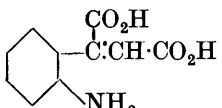
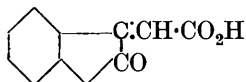
CCCLXXXVII.—*The Relative Stability of the Quinolone and Indolinone Rings.*

By JOHN ALFRED AESCHLIMANN.

Two lactams are derivable from β-carboxy-*o*-aminocinnamic acid (I), and when ring closure takes place on acidification of its alkaline solution either the indolinone (II) or the quinolone (III) will be produced according as the one or the other is the more stable.



(I.)



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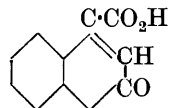
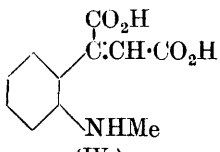


(III.)

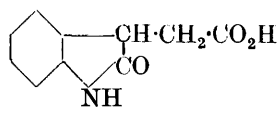
Koenigs and Nef (*Ber.*, 1879, **12**, 100) and Koenigs and Koerner (*Ber.*, 1883, **16**, 2152) oxidised quinoline-4-carboxylic acid by fusion with potash to an acid to which the structure (III) was assigned on account of the production of carbostyril by distillation of the silver salt. This evidence, however, is not conclusive in

view of the high temperature involved. The same acid was obtained by Camps (*Arch. Pharm.*, 1899, **237**, 687) by the action of alkali on 1-acetylisatin and by Borsche and Jacobs (*Ber.*, 1914, **47**, 354) from malonic acid and isatin in acetic acid solution. The last reaction has now been found to take the same course in absence of solvents at 200°, and the identity of the product with that of Camps has been confirmed, even when it was purified by means of non-aqueous solvents to avoid the possibility of isomerisation during purification—a possibility that was overlooked by Borsche and Jacobs. This synthesis would appear to favour the indolinone structure (II) for the acid, which is reducible to a compound formerly described as " oxindole-3-acetic acid " (*vide infra*), but that the acid rightly receives the constitution (III) is shown by its methylation with methyl sulphate and alkali, or by the action of methyl iodide on its methyl ester, producing *methyl* 1-*methyl*-2-*quinolone*-4-*carboxylate* identical with that obtained by esterification of 1-methyl-2-quinolone-4-carboxylic acid. Borsche and Jacobs failed to effect methylation of the acid.

Just as 2-quinolone-4-carboxylic acid (III) is produced from isatin and malonic acid in boiling acetic acid solution by rupture of the indolinone ring and subsequent formation of the quinolone, so also is 1-methyl-2-quinolone-4-carboxylic acid obtained from 1-methylisatin and malonic acid. Borsche and Jacobs (*loc. cit.*), who examined this reaction in acetic acid at 100°, isolated β-carboxy-*o*-methylaminocinnamic acid (IV), but did not convert it into 1-methyl-2-quinolone-4-carboxylic acid. The latter acid, however, is formed under the above conditions, being the " amorphous product " neglected by these authors, and becomes the chief product when the reaction is carried out in boiling acetic acid. Its constitution is proved by its esterification to ethyl 1-methyl-2-quinolone-4-carboxylate identical with a specimen kindly supplied by Dr. Thielepape and prepared by dehydration of α-ethoxalyl-*N*-methylacetanilide (*Ber.*, 1922, **55**, 127). This ester is the only compound of those mentioned above whose synthesis excludes the possibility of its possessing an indolinone structure, and it had not



(IV.)



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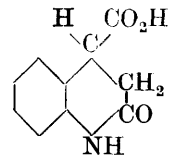
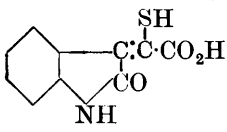


(VI.)

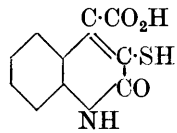
previously been prepared from the acid. The acid (IV) is not dehydrated by prolonged heating in a vacuum at 100—110°, but

above 120°, or in boiling acetic acid solution, ring closure takes place and 1-methyl-2-quinolone-4-carboxylic acid is formed, and this acid is not hydrated by crystallising from water. These facts appear to indicate that the acid (IV) possesses a maleinoid configuration, because the corresponding acids (I) and (III) are readily interconvertible.

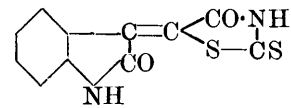
2-Quinolone-4-carboxylic acid is converted by acid or alkaline reducing agents into 2-*keto*-1 : 2 : 3 : 4-*tetrahydroquinoline*-4-*carboxylic acid* (VI), and its methyl ester is reduced by aluminium amalgam in alcohol to the *methyl* ester of (VI), proving that the quinolone ring has remained intact during reduction. The acid (VI) is identical with the " oxindole-3-acetic acid " (V) prepared by Gränacher and Mahal (*Helv. Chim. Acta*, 1923, **6**, 467) by reduction of " oxindole-3-α-thiolacetic acid " (VII), which was obtained by alkaline hydrolysis of 3-rhodanylideneoxindole (IX). Under such conditions the lactam ring would be opened * and subsequent closure would, by analogy with the above cases, produce a thiolquinolone (VIII) reducible to 2-keto-1 : 2 : 3 : 4-tetrahydroquinoline-4-carboxylic acid (VI). The quinolone structure of the thiol acid would account for the stability of the thiol group to ammonia, and is in accordance with its other reactions; a revision of the structural formulæ of its derivatives, however, is necessary. The product obtained by condensing the thiol acid with *o*-phenylenediamine was not dissolved by cold dilute alkalis, probably owing to internal salt formation.



(VII.)



(VIII.)



(IX.)

1-Methyl-2-quinolone-4-carboxylic acid is reduced to 2-*keto*-1-*methyl*-1 : 2 : 3 : 4-*tetrahydroquinoline*-4-*carboxylic acid*, m. p. 171°,

* It appears probable that when Thioindigo Scarlet R is hydrolysed by alkali a similar fission of the lactam ring occurs, since one of the products, which is described as oxindole-3-aldehyde (Friedländer and Kielbasinski, *Ber.*, 1911, **44**, 3101), has acidic properties and is similar to indole-3-carboxylic acid. This acid could be formed by such a fission followed by ring closure between the aldehydo- and the amino-group—the carboxyl group being unable to undergo condensation in presence of alkali.

The production of quinoline-4-carboxylic acids from sodium isatate and compounds containing the $-CO\cdot CH_2-$ group is also a result of the unequal competition between a carboxyl and an aldehydic group for condensation with the amino-group and does not prove the greater stability of the six-membered ring.

identical with the acid formed by methylating 2-keto-1 : 2 : 3 : 4-tetrahydroquinoline-4-carboxylic acid (VI).

In the above cases where there is direct competition between two carboxyl groups for condensation with an amino-group, the production of the quinolone indicates that it is more stable than the indolinone. The preferential formation of the six-membered ring is in agreement with the theory of induced alternate polarities, but this theory would also predict the non-formation of all rings with an odd number of atoms (compare Flürscheim, *Chem. and Ind.*, 1925, **44**, 79).

The colour reaction of 3-methyl-2-indolinone and other oxindole derivatives with potassium dichromate and sulphuric acid (Brunner, *Monatsh.*, 1897, **18**, 536) is given also by the dihydroquinolone-carboxylic acids described in this paper. This fact, however, is not evidence against the quinolone structure of these substances, for the same reaction is given by acetanilide. The reaction is apparently more general than has been supposed, although it seems to be confined to compounds containing the $\cdot C_6H_4\cdot NH\cdot CO\cdot CHR\cdot$ group.

When 2-ketotetrahydroquinoline-4-carboxylic acid (VI) is heated with phosphorus pentachloride, dehydrogenation takes place and 2-chloroquinoline-4-carboxylic acid (Koenigs, *loc. cit.*) is produced. This result is confirmed by the formation of ethyl 2-quinolone-4-carboxylate from the product by the action of alcoholic sulphuric acid. Ethyl 2-chloroquinoline-4-carboxylate, obtained by Thielepape (*loc. cit.*) from ethyl 1-methyl-2-quinolone-4-carboxylate by the action of phosphorus pentachloride and oxychloride, was obtained in small yield under similar conditions from ethyl 2-quinolone-4-carboxylate, additional evidence for its structure thus being furnished. Attempts to replace the chlorine atom of 2-chloroquinoline-4-carboxylic acid by hydrogen and to oxidise 4-methylcarbostyril to the acid (III) were unsuccessful.

Isatin condenses with phenylacetic acid (Gysae, *Ber.*, 1893, **26**, 2484) and with its anhydride (Hübner, *Ber.*, 1908, **41**, 486) to give 3-phenyl-2-quinolone-4-carboxylic acid in each case (Borsche and Jacobs, *loc. cit.*). This acid has now been prepared by the action of hot dilute alkali on 1-*phenylacetylisatin*, obtained by the action of phenylacetyl chloride on 1-sodioisatin. The acid could not be esterified by alcoholic sulphuric acid, in agreement with the structure indicated, containing an ortho-substituent on each side of the carboxyl group.

Halogen Derivatives.

At the time when the available evidence seemed to indicate the indolinone structure for " oxindole-3-acetic acid," it was of interest

to prepare its iodo-derivatives on account of their possible similarity to thyroxin (Kendall, *Ind. Eng. Chem.*, 1925, **17**, 526; *J. Amer. Chem. Soc.*, 1926, **48**, 1384). The conclusive results of Harington (*Biochem. J.*, 1926, **20**, 300) showed, however, that no such similarity could exist.

6-Iodo-2-quinolone-4-carboxylic acid has been prepared by condensing 5-iodoisatin (Borsche and others, *Ber.*, 1924, **57**, 1770) with malonic acid, and is also formed by the action of iodine monochloride on 2-quinolone-4-carboxylic acid in acetic acid and of alkali on 5-*iodo*-1-*acetylisatin*.

2-Ketotetrahydroquinoline-4-carboxylic acid (VI) is not affected by iodine in presence of alkali, but is converted by the action of iodine monochloride in acetic acid solution into a 6(?)-iodo-derivative, the halogen atom of which is stable to alcoholic potash. The monohydrated form in which this derivative crystallises from water is probably the dicarboxylic acid produced by fission of the quinolone ring, for although it behaves as a monobasic acid on titration, as does also the acid (IV), it is dehydrated only in a vacuum at 100°. 2-*Aminophenylsuccinic acid* forms a lactam (VI) more readily than 5-*iodo*-2-*aminophenylsuccinic acid*, an open-ring structure being favoured by the presence of iodine in the benzene nucleus (compare Kendall, *loc. cit.*). 6-Iodo-2-quinolone-4-carboxylic acid also is formed, to the extent of 20%, when iodine monochloride acts on 2-ketotetrahydroquinoline-4-carboxylic acid in acetic acid solution at 100°, the product being characterised by conversion into its *methyl* and *ethyl* esters. Dehydrogenation therefore takes place in the 3 : 4-positions, and an iodine atom enters in the 6-position. A similar dehydrogenation of Kendall's oxindole-3-propionic acid appears much more probable than the imino-ring-structure he suggests.

EXPERIMENTAL.

2-*Quinolone*-4-*carboxylic Acid* (III).—(*a*) A solution of 10 g. of isatin, 0·5 g. of fused sodium acetate, and 7 g. of malonic acid in 50 c.c. of glacial acetic acid was heated for 2 hours. The crystals (8 g.) that separated were washed with alcohol and ether, and a portion for analysis was crystallised from alcohol and sublimed in a vacuum. The acid is more conveniently purified by decolorising an ammoniacal solution with carbon.

(*b*) To a boiling solution of 12 g. of sodium hydroxide in 750 c.c. of water, 25 g. of acetylisatin (or acetylisatic acid) were added and the boiling was continued for an hour. The hot solution was then acidified and the flocculent precipitate at once removed and purified as above. From the filtrate about 4 g. of isatin separated on

cooling. Concentrated or alcoholic alkali produces a greater proportion of isatin (compare Suida, *Ber.*, 1878, **11**, 586).

(*c*) Acetylisatin or acetylisatic acid (but *not* isatin) was converted into the above acid by heating it with crystalline sodium acetate (8 parts) until the solid mass began to fuse for the second time, the temperature being kept at 220° for 10 minutes. The aqueous extract was acidified and the precipitated acid purified as usual.

Only acetylisatic acid was produced by the action of boiling solutions of sodium carbonate, borate or acetate on acetylisatin, or by 1% sodium hydroxide solution at 90°.

The specimens of 2-quinolone-4-carboxylic acid prepared by the above methods melted at 343° (corr.), either alone or mixed (Found : C, 63·0, 63·5; H, 3·9, 3·9; N, 7·2. Calc. : C, 63·5; H, 3·7; N, 7·4%). The monohydrated form crystallises from hot water, in which it is slightly soluble, and behaves as a monobasic acid on titration. It is probably *o*-aminophenylfumaric acid.

The methyl and ethyl esters were formed on boiling alcoholic solutions of the acid with sulphuric acid for 1 hour; they were crystallised from alcohol or benzene. The methyl ester, m. p. 241°, prepared from specimens of the acid obtained by different methods, gave C, 65·0, 65·3; H, 4·35, 4·3 (Calc. : C, 65·0; H, 4·3%). The ethyl ester melted at 205° after sintering at 196°, as did that obtained by Koenigs by the action of ethyl iodide on the silver salt.

2-*Keto*-1 : 2 : 3 : 4-*tetrahydroquinoline*-4-*carboxylic acid* (VI) was prepared by the action of 100 g. of 4% sodium amalgam on a solution of 8 g. of the above acid in dilute alkali for 12 hours. The acid was liberated from the filtered solution and crystallised from hot water or alcohol. Zinc and acetic acid, or boiling hydriodic acid and phosphorus (contrast Koenigs, *loc. cit.*, for the action at 200°), or aluminium amalgam in neutral solution also effects the reduction. The monohydrated form (*o*-aminophenylsuccinic acid) obtained from aqueous solution behaves as a monobasic acid on titration (Equivalent, 209, 210. Calc. : 209). It is dehydrated in 48 hours in a vacuum at room temperature, or in 2 hours at 100° (Loss, 8·6. Calc. for $1H_2O$: 8·6%. Equiv., by titration in alcoholic solution : 190, 190·5. Calc. : 191). The lactam ring is rapidly formed when the disodium salt is acidified. The anhydrous acid melts at 220°, alone or mixed with a specimen of " oxindole-acetic acid " prepared by Gränacher and Mahal's method. The acid was not decomposed by concentrated hydrochloric acid below 200°, and at higher temperatures indefinite products were formed.

The *methyl* ester was formed by the action of methyl-alcoholic

sulphuric acid on the above acid, or by reducing methyl 2-quinolone-4-carboxylate with alcohol and aluminium amalgam or zinc and hydrochloric acid. Crystallised from benzene or alcohol, the specimens melted at 164°, separately or mixed (Found: C, 64·2; H, 5·3. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4%). The *ethyl* ester, m. p. 146°, was obtained by the action of alcoholic sulphuric acid on the acid.

1-Methyl-2-quinolone-4-carboxylic acid was obtained by heating 3·2 g. of 1-methylisatin with 2·1 g. of malonic acid in 10 c.c. of boiling acetic acid for 16 hours. A paste of crystals formed on cooling, and these were separated from the mother-liquor (containing β-carboxy-*o*-methylaminocinnamic acid) and recrystallised from absolute alcohol. Yield 1·6 g.; m. p. 250° (Found: C, 64·5; H, 4·5; equiv., 201, 200. Calc. for $C_{11}H_9O_3$: C, 65·0; H, 4·3%; equiv., 203). It was unchanged by alkali or water.

The ethyl ester was obtained by boiling the acid with alcoholic sulphuric acid. After crystallisation from benzene and alcohol it melted at 134—135°, alone or mixed with a specimen of ethyl 1-methyl-2-quinolone-4-carboxylate obtained from Dr. Thielepape.

The *methyl* ester was obtained by esterification, and also by heating 4 g. of 2-quinolone-4-carboxylic acid (III) in 30 c.c. of methyl alcohol with 4 g. of methyl sulphate for 4 hours, then adding 2 g. of sodium hydroxide and heating for a further 2 hours. The cold product was diluted with water and the crystals that separated were dried and extracted with hot benzene. The residue, and the product separating from the extract on cooling, was methyl 2-quinolone-4-carboxylate. By evaporating the benzene solution and crystallising the residue from a little methyl alcohol, *methyl 1-methyl-2-quinolone 4-carboxylate* was obtained, m. p. 120° (Found: C, 66·2; H, 5·1. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1%). A small yield of this ester was obtained by heating methyl 2-quinolone-4-carboxylate with methyl iodide for 48 hours at 100°.

β-Carboxy-*o*-methylaminocinnamic acid (IV) was obtained by heating 1-methylisatin (4·5 g.) and malonic acid (3·7 g.) with 5 c.c. of acetic acid at 100° for 48 hours. A small quantity of 1-methyl-2-quinolone-4-carboxylic acid was removed, and the aqueous solution concentrated in a vacuum; the dicarboxylic acid then separated. It melts at 163°, is much more soluble in water or alcohol than the quinolone, and behaves as a monobasic acid on titration (Equiv., 221. Calc.: 221).

2-Keto-1-methyl-1 : 2 : 3 : 4-tetrahydroquinoline-4-carboxylic acid is formed by reduction of 1-methyl-2-quinolone-4-carboxylic acid (IV) in dilute alkali by sodium amalgam, and also by treating a solution of 2-keto-1 : 2 : 3 : 4-tetrahydroquinoline-4-carboxylic acid (VI

(2·5 g.) in 10 c.c. of 10% caustic soda with excess of methyl sulphate (seven portions of 1 c.c. each) with shaking. The product is heated with excess of 20% sodium hydroxide solution (30 c.c.) and acidified. The oil which separates is crystallised from water, and then melts at 171° (Found: C, 64·5; H, 5·2. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·3%).

The *methyl* ester, m. p. 80°, is obtained when methyl 1-methyl-2-quinolone-4-carboxylate is reduced in alcoholic solution by aluminium amalgam.

1-*Phenylacetylisatin* was obtained by heating sodioisatin (Heller, *Ber.*, 1907, **40**, 1294) with a benzene solution of an equal weight of phenylacetyl chloride (prepared by heating the acid with excess of thionyl chloride at 100° for an hour and rectifying the product in a vacuum) for an hour. The mixture was filtered hot, and the residue of sodium chloride extracted several times with boiling benzene. 1-*Phenylacetylisatin* separated from the combined filtrates and was recrystallised from benzene–petrol; m. p. 188° (Found: C, 72·0; H, 4·6. $C_{16}H_{11}O_3N$ requires C, 72·4; H, 4·2%).

3-Phenyl-2-quinolone-4-carboxylic acid was formed when the above compound (1·1 g.) was added to a hot solution of 0·5 g. of sodium hydroxide in 20 c.c. of water. After 5 minutes' boiling the deep red solution became pale yellow and the acid was liberated and crystallised from alcohol. It melted at 295°, alone or mixed with the acid obtained by Gysae (*loc. cit.*) from isatin and phenylacetic acid (Found: C, 72·7; H, 4·4. Calc.: C, 72·4; H, 4·2%). The acid was not obtained by heating a mixture of phenylacetic acid (5 g.), isatin (5 g.), and sodium hydroxide (5 g.) in 40 c.c. of water for 12 hours.

The *quinoxaline* derivative of 3-thiol-2-quinolone-4-carboxylic acid (VIII) (the "oxindole-3-thiolacetic acid" of Gränacher and Mahal) was obtained by heating the acid with 20% excess of *o*-phenylenediamine for 24 hours in methyl or ethyl alcoholic solution until hydrogen sulphide ceased to be evolved. The insoluble, brown, amorphous product was purified by extracting soluble matter with more alcohol in a Soxhlet apparatus. It was insoluble in cold alkalis, but dissolved in boiling sodium hydroxide. The combined alcohol could not be removed in a vacuum without decomposition, but was detected qualitatively (Found: C, 67·2, 67·8; H, 4·7, 5·2. $C_{16}H_{11}O_2N_3,C_2H_5\cdot OH$ requires C, 66·9; H, 5·2%. Found: C, 66·4; H, 4·5. $C_{16}H_{11}O_2N_3,CH_3\cdot OH$ requires C, 66·0; H, 4·8%).

2-Chloroquinoline-4-carboxylic acid (2-chlorocinchoninic acid) was obtained when 2-quinolone-4-carboxylic acid or its dihydro-derivative (VI) (5 g.) was heated with phosphorus pentachloride

(25 g.) for 1 hour at 120°, and finally to 150° to remove phosphorus oxychloride. The products after reprecipitation from dilute sodium carbonate solution and crystallisation from alcohol, were identical, melting at 196—200° (decomp.) (Thielepape, *Ber.*, 1922, **55**, 133). On esterification with ethyl alcohol and sulphuric acid, each gave ethyl 2-quinolone-4-carboxylate (Found : C, 65·9; H, 5·2. Calc. : C, 66·3; H, 5·1%).

Ethyl 2-chloroquinoline-4-carboxylate, m. p. 63°, was, however, formed by heating ethyl 2-quinolone-4-carboxylate with phosphorus pentachloride and oxychloride under the conditions described by Thielepape (*loc. cit.*) for its production from ethyl 1-methyl-2-quinolone-4-carboxylate. It was separated from unchanged ester by its greater solubility in benzene.

5-Iodoisatin (compare *Ber.*, 1924, **57**, 1770) was formed by heating a concentrated solution of isatin and a 10% excess of 2*N*-iodine monochloride solution in glacial acetic acid at 100° for 4 hours. Scarlet crystals (m. p. 285°) separated and were washed with alcohol or acetone. The golden-yellow (enolic ?) form (Morton and Rogers, J., 1925, **127**, 2699) crystallised from a solution of the scarlet form in alkali on acidification, but was reconverted into the scarlet form on recrystallisation. The colour, therefore, probably depends on the state of division.

A di-iodo-derivative was not formed by using excess of iodine monochloride.

5-*Iodo*-1-*acetylisatin* separated when a solution of 10 g. of 5-iodoisatin in 50 c.c. of acetic anhydride which had been boiled for 1 hour was cooled. The golden crystals, m. p. 195°, were readily soluble in alcohol, less so in cold benzene or ether (Found : C, 37·5; H, 2·1. $C_{10}H_6O_3NI$ requires C, 38·1; H, 1·9%).

6-Iodo-2-quinolone-4-carboxylic acid was prepared by boiling a solution of 5-iodoisatin (8 g.) and malonic acid (8 g.) in acetic acid (400 c.c.) for 5 hours. The solid which separated (6 g.) was washed with acetone and recrystallised from boiling alcohol. The acid is very slightly soluble in organic solvents and does not melt below 300° (Found : C, 38·1; H, 2·3; N, 4·4. Calc. : C, 38·1; H, 1·9; N, 4·4%). The same acid is formed by boiling 5-iodo-1-acetylisatin (5 g.) with 1% sodium hydroxide solution (250 c.c.) for 1 hour. The product is freed from 5-iodoisatin by solution in dilute ammonia. Its ammonium salt crystallises from concentrated ammonia solutions.

6-Iodo-2-quinolone-4-carboxylic acid was also obtained when a solution of iodine monochloride (10 g.) and 2-keto-1 : 2 : 3 : 4-tetrahydroquinoline-4-carboxylic acid (10 g.) (or 2-quinolone-4-carboxylic acid) in acetic acid (100 c.c.) was boiled for 4 hours.

The heavy, crystalline precipitate (3·5 g.) was washed with alcohol and ether (Found: C, 38·4; H, 2·0%). The iodine atom was removed on reduction with sodium amalgam. The above products were characterised, and their identity proved, by esterifying them for 8 hours with alcoholic sulphuric acid. The esters can be crystallised from hot alcohol; the *methyl* ester has m. p. 261° (Found: C, 39·9; H, 2·8. $C_{11}H_8O_3NI$ requires C, 40·1; H, 2·4%) and the *ethyl* ester has m. p. 223° (Found: C, 42·1; H, 3·0. $C_{12}H_{10}O_3NI$ requires C, 42·0; H, 2·9%).

6(?)-*Iodo*-2-*keto*-1 : 2 : 3 : 4-*tetrahydroquinoline*-4-*carboxylic acid* was obtained by the action of 2*N*-iodine monochloride solution (12·8 c.c.) on a solution of the parent acid (5 g.) in acetic acid (50 c.c.) during 48 hours at room temperature. The solvent was removed in a vacuum on the water-bath, and the gummy residue boiled with water and crystallised from alcohol or 50% acetic acid. The monohydrated acid (*5-iodo*-2-*aminophenylsuccinic acid*) thus obtained melts at 180° if rapidly heated, but at 208° (the m. p. of the anhydrous acid) when slowly heated. The open-ring form is stable at 100° at atmospheric pressure, but is dehydrated at 110° at 15 mm. pressure (Found: C, 35·9, 35·9; H, 3·2, 3·4; loss on drying, 5·2. $C_{10}H_8O_3NI,H_2O$ requires C, 35·8; H, 3·2; H_2O, 5·3%). Both the hydrated and the anhydrous acid are monobasic under all conditions (Equiv.: found, 330 and 312, respectively. Calc.: 335 and 317). The *ethyl* ester has m. p. 169° (Found: C, 41·2; H, 3·1. $C_{12}H_{12}O_3NI$ requires C, 41·7; H, 3·5%).

6(?)-*Bromo*-2-*keto*-1 : 2 : 3 : 4-*tetrahydroquinoline*-4-*carboxylic acid* was obtained by heating equimolecular quantities of 2-keto-1 : 2 : 3 : 4-tetrahydroquinoline-4-carboxylic acid and bromine in acetic acid solution at 100° for 8 hours and isolated similarly to the iodo-derivative. It melts at 191° (Found, in material dried at 100°: C, 44·4; H, 3·4. $C_{10}H_8O_3NBr$ requires C, 44·4; H, 3·0%).

6-*Iodo*-3-*phenyl*-2-*quinolone*-4-*carboxylic acid* was prepared by heating 5-iodoisatin (5 g.) with phenylacetic acid (5 g.) and fused sodium acetate (0·2 g.) at 190—240° for 1 hour. The product, after being boiled with acetic acid, was crystallised from acetone. It did not melt below 300° and was not esterified by heating for 24 hours with alcoholic sulphuric acid (Found: C, 49·0; H, 2·6. $C_{16}H_{10}O_3NI$ requires C, 49·1; H, 2·3%). This acid and its bromine analogue (described by Gysae, *loc. cit.*, as "brom-isaphensaure") can be reduced by sodium amalgam to 2-keto-3-phenyl-1 : 2 : 3 : 4-tetrahydroquinoline-4-carboxylic acid, m. p. 202°, identical with that obtained by reduction of the unhalogenated acid and described by Gysae as "dihydro-isaphensaure."

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