CCLII.—*Reactions of Displacement in the Tropic Acid Group. Part II.*

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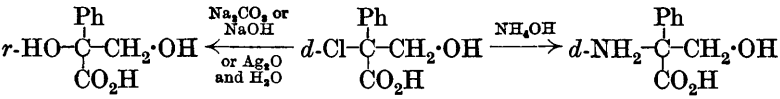
In Part I, the action of sodium carbonate and of concentrated aqueous ammonia on *l*-β-chlorohydratropic acid, $CH_2Cl{\cdot}CHPh{\cdot}CO_2H$, was examined by McKenzie and Strathern (J., 1925, **127**, 82), and it now seemed of interest to prepare the optically active chlorotropic acid, $OH{\cdot}CH_2{\cdot}CPhCl{\cdot}CO_2H$, and to effect the displacement of the chlorine atom in this acid by other groups. The actions of alkali, moist silver oxide, ammonia, and reducing agents on both the active and the inactive acid were marked out for study. Moreover, the displacement of chlorine by hydrogen obviously called for inquiry, since such a change has been investigated only rarely in connexion with the Walden inversion, for example, in the reduction of *l*-chloromalic acid to *d*-malic acid (Kuhn and Zell, *Ber.*, 1926, **59**, 2514).

The preparation of *r*-chlorotropic acid is described by Ladenburg and Rügheimer (*Ber.*, 1880, **13**, 373), who acted on atropic acid with a dilute solution of hypochlorous acid, prepared by passing chlorine into a suspension in water of freshly precipitated, yellow mercuric oxide. The author has found that this acid can be more conveniently prepared by the action of monochlorourea on atropic acid, according to the equation $CH_2{:}CPh{\cdot}CO_2H + NH_2{\cdot}CO{\cdot}NHCl + H_2O = OH{\cdot}CH_2{\cdot}CPhCl{\cdot}CO_2H + CO(NH_2)_2$. Monochlorourea has been successfully used by Detœuf (*Bull. Soc. chim.*, 1922, **102**, 176) in the preparation of the chlorohydrins of unsaturated substances, and was found in the present case to give nearly 80% yields of chlorotropic acid. The resolution of chlorotropic acid into its active components can be accomplished by means of morphine, with methyl alcohol as solvent. *d*-Chlorotropic acid has $[\alpha]_D^{18°} = +12{\cdot}6°$ for $c = 3{\cdot}025$ in methyl alcohol, and melts at

123—124°, whereas the *r*-acid has m. p. 129—130°. The rotations of chlorotropic acid in acetone and in water were considerably lower than in methyl alcohol. The first mother-liquor in the resolution contained an excess of the morphine salt of *l*-chlorotropic acid, and by five recrystallisations of this salt from methyl alcohol a morphine salt resulted which gave *l*-chlorotropic acid with $[\alpha]_D^{15°} = -12{\cdot}4°$ in methyl alcohol ($c = 3{\cdot}586$).

The action of sodium carbonate or caustic soda on *r*-chlorotropic acid gave as a main product atroglyceric acid, $OH{\cdot}CH_2{\cdot}CPh(OH){\cdot}CO_2H$, m. p. 144—145°, as well as a small quantity of a neutral oil which corresponded with the formula $C_8H_8O_2$ but could not be identified with the amount in hand. Aqueous ammonia with chlorotropic acid gave, as was expected, a chlorine-free nitrogenous substance, proved to be α-amino-β-hydroxy-α-phenylpropionic acid. *d*-Chlorotropic acid (1 mol.) when treated with moist silver oxide (2 mols.) gave *r*-atroglyceric acid, with only slight formation of the yellow neutral oil noticed in the case of alkali. The following changes can be brought about:



The action of sodium carbonate solution and of moist silver oxide on *d*-chlorotropic acid led to the formation, in both cases, of optically inactive atroglyceric acid. Such complete racemisation was not to be expected, especially in the case of silver oxide, but a similar case of complete racemisation is to be found in the action of water on *l*-α-chloro-α-phenylpropionic acid and of nitrous acid on *l*-α-amino-α-phenylpropionic acid (McKenzie and Clough, J., 1910, **97**, 1016; 1912, **101**, 390), which compounds are closely allied in structure to chlorotropic acid.

The action of concentrated ammonia on *d*-chlorotropic acid gave, on the other hand, a dextrorotatory α-amino-β-hydroxy-α-phenylpropionic acid with $[\alpha]_D^{16°} = +40{\cdot}6°$ ($c = 6{\cdot}208$) in hydrochloric acid solution. The optical purity of the amino-acid was considered to be high, but the complete proof that the optically pure acid was actually isolated was lacking owing to the difficulty of finding a suitable solvent for it. In the displacement of chlorine by the amino-group, no such extensive racemisation took place as in the formation of *r*-atroglyceric acid from *d*-chlorotropic acid. Explanation of the latter racemisation cannot be traced to the rotatory power of atroglyceric acid being low, as this acid is at present being resolved and is known to have a fairly high specific rotation.

The conversion of *r*-chlorotropic acid into tropic acid by means

of reducing agents was not accomplished, and this is in agreement with the work of McKenzie and Wood (J., 1919, **115**, 828), who found that this conversion could not be effected in the manner described by Ladenburg and Rügheimer (*loc. cit*).

Experimental.

Chlorotropic Acid.—Atropic acid, prepared from tropic acid by Raper's method (J., 1923, **123**, 2558), had m. p. 107—108° when recrystallised from methyl alcohol. Monochlorourea was prepared by Detœuf's method (*loc. cit.*) and its strength estimated by titration with potassium iodide and thiosulphate. Atropic acid (27 g.; 1 mol.) was mixed with 135 c.c. of water, containing 2 c.c. of glacial acetic acid, and monochlorourea solution (1½ mols.) was added. With continuous stirring for 24 hours, most of the atropic acid went into solution, the remainder going pasty. The pasty atropic acid was filtered off, washed free from chlorotropic acid with water, and recrystallised from rectified spirit; 8 g. of atropic acid were recovered. The filtrate and washings were acidified with dilute sulphuric acid and sulphurous acid was added until no reaction with starch–iodide paper was shown. The excess of sulphur dioxide was removed by boiling and the solution extracted seven times with ether. Yield, 18 g. of crude chlorotropic acid. In previous work (Ladenburg and Rügheimer, *loc. cit.*; McKenzie and Wood, *loc. cit.*), chlorotropic acid was purified by washing with cold benzene, but it was found better to recrystallise it from chloroform. Yield, 16 g. of chlorotropic acid, m. p. 129—130°.

Attempted Conversion of Chlorotropic Acid into Tropic Acid.—Ladenburg and Rügheimer (*loc. cit.*) record the reduction of chlorotropic acid with zinc and iron filings in concentrated alkali, but McKenzie and Wood (*loc. cit.*) failed to effect the reduction either by this means or by means of sodium amalgam, zinc and hydrochloric acid, or caustic soda and aluminium. 3 G. of chlorotropic acid, made into a paste with 20 g. of moist copper–zinc couple, were treated with concentrated hydrochloric acid and the mixture was heated on a water-bath for 4 hours. The sludge was separated by decanting off the liquid, and then washed with hot water. Four ether extractions of the acid liquor and washings gave a yellow oil which crystallised on standing. After two recrystallisations from hot chloroform, the crystals melted at 117—122°, but a mixture with pure tropic acid (m. p. 117—118°) had a m. p. 90—93°. After heating 3 g. of chlorotropic acid, 10 g. of copper–zinc, and 100 c.c. of hydrochloric acid (4*N*) for 23 hours, and isolating the product as before, 2 g. of white solid, containing chlorine, and of m. p. 114—116°, were isolated from the ethereal extracts. A fractional

crystallisation of this substance from water gave 0·7 g. of chlorotropic acid (m. p. 128—130°). 3 G. of chlorotropic acid, 50 c.c. of water, and an excess of zinc foil were kept in a platinum basin for two months and then treated with an excess of dilute sulphuric acid. The yellow oil obtained by extraction with ether crystallised to give a solid, m. p. 105—117°, which contained chlorine.

Action of Sodium Hydroxide on r-*Chlorotropic Acid.*—3 G. of chlorotropic acid were neutralised with 155 c.c. of caustic soda (*N*/10), and 154 c.c. of caustic soda further added with a drop of phenolphthalein. After 1 hour's heating on the water-bath the colour of the indicator faded. The cooled mixture was made alkaline, and the neutral oil removed by extraction with ether four times. Yield, 0·5 g. The alkaline solution was made acid with dilute sulphuric acid and extracted five times with ether. From the dried ethereal extracts, 1·1 g. of crystalline acid were obtained, which furnished 0·7 g. of an acid, m. p. 141—145°, when recrystallised from hot ethyl acetate. A second recrystallisation from the same solvent gave 0·5 g. of atroglyceric acid, m. p. 145—147°, (Fittig and Kast, *Annalen*, 1881, **206**, 32, give m. p. 146°) (Found: C, 59·3; H, 5·6. Calc., C, 59·3; H, 5·5%).

Action of Sodium Carbonate on r-*Chlorotropic Acid.*—2 G. of chlorotropic acid were neutralised with approximately *N*-sodium carbonate (9 c.c.), a drop of phenolphthalein was added, and a further 8·5 c.c. of sodium carbonate were run in. After 10 minutes on the water-bath, the colour of the indicator was discharged, and boiling was continued for 20 minutes. The cooled mixture, made alkaline, was extracted with ether to remove a small quantity of neutral oil. Five ether extractions of the acidified liquor gave 1 g. of solid, m. p. 130—138°, which, after recrystallisation from water, had m. p. 144—145°. It was chlorine-free and identified as atroglyceric acid.

α-*Amino*-β-*hydroxy*-α-*phenylpropionic Acid.*—A solution of 3 g. of chlorotropic acid in 50 c.c. of concentrated ammonia, saturated at 0°, was kept in a stoppered bottle for 7 days at the ordinary temperature, and then transferred to a crystallising dish. After 16 hours' standing, 2·2 g. of an acid, washed free from ammonium chloride by water, were separated. The acid was chlorine-free, gave no ammonia with caustic alkali, and behaved as an amino-acid, being soluble in acid and in alkali. It was purified by dissolving it in caustic soda and making the solution exactly neutral with hydrochloric acid. A yield of 1·3 g. of pure acid was obtained from 1·4 g. of crude acid. α-*Amino*-β-*hydroxy*-α-*phenylpropionic acid* has m. p. 285—288° (decomp.) and is insoluble in the commoner organic solvents and in water (Found: C, 59·8; H, 6·0. $C_9H_{11}O_3N$

requires C, 59·7; H, 6·1%). Its *hydrochloride* separates in rhombic prisms, m. p. 225° (decomp.).

Preparation of Optically Active Chlorotropic Acid.—A solution of 30 g. of chlorotropic acid in 300 c.c. of hot methyl alcohol was added to a solution of 45 g. of morphine in 3400 c.c. of methyl alcohol, and the mixture heated just to boiling. On cooling, crystallisation began, and after 18 hours the resulting 45 g. of very fine needles were dissolved by heating in 3750 c.c. of methyl alcohol. On concentration to 1850 c.c., the solution, after 48 hours, gave 24 g. of crystals which were dissolved by heating with 2500 c.c. of methyl alcohol. The solution was concentrated to 1250 c.c. and after 24 hours 15 g. of morphine chlorotropate, crystallising in fine needles, were separated. The acid was obtained by acidification with dilute sulphuric acid and extraction with ether. Yield, 5·8 g. with $[\alpha]_D^{18°} = +11·2°$ ($c = 3·5565$) in methyl alcohol. Three successive crystallisations of this dextro-acid from chloroform gave acids with the following rotations in methyl alcohol: $[\alpha]_D^{17°} = +12·0°$ ($c = 3·052$), $[\alpha]_D^{18°} = +12·5°$ ($c = 3·1245$), $[\alpha]_D^{18°} = +12·6°$ ($c = 3·025$). The pure d-*chlorotropic acid* has therefore $[\alpha]_D^{18°} = +12·6°$ ($c = 3·025$) in methyl alcohol. It melts at 123—124° (Found: C, 53·8; H, 4·5. $C_9H_9O_3Cl$ requires C, 53·8; H, 4·5%). The first mother-liquor in the resolution was evaporated to small bulk, and 29 g. of morphine salt were separated. This was recrystallised five times from methyl alcohol, and the resulting salt on decomposition gave l-*chlorotropic acid* with $[\alpha]_D^{15°} = -12·4°$ ($c = 3·586$) in methyl alcohol.

Action of Sodium Carbonate on d-*Chlorotropic Acid.*—1 G. of dextrorotatory chlorotropic acid, with $[\alpha]_D^{16°} = +10·3°$ in methyl alcohol, was neutralised with 7·4 c.c. of sodium carbonate (0·5745*N*) and 7·2 c.c. of the alkali were further added, with a drop of phenolphthalein. After heating for 10 minutes on the water-bath, the solution became colourless; it was made alkaline, and the neutral oil removed by extraction with ether. The solution was acidified with dilute sulphuric acid, and the acid extracted with ether. 0·3 G. of chlorine-free solid was obtained. This was atroglyceric acid and it was quite inactive ($c = 2·618$) in methyl alcohol.

Action of Silver Oxide on d-*Chlorotropic Acid.*—1 G. (1 mol.) of dextrorotatory chlorotropic acid with $[\alpha]_D^{16°} = +10·3$ in methyl alcohol, and the silver oxide obtained from 1·7 g. (2 mols.) of silver nitrate by precipitation with caustic soda, were mixed with 50 c.c. of water and stirred mechanically for 2 hours. After 60 hours at the ordinary temperature, the mixture was heated for ½ hour, and the silver chloride removed by precipitation with hydrochloric acid. By extraction of the filtrate with ether 0·2 g. of solid, m. p. 143—

146°, was obtained. A mixture of this with atroglyceric acid had m. p. 143—145°, and therefore the substance was atroglyceric acid. It was completely inactive ($c = 1{\cdot}764$) in methyl alcohol.

Action of Aqueous Ammonia on d-*Chlorotropic Acid.*—A solution of 1 g. of *d*-chlorotropic acid with $[\alpha]_D^{18^\circ} = +12{\cdot}6^\circ$ in methyl alcohol, in 10 c.c. of concentrated ammonia, saturated at 0°, was kept in a stoppered bottle for 10 days and then transferred to a crystallising dish. After 3 days, all the solvent had evaporated and the remaining solid was washed free from ammonium chloride and dried. Yield, 0·6 g. of α-amino-β-hydroxy-α-phenylpropionic acid. The rotation of the amino-acid was $[\alpha]_D^{16^\circ} = +40{\cdot}6^\circ$ in *N*-hydrochloric acid ($c = 6{\cdot}208$). Failure attended the attempts to raise the rotation of this acid, either by repeated precipitation from its solution in caustic soda by means of hydrochloric acid, or by recrystallisation from concentrated aqueous ammonia. A saturated solution of ammonia in *sec.*-octyl alcohol does not convert chlorotropic acid into the corresponding amino-acid.

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