133. *The Synthesis of Chelating Agents Related to Cyclohexane-1,2-diamine-*NNN′N′*-tetra-acetic Acid.*

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trans-Cyclopentane-1,2-diamine-*NNN′N′*-, 4-methylcyclohexane-*trans* *-1,2-diamine-*NNN′N′*-, and *trans* *-cycloheptane-1,2-diamine-*NNN′N′*-tetra-acetic acid have been synthesised from the corresponding *vic*-dioximes *via* the *vic*-diamines. The new complexans have been prepared as potential analytical reagents; they possess some interesting properties which may prove of value.

SINCE the introduction by Schwarzenbach and Ackermann [1] of ethylenediamine-*NNN′N′*-tetra-acetic acid (EDTA) as an analytical complex-forming reagent of outstanding importance there has been an increasing search for similar reagents with more selective or more desirable physical properties. The report [2] of the high chelating power of *trans*-cyclohexane-1,2-diamine-*NNN′N′*-tetra-acetic acid (CDTA) and the prediction [3] that the cyclopentane homologue should have even greater power led to our synthesising the compounds described below.

Analogues of EDTA are best prepared by reaction of the diamine with chloroacetic acid [4] or by condensation of the diamine with formaldehyde and hydrogen cyanide followed by hydrolysis of the tetra-nitrile.[5] The diamines are conveniently prepared by reduction of the corresponding *vic*-dioximes which in turn are prepared from the readily available monoketones.[6]

Jaeger and Blumendal [7] reduced cyclopentane-1,2-dione dioxime with sodium and ethanol and obtained *trans*-cyclopentane-1,2-diamine. We have used the same method for the preparation of 4-methylcyclohexane-1,2-diamine and cycloheptane-1,2-diamine and therefore we assume that the amine groups have the *trans*-configuration. Condensation of chloroacetic acid with both *cis*- and *trans*-cyclohexane-1,2-diamine failed to give the *cis*-tetra-acetic acid derivative, but readily afforded the *trans*-tetra-acetic acid derivative.[8] The ease with which the following tetra-acetic acid derivatives were synthesised is adduced

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* The configuration of these diamines is not known, but for reasons given in the text the *trans*-configuration is strongly indicated.

[1] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1947, **30**, 1798.

[2] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1949, **32**, 1682.

[3] Martell and Calvin, " Chemistry of the Metal Chelate Compounds," Prentice Hall, New York, 1952, p. 180.

[4] Schwarzenbach and Ackermann, *Helv. Chim. Acta*, 1948, **31**, 1029.

[5] B.P. 651,990.

[6] Belcher, Hoyle, and West, *J.*, 1958, 2743.

[7] Jaeger and Blumendal, *Z. anorg. Chem.*, 1928, **175**, 164.

[8] Hoyle, Ph.D. Thesis, University of Birmingham, 1959.

to confirm their *trans*-configuration though in no case was this point investigated experimentally.

trans-Cyclopentane-1,2-diamine was easily converted into *trans*-cyclopentane-1,2-diamine-*NNN'N'*-tetra-acetic acid (CPDTA) by condensation with chloroacetic acid. CPDTA was found to be insoluble in all common solvents except formamide, and was purified by repeated precipitation from alkaline solution with acid. The rigidity of the cyclopentane ring and the symmetry of the molecule may account for this very poor solubility compared with that of the higher homologues.

4-Methylcyclohexane-*trans*-1,2-diamine was prepared by reduction as mentioned above, and isolated as the hydrogen sulphate, since the hydrochloride is very deliquescent. Though the diamine has been reported [9] no derivatives were recorded; we characterised the diamine as the dibenzoyl derivative and picrate. Condensation of the diamine with chloroacetic acid gave a poor yield (*ca.* 30%) of 4-methylcyclohexane-*trans*-1,2-diamine-*NNN'N'*-tetra-acetic acid (MCDTA) which could not be isolated from the mother-liquor.[10] Because of the small quantities of materials involved, the complicated distillation procedure of Schwarzenbach *et al.*[4] was not attempted, but a method using the intermediate formation of the tetra-nitrile was adopted. Hydrolysis of the tetra-nitrile with sulphuric acid and with sodium hydroxide was incomplete; barium hydroxide solution proved more satisfactory,[11] though some difficulty was experienced in obtaining the acid from solution owing to its tendency to form syrups. The high solubility of this compound in water and in ethanol may be due to the lack of symmetry of the molecule.

trans-Cycloheptane-1,2-diamine was prepared by reduction of the dioxime and was isolated as the hydrochloride. The literature of this compound lists no derivatives.[12] Treatment of the diamine with chloroacetic acid gave *trans*-cycloheptane-1,2-diamine-*NNN'N'*-tetra-acetic acid (CHDTA) which was isolated by acidification of the mother-liquor. Careful acidification of a solution of the tetrapotassium salt gave a precipitate which had the composition of a monopotassium derivative and could be crystallised to constant melting point. The formation of a monoalkali derivative of a complexan is interesting: it is thought that the compound is a salt and not a chelate, but as yet no further investigation has been made.

The complexans described possess several unusual properties which may prove of value in applications to specific problems. There are considerable differences in their solubilities: CPDTA is insoluble in most solvents, whereas MCDTA is appreciably soluble in water and ethanol. No increase in selectivity has been observed but under certain conditions of pH some increase of chelating power has been noticed with CHDTA. The increasing half-wave potential of the polarographic reduction wave of the copper and cadmium chelate waves shows that the chelating power increases in the order CPDTA $<$ CDTA $\leqslant$ MCDTA $<$ CHDTA. The polarographic data [13] are supported by the potentiometric titration curves,[8] and the order of chelation is confirmed by the ability of all the complexans but CPDTA to inhibit the precipitation of cobalt and manganese sulphides in the presence of calcium ions.[10]

EXPERIMENTAL

trans-*Cyclopentane*-1,2-*diamine*.—Crude cyclopentane-1,2-dione dioxime [6] was reduced with sodium and ethanol by Jaeger and Blumendal's method.[7] The diamine was isolated by steam-distillation and the dihydrochloride was obtained by evaporation of the acidified distillate under reduced pressure. The crude residue was washed with ethanol and trans-*cyclopentane*-1,2-*diamine dihydrochloride* was obtained as a white powder, m. p. 315—320° (decomp.), in 70% yield (Found: C, 35·1; H, 8·1; N, 16·2. $C_5H_{14}N_2Cl_2$ requires C, 34·7; H, 8·2; N, 16·2%).

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[9] Jaeger and Van Dijk, *Proc. Acad. Sci. Amsterdam*, 1936, **39**, 384.

[10] Hoyle, M.Sc. Thesis, University of Birmingham, 1957.

[11] Schwarzenbach, Senn, and Anderegg, *Helv. Chim. Acta*, 1957, **40**, 1886

[12] Bertsch, Fernelius, and Block, *J. Phys. Chem.*, 1958, **62**, 444.

[13] Hoyle and West, *Talanta*, 1959, **2**, 158.

trans-*Cyclopentane-*1,2-*diamine-*NNN′N′-*tetra-acetic Acid.*—A solution of chloroacetic acid (11·6 g.) in water (20 ml.) was neutralised with part of a solution of sodium hydroxide (12 g.) in water (20 ml.), the temperature being kept below 20°. *trans*-Cyclopentane-1,2-diamine dihydrochloride (4·7 g.) was added to the solution of sodium chloroacetate, then sufficient sodium hydroxide solution to liberate the free amine. The temperature of the solution was raised to 40° and maintained while one-half of the residual sodium hydroxide solution was added dropwise from the burette during 2½ hr. The other half of the sodium hydroxide solution was added during a further 2½ hr., with the temperature of the reaction mixture at 60°. The temperature was then raised to 90—100° and maintained thereat for 1 hr. The mixture was filtered and acidified at 0° to *ca.* pH 2 by addition of concentrated hydrochloric acid. The colourless crystals formed were removed and purified by repeated precipitation with hydrochloric acid from solutions of the sodium salt treated with charcoal. Colourless crystals of trans-*cyclopentane-*1,2-*diamine-*NNN′N′-*tetra-acetic acid* (CPDTA) were obtained, (5·7 g., 63%), which after drying *in vacuo* decomposed at *ca.* 250° (Found: C, 46·7; H, 5·7; N, 8·5. $C_{13}H_{20}N_2O_8$ requires C, 47·0; H, 6·1; N, 8·4%). Assay by complexometric titration 99—100%.

4-*Methylcyclohexane-*trans-1,2-*diamine.*—4-Methylcyclohexane-1,2-dione dioxime (10 g.) was reduced in ethanol solution (340 ml.) by sodium (61 g.) (cf. Jaeger and Blumendal [7]). The diamine was isolated by steam-distillation and converted into the di(hydrogen sulphate). Evaporation of the distillate under reduced pressure yielded a pink residue of crude 4-methylcyclohexane-*trans*-1,2-diamine di(hydrogen sulphate) (11·4 g., 78%). A white product was obtained by washing the crude salt with ethanol. The salt led to a *dibenzoyl derivative,* m. p. 315—316° (from ethanol) (Found: C, 75·2; H, 7·1; N, 8·1. $C_{21}H_{24}N_2O_2$ requires C, 75·0; H, 7·2; N, 8·3%), and a *picrate* (obtained by very slow crystallisation from water), m. p. 221° (decomp.) (Found: C, 39·1; H, 3·7. $C_{19}H_{22}N_8O_{14}$ requires C, 38·9; H, 3·8%).

4-*Methylcyclohexane-*trans-1,2-*diamine-*NNN′N′-*tetra-acetonitrile.*—To 4-methylcyclohexane-*trans*-1,2-diamine di(hydrogen sulphate) (10 g.) were added water (10 ml.) and concentrated sulphuric acid (9·55 g.). The solution was cooled to $<20°$ and 36% aqueous formaldehyde (16·2 ml.) was then added. 15 Ml. of 30% w/v aqueous solution of sodium cyanide were added dropwise to the stirred reaction liquor at 20° during 3 hr. The remainder of the cyanide solution (17 ml.) was added during 3 hr. at 30°. The mixture was then heated to 35° in 1 hr. and to 50° in a further ¾ hr. The whole was allowed to cool and set aside at room temperature for 15 hr., then warmed to 40° to dissolve most of the sodium sulphate. The light brown product was removed by filtration. A single recrystallisation from methanol gave off-white crystals, m. p. 131—133° (4·0 g., 32%). 4-*Methylcyclohexane-*trans-1,2-*diamine-*NNN′N′-*tetra-acetonitrile* was obtained as colourless crystals, m. p. 133—134°, from methanol (Found: C, 63·4; H, 7·1; N, 29·6. $C_{15}H_{20}N_6$ requires C, 63·4; H, 7·1; N, 29·6%).

4-*Methylcyclohexane-*trans-1,2-*diamine-*NNN′N′-*tetra-acetic Acid.*—To hydrated barium hydroxide (6·31 g.), dissolved in water (50 ml.), 4-methylcyclohexane-*trans*-1,2-diamine-*NNN′N′*-tetra-acetonitrile (1·42 g.) was added. The mixture was boiled gently for 4½ hr. and the volume was maintained by addition of water. The barium was precipitated by the calculated amount of 10% sulphuric acid and removed. The filtrate was evaporated to low bulk, the syrup which had been formed deposited off-white crystals slowly. 4-*Methylcyclohexane-*trans-1,2-*diamine-*NNN′N′-*tetra-acetic acid* (MCDTA) was obtained as colourless crystals (from aqueous ethanol), m. p. 177° (decomp.) (0·36 g., 20%) (Found: C, 44·6; H, 7·3; N, 6·8. $C_{15}H_{24}N_2O_8,2\frac{1}{2}H_2O$ requires C, 44·45; H, 7·2; N, 6·9%).

trans-*Cycloheptane-*1,2-*diamine.*—*trans*-Cycloheptane-1,2-diamine dihydrochloride was obtained by reduction of cycloheptane-1,2-dione dioxime (10 g.) by the method described above for 4-methylcyclohexane-*trans*-1,2-diamine. The light-brown hygroscopic *dihydrochloride* (8·5 g., 68%) was purified from ethanolic solution, with ether, as a flocculent precipitate, m. p. 245—265° (decomp.) (Found: C, 42·2; H, 9·0; N, 14·0. $C_7H_{18}N_2Cl_2$ requires C, 41·8; H, 9·0; N, 13·9%). This led to a *dibenzoyl derivative,* m. p. 340—341° (decomp.; sealed tube) (from pyridine) (Found: C, 74·6; H, 7·2; N, 8·6. $C_{21}H_{24}N_2O_2$ requires C, 75·0; H, 7·2; N, 8·3%).

trans-*Cycloheptane-*1,2-*diamine-*NNN′N′-*tetra-acetic Acid.*—Chloroacetic acid (17·9 g.) in water (35 ml.) was condensed with *trans*-cycloheptane-1,2-diamine dihydrochloride (8·5 g.) in the presence of sodium hydroxide (18·7 g., total) as described for the preparation of CPDTA. The sodium hydroxide was added in two periods of 3 hr. each at 40° and 60° respectively. The reaction was completed as before; and the liquor was filtered to remove a brown contaminant.

Colourless crystals were deposited on acidification of the mother-liquor to pH <2 with concentrated hydrochloric acid, and after recrystallisation from water trans-*cycloheptane*-1,2-*diamine*-NNN′N′-*tetra-acetic acid* (CHDTA) was obtained (4·8 g., 31%). Dehydration *in vacuo* at 140° gave pure CHDTA as a white powder, m. p. 181—182° (decomp.) (Found: C, 49·8; H, 6·5; N, 7·7. $C_{15}H_{24}N_2O_8$ requires C, 50·0; H, 6·7; N, 7·8%).

This acid was dissolved in potassium hydroxide solution and then carefully acidified with concentrated hydrochloric acid to pH *ca.* 2. A white precipitate was obtained which, readily recrystallised from water, had m. p. 264—266° (Found: H, 6·1; N, 6·9. $C_{15}H_{23}KN_2O_8$ requires H, 5·8; N, 7·0%). Assay by complexometric titration gave 99—100% purity.

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