

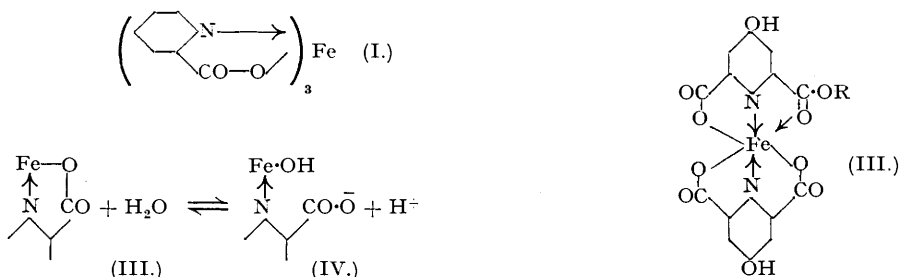
14. Iron Derivatives of Heterocyclic Acids. Part I. Ferric Complexes of Chelidamic Acid.

By JOHN H. GORVIN.

Brownlee, Bainbridge, and Thorp (*Quart. J. Pharm.*, 1942, **15**, 148) have established the value as hæmoglobin producers of certain ferric chelidamate derivatives prepared in these laboratories. These substances are neutralisation products of *dichelidamatoferric acid*, which contains one free and one masked carboxyl group, and gives rise to two series of water-soluble salts. The light-absorption of these complexes has been studied. Structural formulæ are assigned to them and to their insoluble *silver* and *iron* derivatives. The study is being extended to related derivatives of other pyridine- α '-dicarboxylic acids.

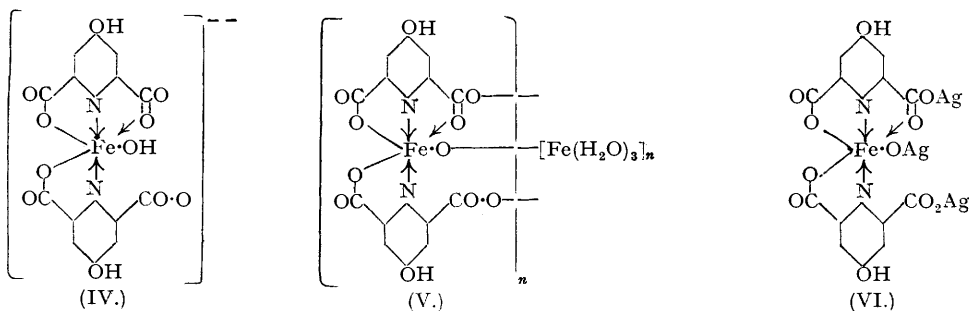
A PRELIMINARY survey of ferric derivatives of pyridine- α -carboxylic acids has shown that either two or three molecules of picolinic acid may react with an atom of ferric iron. *Tripicolinatoiron* (I) (compare the analogous cobaltic complex of Ley and Ficken, *Ber.*, 1917, **50**, 1133) is readily formed from the acid and ferric hydroxide, and a compound of the type (Acid)₂FeOH (II) has been described by Ley, Schwarte, and Münnich (*Ber.*, 1924, **57**, 355).

In substituted picolinic acids, spatial considerations favour formation of the smaller molecule; thus, 4-chloropicolinic acid forms only a *complex* of type (II) with ferric hydroxide. The case of chelidamic acid is similar, with the additional factor of elimination of the hydroxo-group by ring closure. Crystalline *dichelidamatoferric acid* has been assigned an octahedral structure (III; R = H), requiring a six-co-ordinate iron atom associated with two tridentate acid molecules in right-angular planes (compare Morgan and Burstall, J., 1937, 1649), with one strongly acidic carboxyl group available for salt formation. The acid has a pK value of approximately 1.6 in 0.01M-solution.



The crystalline *dichelidamatoferrates* (III; R = kation) give orange-coloured aqueous solutions in which they behave as weak acids (pK = 4.0 in 0.01M-solution); the colour intensity of the solutions is almost independent of concentration over a wide range. These effects can be explained by the partial opening of a five-membered ring, setting up the equilibrium (III) \rightleftharpoons (IV). These acidic salts, on neutralisation, give solutions containing the dichelidamatohydroxoferrate ion (IV), the intense blood-red colour of which is attributed to resonance in the ring system containing the strongly polarising iron atom. The highly soluble dichelidamatohydroxoferrates have not been obtained crystalline, for, in concentrated solutions, the equilibrium usually

moves to the left, with separation of the less soluble dichelidamatoferrate. The crystalline *di-p-toluidine* salt appears to be the dichelidamatoferrate with "*p-toluidine* of crystallisation."



The formation of dichelidamatohydroxoferrates is usually accompanied by some decomposition of the anion by the added base; the liberated ferric hydroxide combines with unchanged anion to give an insoluble ferric derivative (V; the value of n is uncertain), also slowly formed by the action of ferric ions on dichelidamatoferric acid and its salts.

Dichelidamatohydroxoferrate solutions, filtered to remove ferric complex, remain stable at temperatures up to 100° . Unless there is crystallisation of dichelidamatoferrate, they are unchanged on evaporation, and finally give deep red scales, or, in the case of the *nor-d-ψ-ephedrine* compound, a highly soluble red powder shown by analysis to be analogous to the *di-p-toluidine* salt. Their aqueous solutions react immediately with silver ions to form the insoluble *trisilver dichelidamato-oxoferrate* (VI), in contrast to dichelidamatoferrate solutions which give mainly *silver dichelidamatoferrate* (III; $\text{R} = \text{Ag}$).

The substitution of iron and silver in the hydroxo-group, which appears to occur in compounds (V) and (VI), may be compared with the intermolecular condensation of $\text{Fe}(\text{OH})_3$ to ortho-ferric hydroxide $(\text{FeO}_2\text{H})_4$, and with the formation of silver ferrite $\text{Ag}_3\text{H}(\text{FeO}_2)_4$ by substitution in the active hydroxo-groups of this complex (Krause, *Ber.*, 1936, 69, 1982).

Evidence that the dichelidamatohydroxoferrate ion (IV) has a definite existence in aqueous solution is provided by light-absorption curves plotted at several dilutions, which indicate that solutions of the bistrichiethanolamine salt substantially obey Beer's law over the range of dilution 0.000025—0.0025M. The presence of an extra mol. of base does not radically affect the absorption, but, as (IV) is in equilibrium with (III) in solutions of dichelidamatohydroxoferrates of weak bases, the resulting pH increase may lead to a somewhat higher concentration of the strongly absorbing ion (IV) (compare the curves for 0.00025M-solutions). The curves supply no evidence for any ionisation of the hydroxo-group, but dichelidamatohydroxoferrates of strong bases were not studied in this connection, owing to the considerable decomposition which occurs in their preparation.

In the case of *ammonium dichelidamatoferrate* (III; $\text{R} = \text{NH}_4$), the increased ring-opening on dilution is accompanied by relative intensification of absorption in the blue-green region, and at 0.000025M-dilution, the form of the curve resembles that of the dichelidamatohydroxoferrates. The absorption of dichelidamatoferric acid, although similarly dependent on concentration, is always weaker than that of its salts at corresponding dilution, as ring opening is largely suppressed by hydrions from the free carboxyl group.

EXPERIMENTAL.

Analytical figures for the following compounds were determined after drying at 120° in a vacuum; the loss in weight of the desiccator-dried substance is given as molecules of water of crystallisation. Hydrated crystals became opaque on drying, but no marked colour changes occurred. Unless otherwise stated, the compounds were stable up to 300° and insoluble in organic solvents. They were decomposed by excess of strong acids or alkalis.

Tripicolinatoiron (I).—Freshly prepared ferric hydroxide (1 mol.) was dissolved in a hot aqueous solution of picolinic acid (3.5 mols.). *Tripicolinatoiron* separated rapidly in yellow, crystalline flakes (H_2O), insoluble in water, decomposing at 282° (corr.) (Found: C, 50.1; H, 3.0; N, 10.0; Fe, 13.4. $\text{C}_{18}\text{H}_{12}\text{O}_6\text{N}_3\text{Fe}$ requires C, 51.2; H, 2.9; N, 10.0; Fe, 13.2%).

Di-(4-chloropicolinato)hydroxoiron.—Prepared by analogous procedure from 4-chloropicolinic acid (Graf *et al.*, *Ber.*, 1931, 64, 22), this complex formed a yellow, crystalline powder, insoluble in water; it darkened at 260 — 270° (Found: C, 37.3; H, 1.8; N, 7.4. $\text{C}_{11}\text{H}_6\text{O}_5\text{N}_2\text{Cl}_2\text{Fe}$ requires C, 37.3; H, 1.8; N, 7.3%).

Dichelidamatoferric Acid (III, $\text{R} = \text{H}$).—A suspension of ferric hydroxide (1.05 mols.) in water (10 l.) was boiled with chelidamic acid (2 mols.) and the solution then left overnight. After insoluble material had been filtered off, the orange-yellow solution was scratched to initiate crystallisation, giving *dichelidamatoferric acid* as a fine golden crystalline powder ($2\text{H}_2\text{O}$). The crop was filtered without delay, as insoluble impurity slowly separated from concentrated solutions of the acid (Found: C, 39.8; H, 1.9; N, 6.8; Fe, 13.2. $\text{C}_{11}\text{H}_7\text{O}_{10}\text{N}_2\text{Fe}$ requires C, 40.1; H, 1.7; N, 6.7; Fe, 13.3%).

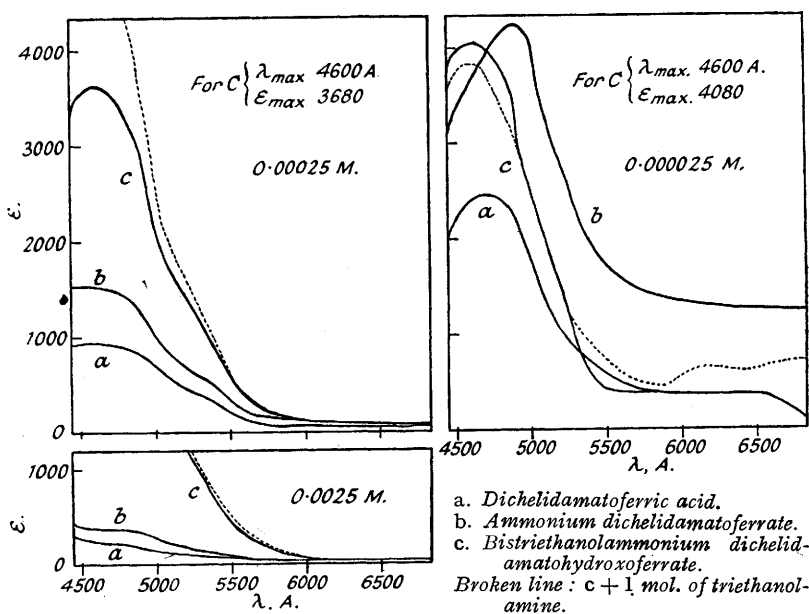
Salts of Dichelidamatoferric Acid.—These salts were prepared, either by adding 1.1 equivs. of the appropriate base, dissolved in water or alcohol, to a warm aqueous solution of the acid (1 mol.) (method I), or by treating an aqueous solution of ammonium dichelidamatoferrate (see below) with a soluble salt of the base (method II). The salts were recrystallised from water in each case.

Ammonium salt. Prepared by method I, or by treating strontium chelidamate with ferric ammonium sulphate, the ammonium salt formed yellow-green crystals ($2.5\text{H}_2\text{O}$) (Found: C, 38.9; H, 2.4; N, 9.6; Fe, 12.9. $\text{C}_{11}\text{H}_{10}\text{O}_{10}\text{N}_3\text{Fe}$ requires C, 38.5; H, 2.3; N, 9.6; Fe, 12.8%). This salt was referred to by Brownlee *et al.* (*loc. cit.*) as iron mono-ammonium chelidamate.

Tetraethylammonium salt (method I), olive-green rods ($2\text{H}_2\text{O}$) (Found: N, 7.7; Fe, 10.0. $\text{C}_{22}\text{H}_{26}\text{O}_{10}\text{N}_3\text{Fe}$ requires

N, 7.7; Fe, 10.2%). *o*-Toluidine salt (method I), brown crystals with gold reflex (Found: C, 47.9; H, 3.0; Fe, 10.6. $C_{21}H_{16}O_{10}N_3Fe$ requires C, 47.9; H, 3.1; Fe, 10.6%). Pyridine salt (method I), golden-yellow flakes (Found: C, 45.9; H, 2.4; Fe, 11.3. $C_{19}H_{12}O_{10}N_3Fe$ requires C, 45.8; H, 2.4; Fe, 11.2%). Quinoline salt (method I), flat yellow needles (Found: C, 50.3; H, 2.7; Fe, 10.2. $C_{23}H_{14}O_{10}N_3Fe$ requires C, 50.4; H, 2.6; Fe, 10.2%). Quinine salt (method I or II), small lemon-yellow needles, sparingly soluble in hot water (Found: C, 49.3; H, 3.6; N, 7.3; Fe, 9.5. $C_{48}H_{38}O_{22}N_6Fe_2$ requires C, 49.6; H, 3.3; N, 7.2; Fe, 9.6%). Sodium salt (method I), green crystals ($2H_2O$) (Found: C, 38.1; H, 1.7; N, 6.4. $C_{14}H_8O_{10}N_2FeNa$ requires C, 38.1; H, 1.4; N, 6.4%). Potassium salt (method I), yellow-green crystals ($2H_2O$) (Found: C, 37.1; H, 1.4; N, 6.2. $C_{14}H_8O_{10}N_2FeK$ requires C, 36.8; H, 1.3; N, 6.1%). Silver salt (method II), orange-yellow crystalline powder ($2H_2O$) sparingly soluble in hot water (Found: C, 31.7; H, 1.3; N, 5.4. $C_{14}H_8O_{10}N_2FeAg$ requires C, 31.9; H, 1.2; N, 5.3%). Barium salt (method I or II), yellow brown prisms ($2.5 H_2O$), efflorescing in air (Found: C, 34.9; H, 1.4; N, 5.9. $C_{28}H_{12}O_{20}N_4Fe_2Ba$ requires C, 34.5; H, 1.2; N, 5.8%).

The Dichelidamatohydroxoferrates (IV).—Neutralisation of dichelidamatoferric acid with 2 mols. of a base, or of a dichelidamatoferrate with 1 mol., yielded an intense blood-red solution of a dichelidamatohydroxoferrate. Simultaneously the anion underwent decomposition to an extent depending on the strength of the added base, with separation of a fine precipitate of triaquoferric dichelidamato-oxoferrate (see below) and liberation of an equivalent amount of chelidamate ion in the solution. Separation of the insoluble complex was usually complete after leaving overnight; it was removed from the solution by filtration through kieselguhr. The formation of the diammonium salt (the iron diammonium chelidamate of Brownlee *et al.*, *loc. cit.*) and of the disodium and dipotassium salts was accompanied by appreciable decomposition of the anion, and evaporation of the solutions to dryness gave deep red scales of indefinite composition, highly soluble in water. On allowing the concentrated solution to stand, crystallisation of dichelidamatoferrate occurred, with decrease in the intensity of the colour. Complete conversion into the dichelidamatoferrate was achieved by dehydrating the solid scale with alcohol, or by passing sulphur dioxide through its aqueous solution.



Effect of dilution on light-absorption of the complexes.

The bistriethanolamine salt (the iron triethanolamine chelidamate of Brownlee *et al.*, *loc. cit.*), prepared with only slight decomposition, gave a red scale on evaporation, with no tendency to crystallisation. The substance in aqueous solution passed readily through a collodion membrane.

The dipyridine salt was formed without any decomposition of the anion, but pyridinium dichelidamatoferrate began to crystallise almost immediately, with fading of the deep red colour. Addition of excess pyridine lessened, but did not entirely inhibit, the crystallisation. A similar, but less rapid, effect occurred in the case of the di-*o*-toluidine salt.

Di-p-toluidine salt. On addition of *p*-toluidine (0.54 g., 2 mols.), dissolved in alcohol, to a solution of dichelidamatoferric acid (1 mol.), a deep red solution was formed, which deposited a trace of insoluble material on standing. Filtration and concentration to 20 c.c. caused separation of orange-brown leaflets ($1H_2O$) of the *di-p-toluidine* salt, decomposing at $220-225^\circ$, soluble in hot water to a deep red solution (Found: C, 52.4; H, 4.1; N, 9.0; Fe, 8.9. $C_{21}H_{16}O_{10}N_3Fe$, C_7H_8N requires C, 53.1; H, 4.0; N, 8.9; Fe, 8.8%).

Dimor-d-ψ-ephedrine salt. The deep red solution, prepared by the above method, using 2.1 mols. of nor-*d-ψ*-ephedrine, was evaporated to dryness and dried at 120° in a vacuum. The salt formed a red powder, very soluble in water and in alcohol (Found: C, 53.2; H, 4.7; N, 7.9; Fe, 7.8. $C_{23}H_{20}O_{11}N_3Fe, C_9H_{13}ON$ requires C, 53.3; H, 4.6; N, 7.8; Fe, 7.7%).

Trisilver Dichelidamato-oxoferrate (VI).—A 5% aqueous solution of silver nitrate was added in excess to a solution of bistriethanolammonium dichelidamatohydroxoferrate. A fine purple precipitate formed in the cold, but was brown and less finely divided in the hot. The dry silver derivative was a dark purple-brown powder, insoluble in water (Found: C, 22.5; H, 0.8; N, 3.7; Fe, 7.4; Ag, 42.6. $C_{14}H_8O_{11}N_2FeAg_3$ requires C, 22.2; H, 0.8; N, 3.7; Fe, 7.4; Ag, 42.7%).

Triaquoferric Dichelidamato-oxoferrate (V).—A suspension of ferric hydroxide (1 mol.) was treated with aqueous dichelidamatoferric acid (1.2 mols.), and the solution heated on the water-bath for 3 hours. The ferric derivative separated as a golden-brown mass of rod-shaped, yellow crystals ($4H_2O$), insoluble in water (Found: C, 31.1; H, 2.2; N, 5.3; Fe, 20.6. $C_{14}H_8O_{11}N_2Fe_3 \cdot 3H_2O$ requires C, 30.9; H, 2.2; N, 5.2; Fe, 20.5%). The same compound was obtained as an orange-red powder (approx. $2H_2O$) by treating ammonium dichelidamatoferrate solution with ferric chloride, or by

filtering and washing the precipitate obtained during the preparation of dichelidamatohydroxoferrates of strong bases (see above).

Acid Dissociation Constants for the Dichelidamatoferrates.—The figures were calculated from the pH values of solutions of the ammonium and potassium salts at several dilutions, measured on a standard Cambridge pH meter. Solutions were made in boiled distilled water from known amounts of the recrystallised salt, dried to constant weight at 120° in a vacuum.

	Molarity.	pH (11.5°).	$K_a \times 10^4$.	pK_a .		Molarity.	pH (11.5°).	$K_a \times 10^4$.	pK_a .
NH ₄ salt	0.0125	3.00	0.87	4.06	K salt	0.0125	2.97	1.01	4.00
"	0.0100	3.05	0.87	4.06	"	0.0100	3.03	0.96	4.01
"	0.0083	3.09	0.88	4.06	"	0.0083	3.06	1.02	3.99

First Dissociation Constant for Dichelidamatoferric Acid.—Owing to the difficulty of obtaining an absolutely pure specimen of the crystalline acid, a known concentration of the pure acid was prepared in solution by dissolving ferric hydroxide in a slight excess of chelidamic acid, then removing the excess by the addition of half the previous quantity of ferric hydroxide. The insoluble ferric complex, which crystallised overnight, was filtered off and dried to constant weight. The known iron content of the complex gave a figure for the iron remaining in the dichelidamatoferric acid solution, which was then diluted to the required concentrations ($K_2 = 1.0 \times 10^{-4}$).

Molarity.	pH (15°).	$K_1 \times 10^2$.	pK_1 .	Molarity.	pH (15°).	$K_1 \times 10^2$.	pK_1 .
0.0112	2.06	2.9	1.54	0.0077	2.20	2.6	1.58
0.0095	2.13	2.5	1.60				

The Absorption Curves.—These were constructed from readings of percentage transmission and wave-length of light obtained on a wave-length monochrometer using a selenium "barrier-layer" type cell. Aqueous solutions of dichelidamatoferric acid and its ammonium salt, and of the bistrisethanolamine salt, with and without an additional mol. of triethanolamine, were prepared, and diluted to the required concentrations. In 0.0025M-solution, the transmission in the blue-green region by the triethanolamine solutions was too weak for accurate readings to be taken.

The author's thanks are due to Dr. T. A. Henry and Mr. H. Paget, whose preliminary work on injectable iron solutions suggested this investigation, to Dr. Brownlee for the absorption measurements, to Mr. D. T. Warren for experimental assistance, and to Messrs. A. Bennett and H. C. Clarke for the micro-analyses.

WELLCOME BUREAU OF SCIENTIFIC RESEARCH, LONDON, N.W.1.

[Received, October 9th, 1943.]