365. *The* Senecio *Alkaloids. Part IV. The Structure of Retronecic and Isatinecic Acids.*

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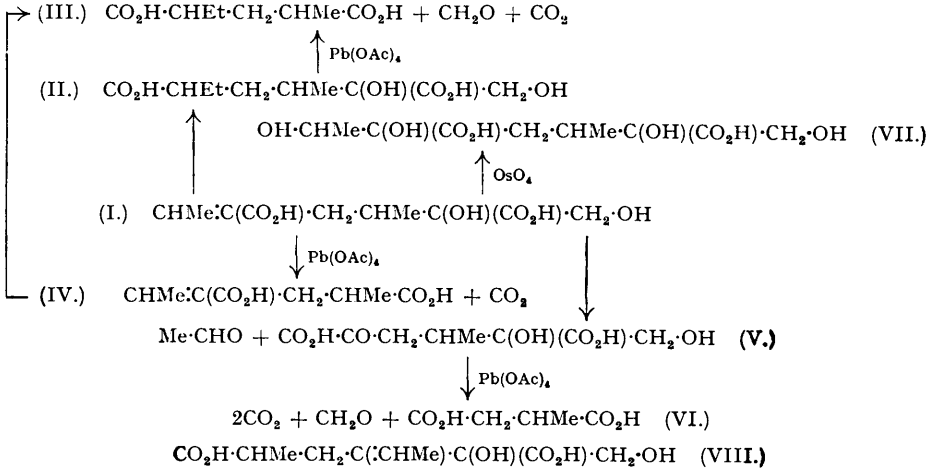
Isatinecic and retronecic acids are cis- and trans-1 : 2-*dihydroxy*-3-*methylhept*-5-*ene*-2 : 5-*dicarboxylic acid*, (I*b*) and (I*a*), respectively.

The glycol moiety is established by the rapid absorption of two equivalents of oxygen and the formation of formaldehyde with periodic acid and with lead tetra-acetate. The slower consumption of a third equivalent of oxygen with these reagents indicated an α-hydroxy-acid grouping, which was established by the quantitative production of carbon monoxide on treatment with concentrated sulphuric acid, and of carbon dioxide on treatment with lead tetra-acetate.

The two acids give, with lead tetra-acetate in aqueous solution, cis- and trans-*α-methyl-γ-ethylideneglutaric acid*, both of which yield the trans-*imide*, whilst the *trans*-acid is hydrogenated to α-methyl-γ-ethylglutaric acid, which in turn is obtained directly by treatment of both dihydroisatinecic and dihydroretronecic (II) acid with lead tetra-acetate. Ozonolysis of retronecic and isatinecic acids, followed by treatment with lead tetra-acetate, gives methylsuccinic acid.

Preliminary experiments with isatinecic acid showed that it contained a glycol grouping because it was readily oxidised with both lead tetra-acetate and periodic acid. With either of these reagents two equivalents of oxygen were rapidly taken up, after which a slower oxidation continued until a third equivalent had been used. The primary nature of one of the hydroxyl groups was revealed by Criegee's glycol test (*Ber.*, 1931, **64**, 260), and by oxidation with two equivalents of lead tetra-acetate to give 0·75 mole of formaldehyde, identified as its dimedon compound. The consumption of the third equivalent of oxygen indicated that the second hydroxyl group was in an α-position to a carboxyl group. That isatinecic acid was an α-hydroxy-acid was confirmed by the formation of a yellow colour with dilute ferric chloride solution (cf. Mitchell, Weinstock, Snell, Stanbery, and Williams, *J. Amer. Chem. Soc.*, 1940, **62**, 1776; Berg, *Bull. Soc. chim.*, 1894, [iii], **11**, 883) and by the production of 0·75 mole of carbon monoxide on treatment with concentrated sulphuric acid (cf. Mitchell *et al.*, *loc. cit.*; Bistrzycki and Siemiradzki, *Ber.*, 1906, **38**, 52).



(III.) $CO_2H{\cdot}CHEt{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H + CH_2O + CO_2$

(II.) $CO_2H{\cdot}CHEt{\cdot}CH_2{\cdot}CHMe{\cdot}C(OH)(CO_2H){\cdot}CH_2{\cdot}OH$

$OH{\cdot}CHMe{\cdot}C(OH)(CO_2H){\cdot}CH_2{\cdot}CHMe{\cdot}C(OH)(CO_2H){\cdot}CH_2{\cdot}OH$ (VII.)

(I.) $CHMe{:}C(CO_2H){\cdot}CH_2{\cdot}CHMe{\cdot}C(OH)(CO_2H){\cdot}CH_2{\cdot}OH$

(IV.) $CHMe{:}C(CO_2H){\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H + CO_2$

$Me{\cdot}CHO + CO_2H{\cdot}CO{\cdot}CH_2{\cdot}CHMe{\cdot}C(OH)(CO_2H){\cdot}CH_2{\cdot}OH$ (V.)

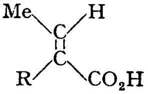
$2CO_2 + CH_2O + CO_2H{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H$ (VI.)

$CO_2H{\cdot}CHMe{\cdot}CH_2{\cdot}C({:}CHMe){\cdot}C(OH)(CO_2H){\cdot}CH_2{\cdot}OH$ (VIII.)

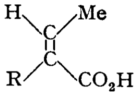
Use of exactly two equivalents of lead tetra-acetate in glacial acetic acid gave only an oily product, so an attempt was made to effect oxidative degradation with the same reagent in aqueous solution whereby the intermediate keto-acid would also be oxidised (cf. Baer, *J. Amer. Chem. Soc.*, 1940, **62**, 1597). Dihydroisatinecic acid was treated in the same manner, whereby, after an initial induction period probably associated with the primary fission of the glycol, a steady evolution of one mole of carbon dioxide was observed.

The oily reaction product slowly deposited a few crystals of an acid, m. p. 67°, and the oil gave an imide, $C_8H_{13}O_2N$, m. p. 113—114°, corresponding to α-methyl-γ-ethylglutaric acid (III) and its imide which Rydon (*J.*, 1936, 1444) reports as melting at 63° and 116°, respectively. Repetition of this oxidation with dihydroretronecic acid gave the same imide. In the absence of an authentic specimen further degradation was necessary. Retronecic and isatinecic acid were accordingly first ozonised and then oxidised with lead tetra-acetate. In conformity with structure (I) for these two acids and with the intermediate formation of the acid (V) on ozonisation, the treatment with lead tetra-acetate gave two moles of carbon dioxide and methylsuccinic acid (VI), characterised further as its acid strychnine salt.

Structure (VIII) would also be capable of giving degradation products (III) and (VI); but this formula was excluded in that oxidation of isatinecic acid with osmium tetraoxide gave a compound with equivalent weight corresponding to dihydroxydihydroisatinecic acid, $C_{10}H_{18}O_8$, m. p. 245°. A compound with structure (VIII) would yield a γ-hydroxy-acid which would be expected to give a lactone. Furthermore, formula (I) is in agreement with spectroscopic data for both retronecic and isatinecic acid (Christie, Kropman, Leisegang, and Warren, preceding paper).



(I*a*.), m. p. 180—181·5°
(IV*a*.), m. p. 151°



(I*b*.), m. p. 148·5°
(IV*b*.), m. p. 95°

(I*a*.) and (I*b*.) : R = $-CH_2\cdot CHMe\cdot C(OH)(CO_2H)\cdot CH_2\cdot OH$
(IV*a*.) and (IV*b*.) : R = $-CH_2\cdot CHMe\cdot CO_2H$

That the two acids were geometrical isomers was shown by oxidation with aqueous lead tetra-acetate to remove the glycol grouping and preserve the ethylenic centres. Retronecic acid yielded trans-α-*methyl*-γ-*ethylideneglutaric acid*, $C_8H_{12}O_4$ (IV) and (IV*a*), m. p. 151°, which gave the trans-*imide*, $C_8H_{11}O_2N$, m. p. 90°, and which on catalytic hydrogenation gave α-methyl-γ-ethylglutaric acid (III) (identified as the imide, m. p. 120—121°). Isatinecic acid, on the other hand, gave cis-α-*methyl*-γ-*ethylideneglutaric acid* (IV) and (IV*b*), m. p. 95°, which yielded an imide, m. p. 90°, identical with that from the *trans*-acid (IV*a*). Hydrolysis of the imide gave the *trans*-acid (IV*a*.). These geometrical configurations are assigned from consideration of the higher melting point of the *trans*-acid and the ready conversion of the *cis*-form into the *trans*-imide.

These structures are in complete accord with the configurations assigned to isatinecic and retronecic acids as *cis*- and *trans*-isomers, which may now be formulated as (I*b*) and (I*a*), respectively.

EXPERIMENTAL.

Action of Concentrated Sulphuric Acid.—Isatinecic acid (0·2153 g.) was treated with concentrated sulphuric acid (25 ml.) in a flask connected to a nitrometer. The air was displaced by carbon dioxide, the flask heated at 140—150° for 100 minutes, and the temperature then raised to 180°. The gas was swept into the nitrometer tube, and the carbon monoxide determined by absorption with ammoniacal cuprous chloride (Found: CO, 14·6 ml. Calc. for $C_{10}H_{16}O_6$: CO, 20·8 ml. at N.T.P. for one hydroxy-acid group).

Oxidation of Dihydroisatinecic and Dihydroretronecic Acid.—(*a*) Dihydroisatinecic acid (3·5 g., 0·015 mol.) in water (60 ml.) on a steam-bath was treated during 1 hour with lead tetra-acetate (14 g., 0·03 mol.). After an induction period, carbon dioxide was steadily evolved (Found: CO_2, 304 ml. at N.T.P. Calc. for $C_{10}H_{18}O_6$, 1 mol. of CO_2: 337 ml.). An excess of 5N-sulphuric acid was added, and the lead sulphate filtered off. The ethereal extract of the filtrate gave an oil which after 2 months yielded a few crystals, m. p. 67°. The oily acid was treated with acetyl chloride at 100°, the excess of acetyl chloride removed, and the resulting oil heated to 200° with urea. The product was made alkaline with sodium hydrogen carbonate. An ethereal extract then gave *cis*-α-methyl-γ-ethylglutarimide which crystallised from light petroleum in fine needles, m. p. 113—114° (uncorr.) (Found: C, 61·75; H, 8·64; N, 8·83. Calc for $C_8H_{13}O_2N$: C, 61·90; H, 8·45; N, 9·03%).

(*b*) Dihydroretronecic acid under similar conditions gave *cis*-α-methyl-γ-ethylglutarimide, m. p. 114° (uncorr.), undepressed by admixture with the imide obtained from dihydroisatinecic acid. Recrystallisation from light petroleum gave crystals, m. p. 120—121°, hydrolysed by concentrated hydrochloric acid to *cis*-α-methyl-γ-ethylglutaric acid, m. p. 72—73° (equiv. wt., 86·8). Rydon (*J.*, 1936, 1944) gave m. p.s of *cis*-α-methyl-γ-ethylglutaric acid (unanalysed) and of its imide as 63° and 116°, respectively.

Oxidations of Retronecic and Isatinecic Acids.—(i) *With periodic acid.* (*a*) Isatinecic acid (*ca.* 0·1 g.) was treated with 0·5N-periodic acid (2 ml.) and set aside. The solution was neutralised with sodium hydrogen carbonate and then treated with 0·1N-sodium arsenite (25 ml.) and 20% potassium iodide (1 ml.), and the excess of arsenite determined iodometrically.

(*b*) The oily dihydroisatinecic acid obtained by catalytic reduction of isatinecic acid was dissolved in water, the concentration was determined by titration, and aliquot portions of 0·1 g. were treated as above, with the following results.

Time (hours)	0·25	0·5	1	2	3	4	16½
	Equivalents of oxygen.						
Isatinecic acid	2·01	2·4	—	—	2·9	—	3·6
Dihydroisatinecic acid	1·6	2·0	2·1	2·2	2·4	2·7	2·9

(*c*) Isatinecic acid (208 mg., 1 mol.), allowed to react with 0·1N-periodate for 45 minutes under the conditions of Reeves (*J. Amer. Chem. Soc.*, 1941, **63**, 1476), gave formaldehyde-dimedon (197 mg., 0·75 mol.), m. p. 190—192°, undepressed by admixture with an authentic specimen.

(ii) *With lead tetra-acetate.* (*a*) Isatinecic acid (*ca.* 0·1 g.) was treated with 0·1N-lead tetra-acetate in glacial acetic acid and set aside. The excess of tetra-acetate was later determined iodometrically. Separate determinations showed that after 0·5, 1, 2, 4, and 9 hours 2·1, 2·3, 2·7, 3, and 3·1 equivalents, respectively, of oxygen were absorbed.

(*b*) Retronecic acid (3·4 g.) was treated with lead tetra-acetate as described for the dihydro-acid (Found : CO_2, 309 ml. Calc. for $C_{10}H_{16}O_6$: CO_2, 328 ml. at N.T.P.). The steam-distillate gave with dimedon the formaldehyde compound, m. p. 186° (uncorr.). The solid from the ethereal extract was crystallised from water to give trans-*α-methyl-γ-ethylideneglutaric acid* as needles, m. p. 151° (uncorr.) (Found : C, 55·86; H, 7·10; equiv. wt., 86·2. $C_8H_{12}O_4$ requires C, 55·82; H, 7·03%; equiv. wt., 86·0). The *imide*, prepared as above and obtained as a solid on the addition of the sodium hydrogen carbonate, was crystallised three times from light petroleum, to give needles, m. p. 90° (single crystal) (Found : C, 62·99; H, 6·80; N, 9·35. $C_8H_{11}O_2N$ requires C, 62·72; H, 7·24; N, 9·14%).

Hydrogenation of the acid in the presence of Adams's catalyst gave an oily acid yielding an imide, m. p. 120—121°, undepressed on admixture with *cis*-α-methyl-γ-ethylglutarimide obtained above.

(*c*) Isatinecic acid (3·5 g.) was treated similarly with lead tetra-acetate (Found : CO_2, 334 ml. Calc. for $C_{10}H_{16}O_6$: 336 ml. at N.T.P.). The oily product from the ethereal extract partly solidified on treatment with concentrated hydrochloric acid. The solid, removed from the oil on a porous plate, crystallised from chloroform–light petroleum to give cis-*α-methyl-γ-ethylideneglutaric acid* as colourless microscopic crystals, m. p. 95° (uncorr.) (Found: C, 55·58; H, 7·17; equiv. wt., 89·4. $C_8H_{12}O_4$ requires C, 55·78; H, 7·03%; equiv. wt., 86). The imide, prepared as above, crystallised from light petroleum in needles, m. p. 90°, undepressed on admixture with the imide from the *trans*-acid. Hydrolysis of this imide with concentrated hydrochloric acid gave the *trans*-acid, m. p. 150°, undepressed on admixture with an authentic specimen.

(iii) *With ozone and lead tetra-acetate.* (*a*) Isatinecic acid (3 g., 0·013 mol.) was ozonised as above, and the product decomposed by water and treated at 100° with lead tetra-acetate (18 g., 0·04 mol.) as above (CO_2 evolved : 502 ml. at N.T.P. Calc. for $C_{10}H_{16}O_6$, 2 mols. of CO_2, 578 ml.). Treatment as for the dihydroisatinecic acid gave a solid which, crystallised from benzene, yielded methylsuccinic acid, m. p. 98°, undepressed by an authentic specimen, m. p. 102° (Found : C, 45·55; H, 6·20; equiv. wt., 66·5. Calc. for $C_5H_8O_4$: C, 45·42; H, 6·10%; equiv. wt., 66·0). Hydrogen strychnine methylsuccinate had m. p. 185° (Ladenburg, *Ber.*, 1895, **28**, 1170, gives m. p. 186°).

(*b*) Rectronecic acid, oxidised similarly, gave methylsuccinic acid, m. p. 109—110° (equiv. wt., 68·17) (hydrogen strychnine salt, m. p. 185°).

(iv) *With osmium tetraoxide.* Isatinecic acid (1 g., 0·004 mol.) in anhydrous ether (250 ml.) was treated with osmium tetraoxide (1 g., 0·004 mol.) and set aside at room temperature for 5 days. The solvent was removed, and the residue heated under reflux with sodium sulphite (10 g.) in water (100 ml.) and ethanol (25 ml.) for 3 hours and then filtered. The filtrate was treated with hydrochloric acid and extracted with ether. The extract gave a small quantity of black solid, which was heated under reflux with potassium hydroxide (1 g.) in methanol (20 ml.) for 3 hours and decolorised with charcoal. The solvent was removed, and the solution acidified. Extraction with ether, evaporation, treatment of the residue with ethyl acetate and filtration gave *dihydroxydihydroisatinecic acid* as colourless crystals (20 mg.), m. p. 245° (Found : equiv. wt., 134. $C_{10}H_{18}O_8$ requires equiv. wt., 133).

The authors wish to thank the S. A. Council for Scientific and Industrial Research for research grants to two of them (M. K. and S. M. H. C.), and for a grant from African Explosives and Chemical Industries (to S. M. H. C.).

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[*Received, December 29th,* 1948.]