloroform layer left no residue. After dilution with iced water, and cooling, the acid layer was basified with aqueous sodium hydroxide and continuously extracted with two successive portions of chloroform, carbon dioxide being excluded. Removal of the chloroform from the dried (K_2CO_3) extracts through a small fractionating column left a residue from which the volatile material (4·5 g.) was distilled under reduced pressure. Redistillation at atmospheric

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[6] Skita and Berendt, *Ber.*, 1919, **52**, 1533.

[7] Caronna, *Gazzetta*, 1941, **71**, 189.

[8] Von Auwers and Schmelzer, *Sitzungsber. Ges. Beförd Naturwiss. Marburg*, 1927, **62**, 113 ; Pitzer *et al.*, *J. Amer. Chem. Soc.*, **1947**, **69**, 977, 2488 ; Rossini and Spitzer, *Science*, 1947, **105**, 647.

[9] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492.

pressure afforded a fraction, b. p. 197—198°, and a final distillation gave the diamine (3·9 g.), b. p. 46—48°/0·1 mm., d_4^{20} 0·9515, n_D^{20} 1·4911, $[R_L]_D$ 34·73 (calc. for 1 : 3-diamino*cyclo*hexane, 34·55).

The method employed by Merling [2] gave the diacetyl derivative, needles, m. p. 263° (Found : C, 61·0; H, 9·3; N, 14·4. Calc. for $C_{10}H_{18}O_2N_2$: C, 60·6; H, 9·2; N, 14·1%). Addition of the diamine to *p*-nitrobenzoyl chloride in pyridine gave a very insoluble product, which was lixiviated with successive portions of water, dilute hydrochloric acid, dilute aqueous sodium hydroxide, water, and chloroform. Recrystallisation from acetone gave the *di*-p-*nitrobenzoyl derivative* as needles, m. p. 329—330° (Found : C, 58·3; H, 4·8; N, 13·5. $C_{20}H_{20}O_6N_4$ requires C, 58·3; H, 4·9; N, 13·6%). Addition of the diamine to hot, aqueous picric acid, and recrystallisation of the product from water, gave the *dipicrate monohydrate* as yellow plates, m. p. (corr.) 275° (decomp.) (Found : C, 36·8; H, 3·8; N, 18·9. $C_{18}H_{20}O_{14}N_8,H_2O$ requires C, 36·7; H, 3·8; N, 19·0%), unaffected during 3 hr. at 100°/0·01 mm. The *dihydrochloride*, prepared in chloroform, was obtained after recrystallisation from 95% ethanol as plates, m. p. >360° (Found : C, 38·8; H, 8·6; Cl, 38·1. $C_6H_{16}N_2Cl_2$ requires C, 38·5; H, 8·6; Cl, 37·9%).

trans-1 : 3-*Diamino*cyclo*hexane*.—The method employed for the *cis*-epimer, applied to *trans*-hexahydro*iso*phthalic acid, gave a similar yield of *trans*-1 : 3-diamino*cyclo*hexane, b. p. 197—198°/760 mm., 46—48°/0·1 mm., d_4^{20} 0·9652, n_D^{20} 1·4957, $[R_L]_D$ 34·51.

The *diacetyl derivative*, obtained only after removal of the acetic anhydride, crystallised from acetone as prisms, m. p. 220—221° (Found : C, 61·0; H, 9·1; N, 14·2%). The *di*-p-*nitrobenzoyl derivative*, worked up in the usual manner, was purified by chromatography on alumina. Elution with benzene–chloroform (2 : 1), followed by recrystallisation from acetone–hexane, gave prisms, m. p. 240—241° (Found : C, 58·1; H, 5·1; N, 13·4%). The *dipicrate* crystallised from water as yellow needles, m. p. (corr.) 269° (decomp.) (Found : C, 38·1; H, 3·8; N, 19·5. $C_{18}H_{20}O_{14}N_8$ requires C, 37·8; H, 3·5; N, 19·6%), depressed to 261° on admixture with the *cis*-epimer. The *dihydrochloride* crystallised from 95% ethanol as prisms, m. p. 330° (decomp.) (Found : C, 38·8; H, 8·6; Cl, 37·9%).

Curtius Reaction of cis-*Dimethyl Hexahydro*iso*phthalate*.—The dihydrazide, m. p. 270—272°, was converted through the diazide into the diethylurethane,[1] m. p. 146—147°, and the *dibenzylurethane*, which crystallised from benzene as needles, m. p. 189—190° (Found : C, 69·2; H, 6·8; N, 7·6. $C_{22}H_{26}O_4N_2$ requires C, 69·1; H, 6·9; N, 7·3%).

The latter (1 g.) and W7 Raney nickel (0·5 g.) were shaken for 3 hr. in ethanol with hydrogen at 70°/1000 lb. per sq. in. When cool, the filtered solution was treated with concentrated hydrochloric acid (3 ml.) and evaporated to dryness *in vacuo*. The crystalline residue (0·45 g.) was dissolved in dilute aqueous sodium hydroxide, and the solution filtered, and continuously extracted with chloroform. Removal of the chloroform from the dried extract afforded *cis*-1 : 3-diamino*cyclo*hexane, identified as the dipicrate and diacetyl derivative.

Curtius Reaction of trans-*Dimethyl Hexahydro*iso*phthalate*.—The dihydrazide, m. p. 125—126°, recrystallised from dry methanol–ether (cf. Skita and Rössler [1]), was converted through the diazide into the diethylurethane, m. p. 146—147°, depressed to 113—114° on admixture with the *cis*-epimer, and the dibenzylurethane, which crystallised from aqueous methanol as prisms, m. p. 126·5—127·5° (Found : C, 69·6; H, 6·7; N, 7·6%). Crystallisation of the latter from benzene–hexane gave needles, m. p. 108°, which on admixture with the higher-melting isomorph had m. p. 126—127°. When seeded with prisms a solution of the needles deposited prisms, m. p. 126·5—127·5°.

Hydrogenolysis of the dibenzylurethane was carried out as described for the *cis*-epimer, in similar yield. The product was identified as *trans*-1 : 3-diamino*cyclo*hexane by the dipicrate and diacetyl derivative.

Hydrolysis of the diethylurethane was carried out as described by Skita and Rössler [1] except that the diamine was isolated by extraction with chloroform, and identified as the *trans*-epimer, as before.

Reduction of Dihydroresorcinol Dioxime.—Dihydroresorcinol dioxime (2·1 g.) was hydrogenated in acetic acid under atmospheric conditions with platinum oxide (0·4 g.). Although half of the necessary hydrogen was absorbed in 0·5 hr. the remainder required 14 hr. The bulk of the acetic acid was removed from the filtered solution, which was then basified and continuously extracted with chloroform, giving a diamine (1·3 g.), b. p. 186—190°, n_D^{25} 1·4923. A solution of the derived crude picrate, m. p. 258—260°, in the minimum quantity of boiling water was allowed to cool to 30° and then filtered. The residue (plates) after one recrystallisation from water was identified as pure *cis*-1 : 3-diamino*cyclo*hexane dipicrate (1·2 g.). The filtrate on further cooling deposited needles, which afforded the pure *trans*-epimer (0·2 g.) after three recrystallisations from water. Evaporation of the mother-liquors left the mixed picrates (0·1 g.).

A solution of the crude acetyl derivative (0·56 g.) from the crude diamine, in hot ethanol (1 ml.), was treated with ethyl acetate (30 ml.), allowed to cool, and filtered. The residue after two similar recrystallisations was identified as the pure *cis*-diacetyl derivative (0·26 g.). Evaporation of the filtrate left material which was identified after two recrystallisations from acetone as the pure *trans*-epimer (0·035 g.).

Hydrogenation of NN′-*Diacetyl*-m-*phenylenediamine*.—This substance (10 g.), recrystallised several times from aqueous ethanol, was hydrogenated at 200°/1000 lb. per sq. in. over platinum oxide. After filtration, removal of the acetic acid left a crystalline residue, which was separated into *cis*- (4·6 g.) and *trans-NN′*-diacetyl-1 : 3-diamino*cyclo*hexane (1·9 g.) as described above.

Hydrolysis of these acetyl derivatives was accomplished by boiling concentrated hydrochloric acid in 4 hr. Removal of the acid left the hydrochlorides from which the diamines (*cis*-, n_D^{20} 1·4911; *trans*-, n_D^{20} 1·4962) were obtained in the usual manner.

2 : 4-*Diaza*bicyclo[3 : 3 : 1]*nonan*-3-*one*.—The *cis*-diamine (0·5 g.) and diethyl carbonate (0·5 g.) were heated together in a sealed tube at 200° for 8 hr. The material (0·1 g.) which separated was recrystallised from methanol–ether, yielding 2 : 4-*diaza*bicyclo[3 : 3 : 1]*nonan*-3-*one* as prisms, m. p. 315—316° (Found: C, 60·5; H, 8·3. $C_7H_{12}ON_2$ requires C, 60·0; H, 8·6%). Similar treatment of the *trans*-diamine gave a viscous liquid from which resins were separated. When heated under reflux with carbonyl chloride in water–toluene, the *cis*-diamine yielded its hydrochloride. A similar result occurred in chloroform at 0° in the presence of triethylamine. Only the diethylurethane and the diamine hydrochloride were obtained by reaction with ethyl chloroformate under these conditions. No identifiable product resulted from reaction of the *cis*-diamine and urea by the method of Mulvaney and Evans.[10] Application of hydrazoic acid (2 mols.) to the anhydride of *cis*-hexahydro*iso*phthalic acid as described previously, gave no neutral material but yielded the diamine (15%) (identified as the picrate) and the amino-acid (50%, isolated as the benzoyl derivative).

pK_a *Values*.—Apparent pK_a values were determined by potentiometric titration with standard hydrochloric acid of decinormal solutions of the diamines under nitrogen in a thermostat at 25°.

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[10] Mulvaney and Evans, *Ind. Eng. Chem.*, 1948, **40**, 393.