XCII.—*Constitution of Picrorocellin, a Diketopiperazine Derivative from* Roccella fuciformis.

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IN reviewing the vast number of chemical individuals which have been isolated from lichens, the absence of nitrogenous compounds is particularly noticeable. On this account a special interest attaches to picrorocellin, the colourless, crystalline, bitter substance obtained by Stenhouse and Groves (*Annalen*, 1877, **185**, 14) from *Roccella fuciformis* probably coming from the west coast of Africa, and giving indications of having grown on limestone rocks. At the death of Mr. C. E. Groves, the collection of chemical materials which he had assembled was presented to the Royal Institution by the Misses Groves; it included a specimen of picrorocellin, and by the kindness of Sir James Dewar, to whom our thanks are due, this has been entrusted to us for investigation.

Stenhouse and Groves ascribed to picrorocellin the empirical formula $C_{27}H_{29}O_5N_3$, and found that when heated with aqueous sodium hydroxide it is converted into a compound which they represented by the expression $C_{24}H_{25}O_3N_2$, ammonia being liberated. They also found that hot glacial acetic acid containing a small proportion of hydrochloric acid transforms the original substance into the pale yellow xanthorocellin, appearing to have the composition $C_{21}H_{17}O_2N_2$. Furthermore, they oxidised xanthorocellin with nitric acid, obtaining benzaldehyde and benzoic acid, together with a yellow substance which was stated not to be a nitrobenzoic acid, and a sparingly soluble, colourless compound which was not identified.

Whilst we confirm the foregoing results qualitatively, our own experiments have led us to different conclusions regarding the formulæ. This is probably due to the fact that Stenhouse and Groves dried their materials at 100° before analysis and, as will appear later, varying amounts of water and of methyl alcohol may have been thus removed from two of the compounds. The actual composition of picrorocellin is $C_{20}H_{22}O_4N_2$, whilst the substance obtainable by the action of aqueous sodium hydroxide, and produced more economically by heating picrorocellin at the melting point, has the composition $C_{20}H_{20}O_3N_2$; we therefore propose to call this compound *anhydropicrorocellin*. Xanthorocellin has the empirical formula $C_{19}H_{16}O_2N_2$, and is also produced by the more protracted heating of picrorocellin, which is thus decomposed in two stages involving the loss of water and of methyl alcohol, respec-

tively. This conclusion is confirmed by (1) the behaviour of dimethylpicrorocellin, $C_{22}H_{26}O_4N_2$, which contains two methoxyl groups as against one in picrorocellin, (2) the presence of a single methoxyl group in methylanhydropicrorocellin, and (3) the absence of methoxyl groups from xanthorocellin and methylxanthorocellin.

The oxidation of xanthorocellin with nitric acid yields benzaldehyde with benzoic and *p*-nitrobenzoic acids, the last-named having been overlooked because it forms with benzoic acid a molecular compound which obstinately defies ordinary methods of resolution into its components. The sparingly soluble, colourless compound noticed, but not identified by the previous investigators, has the empirical formula $C_5H_4O_4N_2$ and sublimes at 300°, when a portion decomposes; whilst resisting hot nitric acid, it is very readily hydrolysed by dilute sodium hydroxide, giving oxalic acid (2 mols.), ammonia (1 mol.), and methylamine (1 mol.). The absence of methyl alcohol, formaldehyde, and formic acid as products of this decomposition having been established, there does not appear to be any constitution alternative to that of 2 : 3 : 5 : 6-tetraketo-1-methylpiperazine (2 : 3 : 5 : 6-tetraketo-1-methylhexahydro-1 : 4-diazine),

(I.) $\begin{matrix}CO\cdot N(CH_3)\cdot CO\\ CO—NH—CO\end{matrix}$ or (II.) $\begin{matrix}CO\cdot N(CH_3)\cdot CO\\ CO—N{=}C\cdot OH\end{matrix}$,

first obtained by Dubsky (*Ber.*, 1916, **49**, 1039; 1919, **52**, 216), and corresponding with the tetraketopiperazine described by de Mouilpied and Rule (T., 1907, **91**, 176; 1909, **95**, 549). This conclusion receives confirmation from the behaviour towards (1) aniline, which liberates ammonia, producing oxanilide and phenyloxamide, together with a third substance which may be unsymmetrical phenylmethyloxamide, and (2) phenylhydrazine, which yields oxalylphenylhydrazide. Moreover, the corresponding oxidation product from methylxanthorocellin, having the empirical formula $C_6H_6O_4N_2$, is resolved by dilute aqueous sodium hydroxide into oxalic acid (2 mols.) and methylamine (2 mols.), whilst aniline liberates methylamine and produces oxanilide with symmetrical phenylmethyloxamide; consequently, it appears to be 2 : 3 : 5 : 6-tetraketo-1 : 4-dimethylpiperazine, derived from I.

Thence it follows that the constitution of methylxanthorocellin is that of 2 : 5-diketo-3 : 6-dibenzylidene-1 : 4-dimethylpiperazine,

(III.) $\begin{matrix}C_6H_5\cdot CH{:}C—N(CH_3)\cdot CO\\ CO\cdot N(CH_3)\cdot C{:}CH\cdot C_6H_5\end{matrix}$,

a conclusion which we have now confirmed by synthesis, for 2 : 5-diketo-3 : 6-dibenzylidenepiperazine, the compound obtained by Sasaki (*Ber.*, 1921, **54**, [*B*], 163) on condensing diketopiperazine

(glycine anhydride) with benzaldehyde (2 mols.) yields a dimethyl derivative which we find to be identical with methylxanthorocellin. Consequently, xanthorocellin is 2 : 5-diketo-3 : 6-dibenzylidene-1-methylpiperazine,

(IV.) $C_6H_5\cdot CH{:}C(CO{-}NH{-}C{:}CH\cdot C_6H_5)\cdot N(CH_3)\cdot CO$,

which explains the production of benzaldehyde (2 mols.) and tetraketo-1-methylpiperazine on oxidation with nitric acid. The constitution of picrorocellin itself, however, remains uncertain regarding the position (1 or 4) of the *N*-methyl group in the formula

(V.) $C_6H_5\cdot CH(O\cdot CH_3)\cdot CH(CO{-}NH{-}CH\cdot CH(OH)\cdot C_6H_5)\cdot N(CH_3)\cdot CO$,

which, in all other respects, explains the behaviour of the substance including its conversion into anhydropicrorocellin,

(VI.) $C_6H_5\cdot CH(O\cdot CH_3)\cdot CH(CO{-}NH{-}C{:}CH\cdot C_6H_5)\cdot N(CH_3)\cdot CO$,

at the melting point.

These conclusions are further confirmed by the polarimetric evidence. Whilst xanthorocellin (IV) and methylxanthorocellin (III) are optically inactive, picrorocellin (V) with $[M]_D$ 44° approaches internal compensation, which is profoundly disturbed in anhydropicrorocellin (VI) with $[M]_D$ −1558° and in methyl-anhydropicrorocellin,

(VII.) $C_6H_5\cdot CH(O\cdot CH_3)\cdot CH(CO\cdot N(CH_3)\cdot C{:}CH\cdot C_6H_5)\cdot N(CH_3)\cdot CO$,

with $[M]_D$ −2314°, because in both compounds it will be seen that, of the four asymmetric carbon atoms originally present in picrorocellin, the two which have been suppressed are both situated on one side of the plane traversing the carbonyl groups. On the other hand, it is clear that in dimethylpicrorocellin,

(VIII.) $C_6H_5\cdot CH(O\cdot CH_3)\cdot CH(CO\cdot N(CH_3)\cdot CH\cdot CH(O\cdot CH_3)\cdot C_6H_5)\cdot N(CH_3)\cdot CO$,

there is a plane of symmetry passing through the carbonyl groups, and therefore the condition of internal compensation prevails although four carbon atoms are asymmetric; this is confirmed by its optical inactivity.

Reviewing these experiments, it seems probable that picrorocellin is developed in the lichen by inter-molecular condensation of the two α-amino-acids, α-methylamino-β-methoxy-β-phenylpropionic, $C_6H_5\cdot CH(O\cdot CH_3)\cdot CH(NH\cdot CH_3)\cdot CO_2H$, and α-amino-β-hydroxy-β-phenylpropionic acid, $C_6H_5\cdot CH(OH)\cdot CH(NH_2)\cdot CO_2H$, or

of the corresponding acids in which the *N*-methyl group is transposed. With the object of testing this conclusion, and simultaneously deciding the position of the doubtful *N*-methyl group, we propose to attempt the synthesis of picrorocellin on the lines indicated.

At one time it was hoped that the point might be ascertained from the product of oxidising anhydropicrorocellin (VI). Having found that the methyl derivative (VII) is oxidised in acetone by potassium permanganate to benzaldehyde and 2 : 3 : 5-triketo-6-α-methoxybenzyl-1 : 4-dimethylpiperazine,

(IX.) $C_6H_5\cdot CH(O\cdot CH_3)\cdot \underset{\displaystyle CO\cdot N(CH_3)\cdot CO}{\overset{\displaystyle CH\cdot N(CH_3)\cdot CO}{|\quad\quad|}}$,

it was expected that hydrolysis of this compound would yield oxalic acid, methylamine, and α-methylamino-β-methoxy-β-phenylpropionic acid. Had this happened, the corresponding procedure with anhydropicrorocellin (VI) should have given either the above amino-acid, or α-amino-β-methoxy-β-phenylpropionic acid, thus determining the position of the *N*-methyl group; but, unfortunately, the only aromatic product of hydrolysis is, in both cases, phenylpyruvic acid. This must be due to removal of methyl alcohol, transforming the triketopiperazines into acyl derivatives of α-aminocinnamic acid; it has been observed on previous occasions (E. Erlenmeyer, jun., *Ber.*, 1897, **30**, 2976; Ruhemann and Stapleton, T., 1900, **77**, 246) that such compounds are resolved by hydrolysis into phenylpyruvic acid, and thus α-aminocinnamic acid has hitherto escaped isolation.

In conclusion, it is noteworthy that although W. Brieger's compendium of lichen products, recently appearing in the "Handbuch der biologischen Arbeitsmethoden" (E. Abderhalden), embraces 135 compounds to which empirical formulæ have been ascribed, picrorocellin remains, as it was in 1877, the only one which contains nitrogen.

Experimental.

Picrorocellin, $C_{20}H_{22}O_4N_2$ (V).

The better of two specimens in Mr. Groves's collection was recrystallised from boiling alcohol, 5 grams requiring 60 c.c., and separating in massive, transparent, rectangular prisms melting between 190° and 220°, according to the rate of heating, the melting point recorded by Stenhouse and Groves being 192—194° (Found: C = 67·9, 67·5; H = 6·3, 6·3; N = 8·0, 7·9; $CH_3\cdot O$ = 8·8, 8·9. $C_{20}H_{22}O_4N_2$ requires C = 67·8; H = 6·2; N = 7·9; $1CH_3\cdot O$ = 8·7 per cent.). Picrorocellin is insoluble in cold, dilute aqueous acids or alkalis, and resists the action of potassium permanganate in boiling acetone; it remains unaltered when heated in aqueous

alcohol with hydroxylamine or phenylhydrazine acetate. A solution containing 0·9991 gram in chloroform diluted to 25 c.c. gave α_D 0° 30′ in a 1-dcm. tube, whence $[\alpha]_D$ 12·5°, corresponding with $[M]_D$ 44·3°.

The second specimen, containing also colouring matters, fat, and another nitrogenous compound, was treated three times with boiling benzene to extract the major portion of the colouring matters and fat. The residue was powdered, and in quantities of 25 grams treated with a mixture of alcohol (75 c.c.) and 10 per cent. aqueous sodium hydroxide (75 c.c.), which dissolved the picrorocellin; this was precipitated from the filtrate by acetic acid diluted with an equal volume of alcohol. Repetition of this process gave a product which required only one recrystallisation from boiling alcohol.

Dimethylpicrorocellin, $C_{22}H_{26}O_4N_2$ (VIII).—Ten grams of picrorocellin dissolved in a mixture of 10 per cent. aqueous sodium hydroxide (30 c.c.) and alcohol (30 c.c.) were agitated with excess of methyl sulphate, when the dimethyl derivative rapidly separated in quantitative yield as a colourless solid moderately soluble in boiling alcohol, from which it crystallised in lustrous, transparent, elongated prisms melting at 229° (Found: C = 69·2, 69·1; H = 6·7, 6·8; N = 7·6, 7·4; $CH_3{\cdot}O$ = 15·5, 15·7. $C_{22}H_{26}O_4N_2$ requires C = 69·1; H = 6·8; N = 7·3; $2CH_3{\cdot}O$ = 16·2 per cent.). The substance is insoluble in cold, dilute aqueous acids or alkalis, and does not combine with hydroxylamine or phenylhydrazine; it is optically inactive.

Reduction of Dimethylpicrorocellin.—After estimating the methoxyl content by the Zeisel method (at 140°), it was noticed that a solid remained suspended in the hydriodic acid (*d* 1·26); this was filtered and extracted with aqueous potassium iodide, which diminished the colour from bluish-black to pale brown, recrystallisation from boiling water giving minute, lustrous, colourless plates melting at 165° (Found: C = 74·7, 74·5; H = 6·7, 6·7; N = 8·8. $C_{20}H_{22}O_2N_2$ requires C = 74·5; H = 6·8; N = 8·7 per cent.). The substance is insoluble in dilute, aqueous acids or alkalis, and does not yield ammonia with boiling 10 per cent. aqueous sodium hydroxide. It dissolves in concentrated nitric or sulphuric acid without change, and it does not combine with phenylhydrazine. It is to be regarded as 2 : 5-diketo-3 : 6-dibenzyl-1 : 4-dimethylpiperazine,

(X.) $C_6H_5{\cdot}CH_2{\cdot}\underset{\displaystyle CO{\cdot}N(CH_3){\cdot}\underset{\displaystyle CH{\cdot}CH_2{\cdot}C_6H_5}{|}}{\overset{\displaystyle CO}{|}}{\cdot}CH{\cdot}N(CH_3)$,

being subsequently identified with the product of reducing (see below) the dimethyl derivative of Sasaki's 2 : 5-diketo-3 : 6-dibenzylidenepiperazine.

Anhydropicrorocellin, $C_{20}H_{20}O_3N_2$ (VI).—Picrorocellin was treated with about 10 parts of boiling, aqueous sodium hydroxide (10 per cent.) until the liberation of ammonia ceased and a clear solution was produced. The solid substance precipitated by dilute sulphuric acid was triturated with a solution of sodium carbonate and recrystallised, first from alcohol and then from benzene to which light petroleum was added, separating in needles which melt at 155° (Found : C = 71·2; H = 5·8; N = 8·4; $CH_3{\cdot}O$ = 9·0. $C_{20}H_{20}O_3N_2$ requires C = 71·4; H = 5·9; N = 8·3; $1CH_3{\cdot}O$ = 9·2 per cent.). A less wasteful, but more tedious, method of preparation consists in melting picrorocellin in quantities not exceeding 5 grams, and then maintaining the temperature at 180° during five to ten minutes, aqueous vapour being briskly evolved; the colour becomes deep amber and the product, on cooling, sets to a transparent resin in which crystals are embedded and which dissolves slowly in 10 per cent. aqueous sodium hydroxide. The precipitate formed by acetic acid was boiled with 50 per cent. alcohol, which left a small proportion of xanthorocellin undissolved, the anhydropicrorocellin crystallising from the filtrate. A solution containing 1·0135 grams in chloroform diluted to 25 c.c. gave α_D − 18° 48′ in a 1-dcm. tube, whence $[\alpha]_D$ −463·7°, corresponding with $[M]_D$ −1558°.

Methylanhydropicrorocellin, produced by methyl sulphate from a solution of anhydropicrorocellin in aqueous sodium hydroxide, was crystallised from alcohol followed by benzene to which light petroleum was added, and separated in colourless prisms melting at 139° (Found : C = 72·3, 72·3; H = 6·1, 6·2; N = 8·1; $CH_3{\cdot}O$ = 8·8, 8·8. $C_{21}H_{22}O_3N_2$ requires C = 72·0; H = 6·3; N = 8·0; $1CH_3{\cdot}O$ = 8·9 per cent.). A solution containing 0·4991 gram in chloroform diluted to 25 c.c. gave α_D −13° 12′ in a 1-dcm. tube, whence $[\alpha]_D$ −661·2°, corresponding with $[M]_D$ −2314°.

Xanthorocellin (2 : 5-*Diketo*-3 : 6-*dibenzylidene*-1-*methylpiperazine*), $C_{19}H_{16}O_2N_2$ (IV).

As already stated, xanthorocellin is produced by heating picrorocellin beyond the stage at which anhydropicrorocellin is formed, but the more convenient method is that described by Stenhouse and Groves (*loc. cit.*), who added a few drops of hydrochloric acid to a solution of picrorocellin in hot, glacial acetic acid, when a yellow colour was immediately developed; after being boiled during fifteen minutes, the liquid was poured into a large volume of alcohol, and the felted mass of silky threads recrystallised from boiling alcohol, by which the substance is dissolved very sparingly, separating in long, faintly yellow, slender needles melting at 184° (Found : C = 75·2; H = 5·1; N = 9·2; $CH_3{\cdot}N$ = 9·0. $C_{19}H_{16}O_2N_2$ re-

quires C = 75·0; H = 5·3; N = 9·3; $CH_3 \cdot N$ = 9·5 per cent.). The substance does not contain a methoxyl group and is optically inactive. Although insoluble in cold, dilute, aqueous acids and alkalis, it forms a deep yellow solution in a mixture of 10 per cent. aqueous sodium hydroxide and alcohol; moreover, the substance freshly precipitated from such solutions will dissolve in aqueous alkali hydroxides. It is not benzoylated by the Schotten-Baumann process, and does not combine with hydroxylamine or phenylhydrazine.

Methylxanthorocellin (2 : 5-*Diketo*-3 : 6-*dibenzylidene*-1 : 4-*dimethylpiperazine*) was prepared by heating dimethylpicrorocellin (2 grams) with acetic anhydride (15 c.c.) during four hours under reflux, the yellow solution being then poured into a large volume of water. The pale yellow prisms obtained on adding water to a solution of the solid product in alcohol evidently contained solvent of crystallisation, showing signs of fusion on approaching 90°, resolidifying soon after 100°, and finally melting below 140°. On removing this at 100° and recrystallising from light petroleum, the substance separated in slender, very faintly yellow needles melting at 143°. When prepared by the process which converts picrorocellin into xanthorocellin, the product is usually sticky, and although quite suitable for oxidation to tetraketodimethylpiperazine (see below), the separation of methylxanthorocellin, which is probably contaminated with methylanhydropicrorocellin, becomes difficult and wasteful (Found: C = 75·6, 75·5; H = 5·6, 5·5; N = 8·8. $C_{20}H_{18}O_2N_2$ requires C = 75·5; H = 5·7; N = 8·8 per cent.). The substance does not contain a methoxyl group and is optically inactive; it displays remarkable dimorphism, the above-mentioned needles, which attain half an inch in length, changing during twenty-four hours into pale yellow, transparent, rhomboidal prisms melting at the temperature stated. It was subsequently identified with the product of methylating (see below) Sasaki's 2 : 5-diketo-3 : 6-dibenzylidenepiperazine.

Oxidation Experiments.

Xanthorocellin.—Five grams were dissolved in 10 c.c. of boiling glacial acetic acid and allowed to cool slowly, the cold liquid thus remaining free from crystals; 5 c.c. of concentrated nitric acid having been added, there ensued on gentle heating a very vigorous action which required control by cooling at intervals. Meanwhile, slender, colourless crystals rapidly separated, and when action had been completed on the water-bath the liquid set to a semi-solid paste on cooling. Thirty c.c. of alcohol having been added, the solid (1·65 grams) was filtered, washed three times with small

quantities of alcohol, and recrystallised from boiling, glacial acetic acid, which deposited minute, lustrous, transparent, rectangular plates (Found: C = 38·6; H = 2·5; N = 18·1; CH_3·N = 16·9, 17·0. $C_5H_4O_4N_2$ requires C = 38·5; H = 2·6; N = 17·9; CH_3·N = 18·6 per cent.). The substance dissolves readily in boiling water and separates in minute, transparent, four-sided prisms. It has not a definite melting point, becoming brown at about 280° and in part subliming, in part decomposing, at 300°. Although differing somewhat in this respect from tetraketomethylpiperazine as prepared from oxalyl chloride and methyloxamide by Dubsky (*loc. cit.*), whose product is described as beginning to decompose at 260°, the behaviour on hydrolysis (see below) points unmistakably to that substance having the constitution I or II.

The filtrate and washings from the foregoing compound were subjected to a current of steam, the alcohol being followed by benzaldehyde which was converted into the phenylhydrazone (0·8 gram). The aqueous residue yielded a pale yellow, crystalline solid (2·3 grams) on cooling, and it was only after accumulating this product from a larger quantity of xanthorocellin that its identity was established. The difficulty arose from the fact, which does not appear to have been recorded, that benzoic and *p*-nitrobenzoic acids form a compound, in the molecular proportion 2 : 1, crystallising from light petroleum and melting indefinitely at 182—198°. The material obtained from xanthorocellin was recrystallised from boiling water and the product, melting at 192—208°, treated with slight excess of barium carbonate suspended in a moderate amount of boiling water, the barium salt which crystallised from the filtrate on cooling being that of *p*-nitrobenzoic acid. On acidifying the filtrate from barium *p*-nitrobenzoate and recrystallising the precipitate from water, in which it dissolves much more readily than *p*-nitrobenzoic acid, the product melted at 174—184° and, after crystallisation from light petroleum, at 182—198° (Found: C = 61·7; H = 4·1; N = 3·4. $C_6H_4(NO_2)\cdot CO_2H$ requires C = 50·3; H = 2·9; N = 8·4. $2C_6H_5\cdot CO_2H, C_6H_4(NO_2)\cdot CO_2H$ requires C = 61·3; H = 4·1; N = 3·4 per cent.). Moreover, by mixing benzoic and *p*-nitrobenzoic acids in the proportions indicated, and crystallising the product from the solvents mentioned, an exactly similar material was obtained, thus recalling the observation of Salkowski (*Ber.*, 1876, **9**, 24) that when a mixture of the two acids (1 : 1) is neutralised with barium carbonate, a salt having the composition $C_6H_5\cdot CO_2\cdot Ba\cdot CO_2\cdot C_6H_4\cdot NO_2$ is produced.

Methylxanthorocellin.—Proceeding as in the case of xanthorocellin, colourless crystals rapidly separated from the mixed nitric and acetic acids; these having been treated in the same way were

deposited in minute, lustrous, transparent, rhomboidal plates from hot glacial acetic acid (Found: C = 42·5; H = 3·5; N = 16·3. $C_6H_6O_4N_2$ requires C = 42·4; H = 3·5; N = 16·5 per cent.). From the behaviour on hydrolysis and with hot aniline (see below) the substance must be regarded as 2 : 3 : 5 : 6-*tetraketo*-1 : 4-*dimethylpiperazine*, $\begin{matrix}CO\cdot N(CH_3)\cdot CO\\ |\quad\quad\quad |\\ CO\cdot N(CH_3)\cdot CO\end{matrix}$. It is even more resistant to rise of temperature than the monomethyl compound, beginning to darken at about 340°, when a sublimate collects, and undergoing general decomposition at about 360°.

Anhydropicrorocellin.—A solution containing 1 gram in 50 c.c. of cold acetone required about the same weight of finely powdered potassium permanganate to produce a permanent coloration, but the final stage was not definite. On reducing with sulphurous acid the manganese precipitate suspended in water, there remained a white solid which crystallised from boiling water in lustrous, transparent, six-sided prisms melting at 206° (Found: C = 59·7; H = 5·2; N = 10·9; $CH_3\cdot O$ = 11·6. $C_{13}H_{14}O_4N_2$ requires C = 59·5; H = 5·3; N = 10·7; $1CH_3\cdot O$ = 11·8 per cent.). Thus it is to be regarded as 2 : 3 : 5-*triketo*-6-α-*methoxybenzyl*-1(or 4)-*methylpiperazine*; a solution containing 1·0067 grams in chloroform diluted to 25 c.c. gave α_D 0° 45′ in a 1-dcm. tube, whence $[\alpha]_D$ 18·6°, corresponding with $[M]_D$ 48·7°. On evaporating the acetone there remained crystals suspended in benzaldehyde, and the latter having been allowed to undergo oxidation in air, aqueous sodium carbonate left undissolved a small quantity of unchanged anhydropicrorocellin.

Methylanhydropicrorocellin.—A solution containing 1 gram in 50 c.c. of cold acetone remained permanently pink when the same weight of finely powdered potassium permanganate had been added, the filtrate depositing 0·6 gram of colourless crystals on evaporation. Light petroleum added to a solution of the substance in benzene caused the separation of needles in spherical aggregates, or in transparent, rhomboidal plates when crystallisation was tardy (Found: C = 61·0; H = 5·6; N = 10·4; $CH_3\cdot O$ = 10·9. $C_{14}H_{16}O_4N_2$ requires C = 60·9; H = 5·8; N = 10·2; $1CH_3\cdot O$ = 11·2 per cent.). It melts at 176°, and is to be regarded as 2 : 3 : 5-*triketo*-6-α-*methoxybenzyl*-1 : 4-*dimethylpiperazine* (IX); a solution containing 0·4002 gram in chloroform diluted to 25 c.c. gave α_D −0° 15′ in a 1-dcm. tube, whence $[\alpha]_D$ −15·6°, corresponding with $[M]_D$ −43·0°. The precipitate from which the acetone solution was filtered having been suspended in water and reduced with sulphurous acid, benzoic acid separated from the liquid.

Transformations of the Ketopiperazines.

Hydrolysis of Tetraketomethylpiperazine.—Whilst readily soluble in dilute, aqueous sodium hydroxide or carbonate, it is not reprecipitated by acids, and hydrolysis indicated by liberation of ammonia rapidly becomes discernible. On distilling the solution in aqueous sodium hydroxide, collecting the ammonia and methylamine in standardised hydrochloric acid, adding sulphuric acid to the liquid remaining in the flask, and titrating this with potassium permanganate, the basic equivalent and the liberated oxalic acid were estimated in one operation (Found: $C_2O_2 = 71{\cdot}1$; $N = 18{\cdot}0$. $C_5H_4O_4N_2$ requires $2C_2O_2 = 71{\cdot}8$; $N = 17{\cdot}9$ per cent.). Although this result was confirmed by an estimation of the oxalic acid as calcium oxalate, it seemed advisable to examine the distillate for methyl alcohol and formaldehyde, whilst a search for formic acid was made in the residual liquid. A solution of the substance containing 1 gram in aqueous sodium hydroxide was therefore distilled into dilute sulphuric acid, a portion (5 c.c.) of the distillate being found to remain colourless after five minutes' heating on the water-bath with peptone (0·8 gram), hydrochloric acid (5 c.c.), and ferric chloride (3 drops of a 10 per cent. solution); a negative result also followed the application of this test to the distillate after treatment with potassium permanganate, and the residual liquid, having been freed from oxalic acid, did not reduce mercuric chloride. It was necessary to apply these tests because we were long in doubt regarding the condition of one carbon atom; determinations of *N*-methyl were persistently too low, probably because of the high temperature resisted by the substance.

Action of Aniline on Tetraketomethylpiperazine.—According to de Mouilpied and Rule (*loc. cit.*), tetraketopiperazine itself yields an anilide, and this behaviour delayed our recognition of the compound $C_5H_4O_4N_2$ as its methyl derivative, because the substance is rapidly converted into oxanilide, phenyloxamide, and a compound isomeric with phenylmethyloxamide, but melting at 174°. Two grams were heated with 15 grams of boiling aniline during three hours under reflux, the crystals which separated during the next twelve hours being filtered and washed with 5 c.c. of aniline and 10 c.c. of alcohol. The product (4 grams) was extracted six times with boiling water, which left oxanilide (2 grams) undissolved and deposited crystals on cooling. The aniline–alcohol liquor having been subjected to a current of steam, the filtered residual solution gave crystals which were then associated with those separated from the oxanilide and extracted with benzene; this deposited minute, pale yellow needles melting at 174°, and left phenyloxamide (m. p.

226°) undissolved, identity being established by analysis and the melting point of a mixture with the actual substance. In view of the copious evolution of ammonia during the action, we suspect the compound melting at 174° to be unsymmetrical phenylmethyloxamide (Found: C = 60·9; H = 5·4; N = 15·9. $C_9H_{10}O_2N_2$ requires C = 60·7; H = 5·6; N = 15·7 per cent.). It has not yet been possible to confirm this, because the substance does not appear to have been prepared, and an attempt to produce it by heating oxamethane with methylaniline took another course, yielding tetraketopiperazine; but it is not symmetrical phenylmethyloxamide (m. p. 187°), a mixture with that compound beginning to shrink at 172° and becoming completely fused at 180°.

Hydrolysis of Tetraketodimethylpiperazine.—Although not soluble in aqueous sodium carbonate, the dimethyl derivative is rapidly dissolved by the hydroxide, and is completely hydrolysed to methylamine (2 mols.) and oxalic acid (2 mols.) on heating the liquid (Found: C_2O_2 = 65·1; N = 16·4. $C_6H_6O_4N_2$ requires $2C_2O_2$ = 65·9; N = 16·5 per cent.).

Action of Aniline on Tetraketodimethylpiperazine.—Proceeding as in the foregoing case, oxanilide separated from the aniline on cooling, whilst the more soluble product was found to be symmetrical phenylmethyloxamide, melting at 187° (Found: C = 60·7; H = 5·4; N = 15·6. $C_9H_{10}O_2N_2$ requires C = 60·7; H = 5·6; N = 15·7 per cent.) and not depressing the melting point of that substance when mixed with it.

Hydrolysis of 2 : 3 : 5-Triketo-6-α-methoxybenzyl-1(or 4)-methylpiperazine (m. p. 206°).—Two grams were heated on the water-bath with 10 per cent. aqueous sodium hydroxide (40 c.c.) during one and a half hours, sodium oxalate separating in slender needles which changed to transparent prisms, and methylamine being liberated. The filtrate giving scarcely any precipitate with acetic acid was saturated with salt and extracted with ether, which deposited a small quantity of oily matter giving a green coloration with ferric chloride. A voluminous precipitate then appeared in the salt solution, and after recrystallisation from boiling alcohol containing a little water was found to be sodium phenylpyruvate, from which the phenylhydrazone melted at 160° (Found: N = 11·1. $C_{15}H_{14}O_2N_2$ requires N = 11·0 per cent.). An attempt to identify, by heating with ammonia, the α-amino-acid from which the triketopiperazine is derived also failed, the substance being recovered unchanged.

Hydrolysis of 2 : 3 : 5-Triketo-6-α-methoxybenzyl-1 : 4-dimethylpiperazine (m. p. 176°).—Two grams were heated on the water-bath with 10 per cent. aqueous sodium hydroxide (30 c.c.) during

two hours, sodium oxalate separating and methylamine being liberated. On acidifying the filtrate with dilute sulphuric acid, the precipitate consisted of phenylpyruvic acid and melted, after crystallisation from benzene and light petroleum, at 154°, also developing the characteristic deep green coloration with ferric chloride (Found : C = 65·9; H = 4·9. $C_9H_8O_3$ requires C = 65·9; H = 4·9 per cent.).

Methylation of 2 : 5-*Diketo*-3 : 6-*dibenzylidenepiperazine*.—The piperazine derivative was prepared by condensing diketopiperazine (glycine anhydride) with benzaldehyde (Sasaki, *loc. cit.*), and the solution in equal parts of alcohol and aqueous sodium hydroxide (10 per cent.) was treated with methyl sulphate. The product having been crystallised from light petroleum melted at 143°, and was found to be identical, in all respects including dimorphism, with methylxanthorocellin.

Reduction of 2 : 5-*Diketo*-3 : 6-*dibenzylidene*-1 : 4-*dimethylpiperazine*. —The synthetic methylxanthorocellin, prepared as above, was reduced with hydriodic acid (*d* 1·26) at 140°, the suspended solid being washed and extracted with aqueous potassium iodide. After recrystallisation from boiling water, it melted at 165°, and was found to be identical with the product from dimethylpicrorocellin.

The foregoing experiments were made in the Davy-Faraday Laboratory of the Royal Institution.

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