CCCXCV.—6 : 7-*Dimethoxyisatin,* 5 : 6-*Methylenedioxyisatin, and the Nuclear Degradation of* 3 : 4-*Methylenedioxyquindoline.*

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THE experiments described in this communication were made in the course of exploratory synthetical work, and are here collectively recorded on account of their independent interest.

(A) Numerous unsuccessful attempts were made to prepare 4 : 7-dimethoxyisatin by the ring closure of derivatives of 2 : 5-dimethoxyaniline.

Incidentally, it was noted that the nitration of aceto-4-bromo-2 : 5-dimethoxyanilide (I) gave rise to aceto-4-nitro-2 : 5-dimethoxyanilide (II) by replacement of the bromine atom.


(B) The reduction of 6-nitro-3 : 4-methylenedioxymandelic acid (III) by means of ferrous sulphate and ammonia, followed by air oxidation of the solution, resulted in the formation of 5 : 6-methylenedioxyisatin (IV). The ring fission to the oxamic acid (V) under the influence of nitric acid has been found to be a smooth process; Jones and Robinson (J., 1917, **111**, 908) concluded that such a reaction must occur, but this deduction was based on the results of experiments on the interaction of nitric acid and di(methylenedioxy)indigotin; the behaviour of the isolated methylenedioxyisatin has not been previously noted.
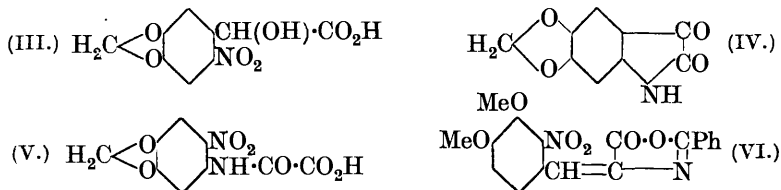

(C) The condensation of 2-nitroveratraldehyde and hippuric acid to a so-called azlactone (VI) was described by Bain, Perkin, and Robinson (J., 1914, **105**, 2403), who found that the product had m. p. 145° and afforded a nitrobenzamidodimethoxycinnamic acid, m. p. 228°. We now find that the melting points are 170° and 224—225°, respectively. Unfortunately, the original specimen

cannot be found, but it is improbable that the substance is dimorphic, and the explanation of the anomaly is, perhaps, to be found in the non-homogeneity of the 2-nitroveratraldehyde formerly employed.

Prolonged hydrolysis of (VI) by means of boiling dilute aqueous-alcoholic sodium hydroxide yielded 6 : 7-*dimethoxyisatin* (VII) and 2-aminoveratric acid (VIII).
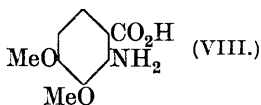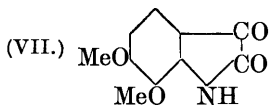

The substance (VII) was also obtained, along with a larger relative amount of an acid, $C_{20}H_{18}O_{10}N_2$, possibly *azodimethoxyphenylglyoxylic acid*, $(MeO)_2C_6H_2(CO \cdot CO_2H) \cdot N_2 \cdot C_6H_2(OMe)_2 \cdot CO \cdot CO_2H$ (IX), by the reduction of 2-*nitro*-3 : 4-*dimethoxymandelic acid* (X) with sodium amalgam. By methods similar to those introduced by Marschalk (*Ber.*, 1912, **45**, 582), the dimethoxyisatin has been reduced to 6 : 7-*dimethoxydioxindole* and 6 : 7-*dimethoxyoxindole* (XI); moreover, the latter substance was independently obtained by the dehydration of 2-*amino*-3 : 4-*dimethoxyphenylacetic acid* (XII).
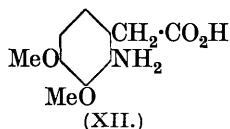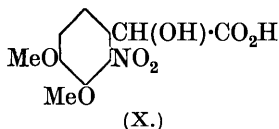
This new method of formation of isatin derivatives involves an intramolecular oxidation–reduction process, and it may be recalled that Robinson and Robinson (J., 1915, **107**, 1753) have previously observed related phenomena in the facile conversion of alkyloxy-2-nitromandelic acids into azoalkyloxybenzoic acids by heating in nitrobenzene solution or by the action of alkalis.

(D) The substance (IV) was originally required for the preparation of 3 : 4-*methylenedioxyquindoline* (XIII), following the analogous quindoline synthesis. Actually, it was found better to obtain (XIII) more directly by condensing 6-aminopiperonal with indoxyl, as illustrated.
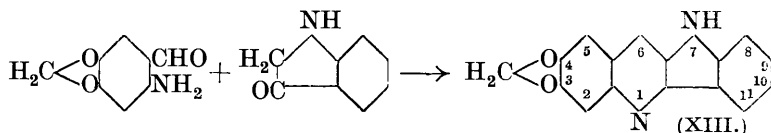
It was hoped to degrade this quindoline derivative to the sole-

remaining unknown simple carboline, namely, δ-carboline,* but, for the reasons mentioned below, this was not accomplished. The breakdown of the methylenedioxy-substituted nucleus by oxidation could not be effected, and no 6-carbolinecarboxylic (or dicarboxylic) acid was obtained in any of the numerous attempts made. When chromic acid was used, a small quantity of an acid, probably correctly represented by the expression (XIV), was isolated.
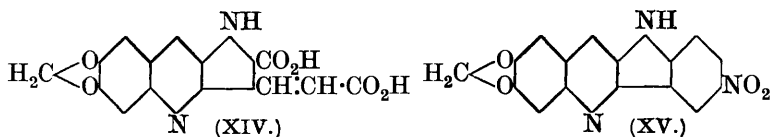

Nitration of 3 : 4-methylenedioxyquindoline gives a mononitro-derivative which is considered to be (XV), because the methylenedioxy-group is stable to hot alcoholic sodium ethoxide (compare Robinson and Robinson, J., 1917, **111**, 929) and on grounds of analogy—for example, with carbazole. Oxidation of (XV) with 47% nitric acid gave traces of an acid which was obtained in somewhat improved yield as the result of the action of boiling 29% or 47% nitric acid on 3 : 4-*dihydroxyquindoline* (XVI). The product initially obtained was a mixture of a dicarboxylic acid, exhibiting the reactions of a pyridine-α-carboxylic acid, and a monocarboxylic acid; this mixture was difficult to separate, and the whole was converted into the monocarboxylic acid by heating with acetic acid.

The analysis and properties of this substance showed that it was 7-*nitro-δ-carboline*-3-*carboxylic acid* (XVII), but the small quantity available did not allow of an extension of the work and another

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* In numbering the carbolines, it has been usual to indicate the carbon atoms common to two rings, but this is not in harmony with the system adopted for other condensed nuclear types. We suggest that the substances previously called 3-carboline (Lawson, Perkin, and Robinson, J., 1924, **125,** 626), 4-carboline (also called *nor*harman; compare Kermack, Perkin, and Robinson, J., 1921, **119,** 1602), 5-carboline (Robinson and Thornley, J., 1924, **125,** 2169), and 6-carboline should really be named 2-, 3-, 4-, and 5-carbolines, respectively, but that possible confusion would be avoided if they were termed the α- β-, γ-, and δ-carbolines, respectively. The numbering will then be independent of the name, and we suggest the adjoined scheme for β-carboline. This has the advantage that it will serve for all the carbolines. The numbers 10, 11, 12, 13 can be used to denote their fused positions, when necessary.
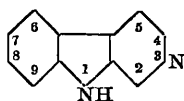
method of synthesis of δ-carboline had to be adopted. This, it is hoped, will be described in a later communication.

(XVI.)

(XVII.)
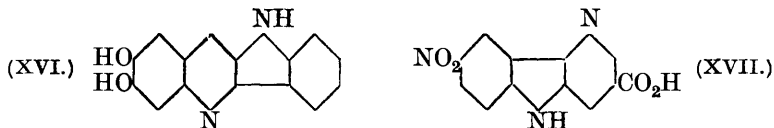
(A) 2 : 5-*Dimethoxyaniline.*—Some difficulty was experienced in the preparation of this substance, and we therefore give details of a convenient process.

Nitroquinol dimethyl ether (100 g.) was gradually added to a well-stirred mixture of water (400 c.c.), acetic acid (10 c.c.), and iron filings (200 g.), steam-heated in a Perkin pot (a metal digester with stirrers rotating in opposite directions). After an hour, following the addition of the last portion of the nitro-compound, the mixture was rendered alkaline and distilled in super-heated steam. Colour-less pearly plates were collected, but it was found advisable to extract the aqueous solution with benzene owing to the solubility of the base in water (yield, 68 g. or 82%).

Di-(2 : 5-*dimethoxyanilino*)*aceto*-2 : 5-*dimethoxyanilide,*

$$[C_6H_3(OMe)_2 \cdot NH]_2 CH \cdot CO \cdot NH \cdot C_6H_3(OMe)_2 \ (?).$$
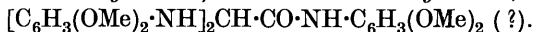
—This substance, which may also have the constitution of a diamino-diphenylmethane derivative, was obtained as the result of an attempt to apply Sandmeyer's *iso*nitrosoacetanilide isatin synthesis (*Helv. Chim. Acta*, 1919, **2**, 234).

Concentrated sulphuric acid (25 c.c.) was quickly added to a mixture of 2 : 5-dimethoxyaniline (5 g.), chloral hydrate (5·41 g.), hydroxylamine hydrochloride (2·27 g.), and water (25 c.c.), the temperature being raised to the boiling point and solution to a greenish-brown liquid occurring. The whole was boiled for 15 minutes, during which the colour of the solution became crimson, and, later, a solid was deposited in needles. After cooling, an equal volume of water was added, and the residue separated by filtration was extracted with boiling dilute sulphuric acid (charcoal). The filtered extracts deposited a solid, which was collected (0·8 g.) and crystallised from dilute sulphuric acid (charcoal); it then separated in white, voluminous, microscopic, tufted needles, m. p. 298° (decomp.), preceded by darkening and shrinking. This material proved to be the sulphate of the base; it was insoluble in alcohol but dissolved in much boiling water, undergoing appreciable hydrolysis, indicated by separation of a small quantity of cream-coloured, prismatic needles of the base on cooling; the majority of

the material remained in the cooled solution as sulphate, addition of sodium hydroxide precipitating white microscopic needles of the base. The *base*, prepared by trituration of the solid sulphate with dilute sodium hydroxide solution, was crystallised by dissolution in a large volume of ethyl alcohol and concentration of the filtrate, followed by refiltration. Recrystallisation gave very pale pink needles, m. p. 210° (Found : C, 62·9, 63·0 ; H, 6·4, 6·2 ; N, 8·8. $C_{26}H_{31}O_7N_3$ requires C, 62·8 ; H, 6·2 ; N, 8·5%).

This substance is sparingly soluble in most organic solvents, but is readily soluble in pyridine or in hot nitrobenzene. Its solution in hot dilute sulphuric acid deposits, on cooling, white, voluminous, microscopic needles of the sulphate.

2 : 5-*Dimethoxyanilinoacetonitrile*, $(MeO)_2C_6H_3 \cdot NH \cdot CH_2 \cdot CN$, *and* 4 : 4′ - *Di(cyanomethylamino)* - 2 : 5 : 2′ : 5′ - *tetramethoxydiphenyl - methane*, $CN \cdot CH_2 \cdot NH \cdot C_6H_2(OMe)_2 \cdot CH_2 \cdot C_6H_2(OMe)_2 \cdot NH \cdot CH_2 \cdot CN$.— Solutions of formaldehyde (2·8 g. of 40%) and sodium bisulphite (3·4 g. in 8 c.c. of water) were mixed, and 2 : 5-dimethoxyaniline (5 g.) gradually added with heating almost to the boiling point and with constant stirring. The portion of the amine present as an oil subsequent to each addition went slowly into solution ; finally, the reaction was continued for a few minutes after complete disappearance of oil. To the resulting mauve solution, powdered potassium cyanide (2·5 g. of 98%) was added, and the whole heated with stirring for 15 minutes. An oil, solidifying on cooling, separated, and this was collected and washed with water. In order to remove any unchanged dimethoxyaniline or acid amide formed by hydrolysis of the dimethoxyanilinoacetonitrile, the product was treated with cold 5% hydrochloric acid with frequent shaking for $\frac{1}{2}$ hour ; the residue was then collected, washed with water, and dried (4·6 g.). This solid was boiled for 10 minutes with 95% ethyl alcohol (400 c.c.) and, after the mixture had been kept over-night, the liquid was filtered (residue X). The filtrate contained the 2 : 5-dimethoxyanilinoacetonitrile, which crystallised after concentration to about 40 c.c. (including a further quantity obtained from the mother-liquor, the total yield was 3·9 g.). The purification of the 2 : 5-dimethoxyanilinoacetonitrile can also be effected by the use of benzene, this nitrile being easily soluble in cold benzene, whilst all the impurities present in appreciable quantity are insoluble in the cold.

2 : 5-*Dimethoxyanilinoacetonitrile* crystallised from methyl alcohol in white leaflets, m. p. 113·5° (Found : C, 62·4 ; H, 6·4 ; N, 14·7. $C_{10}H_{12}O_2N_2$ requires C, 62·5 ; H, 6·3 ; N, 14·6%). It is easily soluble in acetone or in hot methyl and ethyl alcohols, moderately easily soluble in the cold solvents, and in hot water. It is insoluble in cold dilute mineral acids.

The residue X (0·5 g.) crystallised from pyridine in small, parallelogram-shaped plates, m. p. 236° (Found : C, 63·6, 63·4; H, 5·8, 6·1; N, 14·1. $C_{21}H_{24}O_4N_4$ requires C, 63·6; H, 6·1; N, 14·1%).

4 : 4' - *Di(cyanomethylamino)* - 2 : 5 : 2' : 5' - *tetramethoxydiphenyl - methane* is insoluble in water and benzene, slightly soluble in hot ethyl and methyl alcohols, insoluble in the cold solvents, and easily soluble in hot nitrobenzene and pyridine, crystallising on cooling. It is insoluble in cold dilute hydrochloric acid.

2 : 5-*Dimethoxyanilinoacetamide*, $C_6H_3(OMe)_2\cdot NH\cdot CH_2\cdot CO\cdot NH_2$.— 2 : 5-Dimethoxyanilinoacetonitrile was shaken with ten times its weight of concentrated sulphuric acid, and any rise in temperature was checked by cooling in running water. The brown solution was added to crushed ice, and a white solid, which proved to be unchanged nitrile, slowly separated on stirring. When the filtrate was made alkaline, a further quantity of white solid was precipitated; after being washed with water and dried, this crystallised from benzene in leaflets and then from methyl alcohol in elongated prisms, m. p. 164° (Found : C, 57·3; H, 6·6. $C_{10}H_{14}O_3N_2$ requires C, 57·1; H, 6·7%). 2 : 5-*Dimethoxyanilinoacetamide* is easily soluble in methyl and ethyl alcohols, slightly soluble in hot benzene and water, but practically insoluble in the cold. It is soluble in cold dilute hydrochloric and sulphuric acids, being reprecipitated by sodium hydroxide.

Ox-2 : 5-dimethoxyanilic Acid, $C_6H_3(OMe)_2\cdot NH\cdot CO\cdot CO_2H$.—A mixture of 2 : 5-dimethoxyaniline (5·0 g.) and anhydrous oxalic acid (5·5 g.) was heated in an oil-bath for 1 hour, the temperature not being allowed to exceed 130°. The product was extracted with water, and from the filtered extract an easily solidifying oil separated, followed, on further cooling, by a light yellow solid. This was collected and extracted with boiling, very dilute sulphuric acid (1 c.c. of concentrated acid to 55 c.c. of water). The solid deposited on cooling, after being dried in a vacuum (3·56 g.), crystallised from water in pale yellow, elongated prisms which effloresced in the air to a pale pink powder. A specimen, dried in the air for 4 days, lost water in a vacuum desiccator over sulphuric acid corresponding to $\frac{1}{4}H_2O$; this anhydrous material had m. p. 138° (Found : C, 53·1; H, 5·0. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9%).

The anhydrous *acid* is insoluble in light petroleum, but crystallises from hot benzene, in which it is easily soluble, in prisms.

As was the case with 2 : 5-dimethoxyanilinoacetonitrile, all attempts to effect the ring closure of this substituted oxanilic acid were fruitless. Sulphuric acid, phosphorus trichloride and pentachloride, and phosphoryl chloride were ineffective, as was also the action of aluminium chloride or anhydrous ferric chloride on the

chloride of the acid. We may take this opportunity to remark that negative results were also obtained in experiments on the condensation of oxalyl chloride with aceto-2 : 5-dimethoxyanilide and its monobromo-derivative under the influence of aluminium chloride.

Aceto-4-*bromo*-2 : 5-*dimethoxyanilide*, $C_6H_2Br(OMe)_2\cdot NHAc$.—A mixture of 2 : 5-dimethoxyaniline (3·5 g.), acetic anhydride (3·5 c.c.), and glacial acetic acid (10·5 c.c.) was boiled for ½ hour. After cooling, bromine (5·0 g.) in glacial acetic acid (10 c.c.) was gradually introduced with cooling, and in an hour water was added; a few hours later, the solid was collected, well washed with water, and dried (5·4 g.). It crystallised from methyl alcohol, in which it was easily soluble, in colourless rhombic tablets, m. p. 123° (Found : Br, 29·0. $C_{10}H_{12}O_3NBr$ requires Br, 29·2%). This *derivative* is readily soluble in ethyl alcohol and moderately easily soluble in hot water.

A solution of aceto-4-bromo-2 : 5-dimethoxyanilide (2·0 g.) in glacial acetic acid (8·5 c.c.) was cooled by running water, and nitric acid (1·6 c.c.; *d* 1·42) in glacial acetic acid (3·2 c.c.) was gradually added with shaking and further cooling. After an hour, the volume was made up to 50 c.c. with water; a voluminous, light yellow solid was then deposited, which was collected, washed with water, dried, and crystallised from methyl alcohol. The yield, including a further quantity from the mother-liquor, was 0·93 g. The substance melted at 164°, alone or when intimately mixed with aceto-4-nitro-2 : 5-dimethoxyanilide prepared according to Baessler (*Ber.*, 1884, **17**, 2121) or, more conveniently, by the following method. Aceto-2 : 5-dimethoxyanilide (1 g.) was dissolved in cold glacial acetic acid (14 c.c.), and nitric acid (2 c.c.; *d* 1·42), dissolved in glacial acetic acid (6 c.c.), was quickly added in three portions with shaking and cooling in running water; the agitation was continued for 1 minute with further cooling, and was followed by addition of water (total volume, 100 c.c.). The pale yellow product was collected, washed with water, and dried (1·1 g.). It crystallised from methyl alcohol in pale yellow, silky needles, m. p. 164°.

4-*Bromo*-2 : 5-*dimethoxyaniline*, $C_6H_2Br(OMe)_2\cdot NH_2$.—Aceto-4-bromo-2 : 5-dimethoxyanilide (2·0 g.) was shaken with concentrated hydrochloric acid (20 c.c.); partial solution occurred, followed by separation of the hydrochloride. After the crystals had been partly dissolved by heating on the steam-bath, the liquid was boiled for a few minutes. Complete solution occurred, a solid was then deposited, and finally the whole set to a compact mass. Hot water (70 c.c.) was added, the clear solution cooled and filtered, and the filtrate made alkaline with sodium hydroxide. The precipitated *base* (1·54 g.) was crystallised from methyl alcohol in light grey,

rather irregular, elongated prisms, m. p. 107° (Found : Br, 34·3. $C_8H_{10}O_2NBr$ requires Br, 34·5%); it was easily soluble in methyl and ethyl alcohols, and moderately readily soluble in hot water.

(B) 5 : 6-*Methylenedioxyisatin* (IV).—Crude 6-nitropiperonal, containing 4-nitropyrocatechol methylene ether, may be employed for the preparation of 6-nitro-3 : 4-methylenedioxymandelic acid (Robinson and Robinson, J., 1914, **105**, 1466), but the final product should then be purified by dissolution in aqueous sodium carbonate and crystallisation of the recovered acid.

6-Nitro-3 : 4-methylenedioxymandelic acid (40 g.) was dissolved in aqueous ammonia (233 c.c.; *d*, 0·88) and water (797 c.c.), and a boiling solution of crystallised ferrous sulphate (520 g.) in water (1040 c.c.) gradually introduced with vigorous shaking. After the mixture had been heated on the steam-bath with frequent agitation for ½ hour, the liquid was filtered hot, the black residue being washed thoroughly with hot dilute aqueous ammonia. The reddish-brown filtrate and washings were acidified with concentrated hydrochloric acid, and the resulting crimson solution kept over-night. The red deposit was collected, and a further quantity was obtained by passing air through the cold filtrate for 12 hours. The material was agitated with cold dilute aqueous sodium hydroxide, the solution filtered from the inappreciable greenish residue, and air blown through the filtrate for 4 hours. Addition of hydrochloric acid precipitated a crimson solid; after an hour, this was separated and dried (11·6 g.). Crystallisation from boiling water (6 l.) gave crimson needles (10 g., including a quantity recovered from the mother-liquors); further purification, by repetition of the above-described treatment with sodium hydroxide and recrystallisation from water, gave prismatic needles, m. p. 284° (decomp.) (Found : C, 56·5; H, 2·7. Calc. for $C_9H_5O_4N$: C, 56·5; H, 2·6%).

The substance is moderately easily soluble in water and ethyl alcohol, more easily soluble in glacial acetic acid, from which also it can be crystallised. It dissolves in concentrated sulphuric acid to a blue solution; addition of water then gives a red solution and precipitates small needles. Addition of sodium hydroxide to the deep red, aqueous solution gives a purple coloration, quickly disappearing with the formation of a light yellow solution; the red colour returns on addition of hydrochloric acid.

Ox-6-nitro-3 : 4-methylenedioxyanilic Acid (V).—Finely powdered 5 : 6-methylenedioxyisatin (2·85 g.) was quickly added to a mixture of nitric acid (17 c.c.; *d* 1·42) and water (83 c.c.) previously heated to 60°, and the whole heated on the steam-bath with vigorous stirring for 3 minutes. During this period, the powdered isatin was replaced by a thick paste of yellow needles, which were isolated after the

addition of water. The dry product (3·22 g.) was dissolved in boiling ethyl alcohol (500 c.c.); the filtered red solution deposited crystals on long standing and scratching of the containing vessel. These, recrystallised from ethyl alcohol, a comparatively small volume now being required, formed yellow elongated prisms. When dried in an evacuated desiccator, the transparent crystals effloresced, becoming opaque; the material was finally dried at 102° and then had m. p. 183° (decomp.) (Found : C, 42·6; H, 2·5. $C_9H_6O_7N_2$ requires C, 42·5; H, 2·4%). This *acid* is easily soluble in glacial acetic acid and ethyl alcohol, moderately readily soluble in xylene and water, slightly soluble in benzene, and insoluble in ligroin.

When the acid was heated with aqueous sodium carbonate, complete solution first occurred, followed, owing to hydrolysis, by deposition of a solid, which, after cooling, was separated by filtration. The filtrate contained sodium oxalate, and the residue, after crystallisation from ethyl alcohol, gave light red leaflets, m. p. 195°, consisting of 5-nitro-4-aminopyrocatechol methylene ether.

(C) 5-*Keto*-2-*phenyl*-4-(2'-*nitro*-3' : 4'-*dimethoxybenzylidene*)-4 : 5-*dihydro-oxazole* (VI).—This azlactone was obtained in 75% yield when a mixture of fused sodium acetate (12 g.), 2-nitroveratraldehyde (12 g.), hippuric acid (11 g.), and acetic anhydride (20 c.c.) was heated on the steam-bath. The liquid became deep red, and the crystalline product separated in the course of 5 minutes. After the reaction had been completed by heating on the steam-bath for 10 minutes, alcohol (20 c.c. of 70%) was added and the solid was collected, washed with 70% alcohol until pale yellow, treated repeatedly with boiling water to remove excess of hippuric acid, and dried in a vacuum desiccator (15 g.). The azlactone separated from ethyl alcohol or ethyl acetate in yellow felted needles, m. p. 170° (Found : C, 60·5; H, 4·3; N, 7·7. Calc. for $C_{18}H_{14}O_6N_2$: C, 61·0; H, 3·9; N, 7·9%).

2-*Nitro*-α-*benzamido*-3 : 4-*dimethoxycinnamic Acid*.—The hydrolysis of the azlactone took place readily on boiling with 10% sodium hydroxide solution for 10—15 minutes, or by heating on the steam-bath for 30 minutes with dilute alcoholic hydrochloric acid. The acid crystallised from 70% alcohol in colourless needles, m. p. 224—225° (decomp.) (Found in material dried at 100° : C, 58·1; H, 4·3. Calc. for $C_{18}H_{16}O_7N_2$: C, 58·1; H, 4·3%). This acid dissolves readily in sodium carbonate, alcohol, acetone, and acetic acid, less easily in benzene, ether, and chloroform, and is insoluble in cold water. It is stable to boiling concentrated hydrochloric acid during many hours, but is immediately converted into the azlactone on heating with acetic anhydride.

6 : 7-*Dimethoxyisatin* (VII) *and* 2-*Aminoveratric Acid* (VIII).—A

mixture of the azlactone (8·0 g.), sodium hydroxide (5·0 g.), water (40 c.c.), and ethyl alcohol (120 c.c.) was boiled under reflux for $5\frac{1}{2}$ hours; ammonia was evolved. The dark red solution, after being cooled and filtered, was freed from alcohol by distillation, and acidified by a stream of sulphur dioxide. The precipitate, consisting of benzoic and aminoveratric acids, was collected and treated as described below. The filtrate, which contained the bisulphite compound of dimethoxyisatin, was mixed with excess of concentrated hydrochloric acid, boiled to expel sulphur dioxide, cooled, and extracted three times with chloroform. The extract, after being dried with sodium sulphate and distilled, yielded dark red needles (1·7 g.), which were recrystallised from ethyl alcohol. 6 : 7-*Dimethoxyisatin* forms orange needles, m. p. 212—213° (Found : C, 58·1; H, 4·5; N, 6·6; MeO, 29·1. $C_{10}H_9O_4N$ requires C, 58·0; H, 4·3; N, 6·8; 2MeO, 29·9%), which are readily soluble in acetone and chloroform, but less readily soluble in benzene and ether. It is insoluble in cold aqueous sodium carbonate, but in aqueous sodium hydroxide forms a crimson solution, which becomes pale yellow in a few minutes. The isatin is regenerated by acidification and boiling. With concentrated sulphuric acid, an orange colour is developed, which becomes green or greenish-blue when the solution is shaken with thiophen.

The *semicarbazone* was formed when a mixture of dimethoxyisatin (1·5 g.), semicarbazide hydrochloride (0·81 g.), an excess of sodium acetate, and alcohol (15 c.c.) was warmed on the steam-bath for 5 minutes, and mixed with water. The precipitate crystallised from alcohol or dilute acetic acid in small yellow needles, m. p. 254° (decomp.) (Found in material dried at 100° : N, 21·0. $C_{11}H_{12}O_4N_4$ requires N, 21·2%), which dissolve sparingly in the usual solvents and form an orange solution in aqueous sodium hydroxide.

The precipitate of benzoic and aminoveratric acids (see above) was dried in a vacuum desiccator and crystallised from benzene. 2-Aminoveratric acid, which is sparingly soluble in benzene, separated, and was crystallised first from water and then again from benzene, being obtained in colourless flat needles, m. p. 184° (Found : C, 54·9; H, 5·6. Calc. for $C_9H_{11}O_4N$: C, 54·8; H, 5·6%). The colour developed with alcoholic ferric chloride was reddish-brown, and the presence of a primary aromatic amino-group was shown by diazotisation and coupling with β-naphthol to form a scarlet azo-dye.

The acetyl derivative, prepared by warming the acid for a short time with acetic anhydride and crystallising the product from alcohol or acetone, melted at 191°, and there was no depression of the melting points of this derivative and of the amino-acid itself when respectively mixed with the compounds prepared as described

by Pschorr and Sumuleanu (*Ber.*, 1899, **32**, 3405; compare Kühn, *Ber.*, 1895, **28**, 810).

6 : 7-*Dimethoxydioxindole.*—Dimethoxyisatin (3·4 g.) in boiling water (150 c.c.) was reduced by sodium hydrosulphite (10 g.), and the pale yellow filtered solution cooled. The *product*, which separated in a crystalline condition, was recrystallised (charcoal) from water, giving colourless leaflets, m. p. 200° (decomp.) after softening from 170° (Found : C, 57·4; H, 5·4. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3%).

6 : 7-*Dimethoxyoxindole* (XI).—Dimethoxydioxindole (2·0 g.), mixed with alcohol (10 c.c.), sodium bicarbonate (0·5 g.), and water (45 c.c.), was reduced by the gradual addition of sodium amalgam (35 g. of 4%) while a current of carbon dioxide was passed into the liquid. After remaining over-night, the precipitate was collected and extracted with ether, the solvent evaporated, and the residue crystallised twice from water, giving colourless needles, m. p. 192—193°, moderately easily soluble in alcohol (Found : C, 62·3; H, 5·8. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7%).

2-*Amino*-3 : 4-*dimethoxyphenylacetic Acid* (XII).—The fact that *o*-aminophenylacetic acid is stable under the correct conditions was noted by Neber (*Ber.*, 1922, **55**, 826), and we have employed a similar method in the present instance. A solution of 2-nitro-3 : 4-dimethoxyphenylacetic acid (Kay and Pictet, J., 1913, **103**, 947) (1·0 g.) in dilute aqueous ammonia (30 c.c.) was added to a reducing mixture previously prepared from ferrous sulphate (10·5 g.) in water (100 c.c.) and aqueous ammonia (10 c.c.; *d* 0·880). The whole was heated on the steam-bath for 45 minutes, mixed with a little norite to aid filtration, and the liquid filtered while hot. After the clear filtrate had been evaporated to a small volume on the steam-bath, the *amino-acid* separated in needles, or was extracted by ether, when the solution was cold; recrystallised from water, it formed colourless needles, m. p. 154° (efferv.) (Found in material dried at 100° for 15 minutes : C, 57·0; H, 6·1. $C_{10}H_{13}O_4N$ requires C, 56·9; H, 6·1%). It was readily soluble in cold sodium bicarbonate solution, and gave a diazonium derivative which coupled with β-naphthol in alkaline solution. When the acid was heated in a sulphuric acid bath at 160°, vigorous effervescence took place, and the melt immediately crystallised in needles, which, recrystallised from water, melted at 192—193° and were identical in every way with the dimethoxyoxindole prepared by the reduction of dimethoxyisatin.

The reduction of nitrodimethoxyphenylacetic acid was also effected by means of tin and hydrochloric acid, with the result that dimethoxyoxindole (analysis and m. p.) was produced.

2-Nitro-3 : 4-dimethoxymandelic Acid (X).—2-Nitroveratraldehyde (22 g.) was mixed with glacial acetic acid (175 c.c.) and finely powdered potassium cyanide (25 g.) gradually added with cooling in melting ice. The mixture was allowed to reach room temperature and to remain for 4 days, during which time the aldehyde gradually passed into solution. Addition of water to the reaction mixture produced a faintly yellow precipitate; this was isolated and heated with hydrochloric acid (100 c.c.) on the steam-bath until completely decomposed. On addition of water (200 c.c.), a yellowish-green product separated, which crystallised from water in granular crystals, m. p. 127° (yield, 15 g.) (Found : C, 47·1; H, 4·6. $C_{10}H_{11}O_7N$ requires C, 46·7; H, 4·3%). The *acid* is moderately readily soluble in acetic acid, alcohol, or hot water and only slightly soluble in cold water.

Reduction of 2-Nitro-3 : 4-dimethoxymandelic Acid with Sodium Amalgam.—The acid (3·8 g.) was suspended in water (100 c.c.), and sodium amalgam (48 g. of 5%) added in small portions with cooling; the acid slowly dissolved to a faintly yellow solution. When the evolution of hydrogen ceased, the solution was acidified with hydrochloric acid; a yellow crystalline substance separated. On recrystallisation from water, it was obtained in faintly yellow plates, m. p. 178° (decomp.) (Found : C, 54·2, 53·8; H, 4·2, 3·7. $C_{10}H_9O_5N$ requires C, 53·8; H, 4·0%). This *substance* is soluble in aqueous alkalis but insoluble in acids. It is rather readily soluble in hot water and alcohol, and separates again on cooling. From its properties, it was concluded that the substance was an azobenzenedicarboxylic acid of the formula $C_{20}H_{18}O_{10}N_2$, but this is uncertain and provisional. After removal of this substance by filtration, the acid solution was extracted with ether. The ethereal solution was dried and evaporated; the reddish-yellow residue crystallised from alcohol in needles which, alone or mixed with a specimen of 6 : 7-dimethoxyisatin prepared as above from the azlactone, melted at 212° (Found : C, 57·6; H, 4·6%).

(D) *6-Aminopiperonal.*—The details given by Rilliet and Kreitmann (*Helv. Chim. Acta*, 1921, **4**, 588) for the preparation of this substance were followed. 6-Nitropiperonal (800 g.) gave 6-nitro-piperonylidene-*p*-toluidine (930 g.), 6-aminopiperonylidene-*p*-toluidine (437 g.), and 6-aminopiperonal (150 g.). In the first stage, nitropiperonal was worked up in 200-g. quantities; in the second, 96 g. of nitropiperonylidene-*p*-toluidine were used in each operation. By concentrating the aqueous solutions (total volume, 66 l.) from which the aminopiperonal separated, the yield was considerably augmented.

3 : 4-Methylenedioxyquindoline (XIII).—The indoxyl content of

the technical indoxyl fusion used in this preparation was found to be about 15%.

6-Aminopiperonal (59·2 g.) was dissolved in aqueous ethyl alcohol (500 c.c. of 95%) in a flask provided with a reflux condenser and kept filled with coal gas; technical indoxyl fusion (264 g., containing 39·6 g. of indoxyl) was quickly added, and the whole boiled with frequent shaking for 4 hours. During the reaction, the product, which was probably aminopiperonylideneindoxyl, separated from the solution, and finally, after cooling, it was collected, washed thoroughly with water, and dried. Addition of water to the green alcoholic filtrate furnished a further small quantity. The product was now boiled with glacial acetic acid for 3 hours, the resulting solution mixed with a little water, insufficient to cause precipitation, and filtered, and the filtrate basified with sodium hydroxide. The precipitated base was collected and extracted with boiling nitro-benzene and the yellow product separating from the filtered dark-coloured extract was collected, washed with ether, and dried. As a small quantity of the base remained in the nitrobenzene, the combined filtrates from several preparations (total volume, 4 l.) were steam-distilled. The solid residue was dissolved in hot glacial acetic acid and purified as described above. 120 G. of 6-aminopiperonal (theoretical quantity + 15 g.) and 564 g. of technical indoxyl fusion (84·6 g. of indoxyl) gave 150 g. of 3 : 4-*methylenedioxyquindoline*. Crystallisation from toluene and then from pyridine gave the pure base in light yellow prisms, m. p. 280° (Found : C, 73·3; H, 3·8. $C_{16}H_{10}O_2N_2$ requires C, 73·3; H, 3·8%). It is readily soluble in hot pyridine or nitrobenzene, moderately readily soluble in hot toluene, xylene and alcohol, and sparingly soluble in hot benzene and light petroleum. The alcoholic solution exhibits a violet fluorescence.

Addition of dilute hydrochloric or sulphuric acid to the dilute acetic acid solution of the base precipitated the corresponding yellow, sparingly soluble salt. The yellow solution in concentrated sulphuric acid had a blue fluorescence and, when diluted with water, gave a yellow precipitate whose solubility in aqueous alkali indicated sulphonation.

The methosulphate is soluble in hot water, but insoluble in the cold solvent. Its behaviour resembles that of quindoline metho-sulphate (Armit and Robinson, J., 1922, **121**, 827) in that it gives with aqueous alkali a sandy red methohydroxide and no anhydron-ium base soluble in neutral organic solvents.

Oxidation of 3 : 4-*Methylenedioxyquindoline. Formation of an Acid,* $C_{16}H_{10}O_6N_2$ (possibly XIV).—Rapid oxidation occurred when chromic acid was added to a boiling glacial acetic acid solution of the base; in the experiments performed, the quantity of chromic

acid employed varied from the amount necessary for the formation of δ-carbolinedicarboxylic acid to three times this amount. Only attempts involving the use of the minimum of chromic acid had any measure of success.

Chromic acid (11 g.) in water (11 c.c.) was very slowly added during $1\frac{1}{2}$ hours to a boiling solution of 3 : 4-methylenedioxyquindoline (5 g.) in glacial acetic acid (100 c.c.), and the reaction was continued for $\frac{1}{2}$ hour. The mixture, after dilution with water, was evaporated to dryness to remove all the acetic acid, and chromium was eliminated from a solution of the residue by means of ammonia. The yellow filtrate and washings were concentrated until inorganic salts separated from the hot solution (15 c.c.), which was then acidified to Congo-red. After remaining over-night, the solid was collected, washed with water, and extracted with aqueous sodium bicarbonate; the filtered yellow solution was acidified with acetic acid, and the white precipitate collected (0·15 g.). The *acid* crystallised from nitrobenzene in clumps of fine microscopic needles, m. p. 312° (decomp.) (Found in material dried in a vacuum desiccator for 3 days: C, 58·9; H, 3·6; N, 8·5, 8·8, 8·6; loss at 105°, inappreciable. $C_{16}H_{10}O_6N_2$ requires C, 58·9; H, 3·1; N, 8·6%).

This acid is insoluble in water, alcohol, toluene, and xylene, moderately easily soluble in hot nitrobenzene, and very readily soluble in pyridine. Its solution in cold dilute aqueous sodium bicarbonate, when acidified with acetic acid, deposits microscopic diamond-shaped tablets. It does not appear to possess any pronounced basic properties, being insoluble in dilute acetic acid and 10% hydrochloric acid. Although soluble in hot glacial acetic acid, it separates on cooling. The material, however, seemed to be very slightly soluble in hot, moderately concentrated hydrochloric acid, separating when allowed to cool. It does not give the colour reaction with ferrous sulphate characteristic of pyridine-α-carboxylic acids.

10-*Nitro*-3 : 4-*methylenedioxyquindoline* (XV).—Finely powdered 3 : 4-methylenedioxyquindoline (5·0 g.) was gradually added to concentrated nitric acid (100 c.c.; d 1·42) with good stirring and cooling in running water; the mixture was then frequently triturated during $1\frac{1}{2}$ hours. The thin yellow paste of the nitrate was slowly replaced by a thick orange paste, containing a voluminous crystalline solid, which was collected after the addition of water. Cold dilute sodium hydroxide solution was added to an aqueous suspension of this nitrate, and the resulting *base* isolated and dried at 105° (5·8 g.). It was readily soluble in nitrobenzene, from which it crystallised in microscopic red needles (Found : C, 62·3; H, 3·1. $C_{16}H_9O_4N_3$ requires C, 62·5; H, 2·9%). Heated to 360°, it decomposed but did

not melt, and the following colour changes were observed : 250°, change from red to yellow; 301°, light brown; 314°, medium brown; 325°, medium to dark brown; 344°, very dark brown.

The base is insoluble in alcohol and xylene, but easily soluble in pyridine. Concentrated sulphuric acid gave a red solution, and addition of water precipitated the yellow sulphate of the base; addition of alkali to the diluted solution liberated the free base, so that sulphonation had not occurred. Although the base is insoluble in aqueous alkalis, it is moderately easily soluble in cold alcoholic alkali, yielding a crimson solution; boiling ethyl-alcoholic potassium hydroxide does not affect it. The base is sparingly soluble in hot dilute acetic acid, and only slightly soluble in hot glacial acetic acid; needles are deposited from the latter solution on cooling.

The base was oxidised when chromic acid was added to its suspension and solution in boiling glacial acetic acid, but only unchanged material, in the form of a very sparingly soluble chromate, could be isolated. Subsequent to conversion of this chromate into the free base, followed by drying and weighing, it was observed that the amount of chromic acid necessary to oxidise the nitromethylenedioxyquindoline which had disappeared to carbon dioxide and water corresponded approximately to the quantity of chromic acid used.

Whereas boiling 29% nitric acid did not appear to cause appreciable oxidation, boiling 47% nitric acid gave minute quantities of a product having properties identical with those exhibited by the material arising from the interaction of hot 29% or 47% nitric acid and 3 : 4-dihydroxyquindoline (below).

3 : 4-*Dihydroxyquindoline* (XVI).—A mixture of 3 : 4-methylenedioxyquindoline (3·0 g.), phenol (40 g.), resorcinol (5 g.), and hydriodic acid (30 g.; d 1·7) was boiled for 9 hours and subsequently steam distilled to remove phenol. The cooled residue was then made alkaline with sodium hydroxide and shaken for a few minutes, and the liquid filtered, leaving unchanged 3 : 4-methylenedioxyquindoline (1·7 g.). The filtrate and aqueous washings were acidified with dilute sulphuric acid; the sulphate of 3 : 4-dihydroxyquindoline was then precipitated (2·0 g.).

Owing to the unsatisfactory yield, this process was superseded by an application of the method of Späth and Lang (*Ber.*, 1921, **54**, 3071), which gave consistently good results.

3 : 4-Methylenedioxyquindoline (5 g.), along with potassium hydroxide (5 g.) and methyl alcohol (25 c.c.), was heated at 180—190° for 8 hours in an evacuated sealed tube. The product generally consisted of a clear brown liquid; in a few instances, small quantities of unchanged base were also present. The contents of the tubes

were diluted with water and filtered, giving a brown solution having a green fluorescence (all operations in which the reaction product came into contact with the air were carried out as quickly as possible, in order to avoid oxidation); this was acidified with dilute sulphuric acid, and the precipitated sulphate, after collection, was extracted with about 5 l. of boiling dilute sulphuric acid. The filtered extracts, on cooling, deposited the sulphate in a flocculent condition. After separation, it was treated with dilute aqueous sodium hydroxide, followed as quickly as possible by addition of hydrochloric acid to the filtered alkaline extract. The precipitated yellow hydrochloride was collected and dissolved in the minimum quantity of boiling ethyl alcohol. On cooling, the filtered red alcoholic solution deposited a little solid; this was removed, and the resulting solution concentrated to a small volume. The hydrochloride which separated was purified by solution in hot water, addition of hydrochloric acid, and crystallisation of the precipitated hydrochloride from ethyl alcohol. as before. The yellow elongated prisms did not melt at 308°, but darkened from 273° (Found : C, 54·1; H, 5·0; loss at 105—110°, 13·7. $C_{15}H_{10}O_2N_2,HCl,2\frac{1}{2}H_2O$ requires C, 54·3; H, 4·8; H_2O, 13·6%).

The *hydrochloride* is easily soluble in water, moderately easily soluble in alcohol, and practically insoluble in cold dilute hydrochloric acid; the alcoholic solution exhibits a green fluorescence. The anhydrous hydrochloride is very hygroscopic.

The sulphate is practically insoluble in water and alcohol; the solutions nevertheless exhibit a green fluorescence. It is slightly soluble in hot dilute sulphuric acid. When heated, the colour, originally light brown, became dark crimson; decomposition with frothing occurred at 268°.

Owing to the ease with which it is oxidised, the free base was not isolated in a pure condition. By saturation of an alkaline solution with carbon dioxide, it was precipitated as a brown gelatinous mass, quickly darkening through oxidation; this material, after collection, and washing in turn with water, boiling ethyl alcohol, and ether, was a yellow solid. It was practically insoluble in xylene, sparingly soluble in alcohol, easily soluble in pyridine, and moderately easily soluble in nitrobenzene.

7-Nitro-δ-carboline-3-carboxylic Acid (XVII).—The oxidation of 3 : 4-dihydroxyquindoline was effected in various ways, but the only promising method was that involving the use of nitric acid (29% or 47%). The following is a typical experiment.

3 : 4-Dihydroxyquindoline (from 5 g. of methylenedioxyquindoline) was heated on the steam-bath with 29% nitric acid (135 c.c. of water and 67·5 c.c. of nitric acid, *d* 1·42) for $\frac{1}{2}$ hour; a vigorous reaction

then occurred, and finally the reddish solution, containing tar, was boiled for 40 minutes.   The filtered liquid was cooled and rendered alkaline with sodium hydroxide ; a yellowish solid was then pre-cipitated and redissolved.   After filtering, the crimson solution was acidified with acetic acid and (instead of being kept, whereby a solid [A] would have been deposited) boiled for 2 hours, cooled, and kept over-night.   The solid which had separated was collected and dried at 100°.   The heterogeneous products arising from the above and seven similar experiments were mixed and boiled with glacial acetic acid (200 c.c.) for 9 hours.   The extract, filtered while hot, deposited, on cooling, a considerable quantity of a yellowish solid, consisting of the required material and the majority of the impurity ; the residue was subjected five times to this process of boiling with glacial acetic acid (350 c.c.) for 9 hours, followed by filtration.   The acetic acid solutions were diluted with water, and the precipitated solid, after collection, washing with water, and drying, was extracted with boiling nitrobenzene.   The hot filtrate initially deposited a white solid on cooling, but, on further cooling, a transparent gela-tinous material, soluble in warm nitrobenzene, separated.   After 24 hours, the mixture was slowly heated with shaking, in order to dissolve the jelly, and then slowly cooled to 60° and filtered, the solid insoluble at this temperature thus being removed.   The yellowish material deposited from the first hot glacial acetic acid extract was purified in the same way.   Recrystallisation from nitrobenzene gave very pale yellow, microscopic needles, melting after previous darken-ing and softening at 338—339° (decomp.) ; 50 g. of 3 : 4-methylene-dioxyquindoline gave 4·75 g. of this acid.

The specimen analysed was obtained in the first experiment per-formed, in which the solid (A), previously mentioned, was isolated with a view to attempt its purification.   This was insoluble in ben-zene, toluene, xylene, acetone, nitrobenzene, quinoline, and ethyl alcohol.   It was easily soluble in hot water and hot very dilute acetic acid, and in aqueous alkalis to crimson solutions ; it was soluble in cold aqueous sodium carbonate.   Its aqueous solution with ferrous sulphate gave a reddish precipitate, so the substance was probably a pyridine-α-carboxylic acid.   Repeated attempts to crystallise it from very dilute acetic acid and also from aqueous alcohol resulted in the deposition of a yellow gelatinous solid, retain-ing the properties described above.   During the attempts to purify it by means of dilute acetic acid, however, it was observed that a material was being produced which was insoluble in water and dilute acetic acid but crystallisable from nitrobenzene and identical with the substance, m. p. 338—339° (decomp.), prepared as described above.   This was crystallised from nitrobenzene, washed with ether,

and dried at 105° (Found : C, 55·7; H, 2·8; N, 16·0. $C_{12}H_7O_4N_3$ requires C, 56·0; H, 2·7; N, 16·3%).

There is little doubt that the gelatinous material (A) consists essentially of 7-nitro-δ-carboline-3 : 4-dicarboxylic acid. The attempts to purify the intermediate dicarboxylic acid were abandoned because of its easy decomposition and the small yields obtained in the preparation.

7-*Nitro*-δ-*carboline*-3-*carboxylic acid* is very slightly soluble in hot water, insoluble in cold, and very sparingly soluble in alcohol. It is moderately readily soluble in boiling nitrobenzene and easily soluble in hot quinoline; from the latter solvent, clusters of fine microscopic needles slowly separate after cooling. The acid appears to possess feebly basic properties. Aqueous alkalis give reddish solutions and aqueous ammonia a golden-yellow solution. The acid is insoluble in hot and cold dilute acetic acid, but is moderately readily soluble in hot glacial acetic acid, needles separating on cooling; further, it is moderately easily soluble in hot dilute hydrochloric acid to a yellow solution, from which needles separate on keeping. The acid gives no reaction with aqueous ferrous sulphate, a fact which is in harmony with the theory of its formation from the gelatinous acid (A). On reduction on the steam-bath with ferrous sulphate and ammonia in very dilute solution, a very sparingly soluble substance was isolated; this crystallised from pyridine in light brown, microscopic needles, which darkened but did not melt at 360° (Found : N, 18·0, 17·8. $C_{24}H_{14}O_5N_6$ requires N, 18·0%). This substance is practically insoluble in benzene and xylene, sparingly soluble in ethyl alcohol, methyl alcohol, and nitrobenzene, slightly soluble in glacial acetic acid and water, and moderately readily soluble in pyridine and hot phenol. It dissolves in aqueous sodium carbonate, ammonia, and also in dilute hydrochloric acid and in hot dilute sulphuric acid; on cooling, the sulphate is partly deposited as an orange-coloured solid. This sulphate was collected, washed, and boiled with water; it then dissolved, but, after cooling, a flocculent yellowish precipitate of the free base separated, the weak basic properties of the material being demonstrated in this way.

Attempts were made to diazotise the substance, but no evidence of the presence of a primary aromatic amino-group was forthcoming. Its properties lead to the conclusion that it is 7-*azoxy*-δ-*carboline*-3-*carboxylic acid*.

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