

XLIV.—*On some Oxidation- and Decomposition-products of Morphine Derivatives.*

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WHEN solution of caustic potash is added to solution of apomorphine hydrochloride, the base is precipitated, and speedily redissolves in excess of the precipitant. The solution thus obtained, colourless at first, very rapidly becomes dirty purple or brown, and finally black, an insoluble amorphous black deposit being simultaneously produced. This change is accompanied by an absorption of oxygen, which is so energetic that the alkaline solution can be used (like pyrogallol solution) for the determination of oxygen. Thus, 17.9 c.c. of air (reduced to 0° and 760 in an absorption-tube) were allowed to stand in contact

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with 0.1 gram of apomorphine hydrochloride dissolved in caustic potash :—

Oxygen absorbed in 2 hours, 10.7 per cent.

„ „ 16 „ 20.9 „

and in another experiment, 0.2 gram of apomorphine hydrochloride absorbed in five days from 82.9 c.c. of air (at 0° and 760)

20.4 per cent.

Average percentage in air (Bunsen) 20.9 „

If the oxidised solution thus obtained be acidified with hydrochloric acid and agitated with ether, the ether dissolves out a substance which communicates to the ethereal liquid a magnificent red-purple tint resembling that of permanganate solutions. The production of this colour serves indeed as a good qualitative test for apomorphine, a moderately deep tinge being given to a small quantity of ether by a minute fraction of a milligram of that substance, when dissolved in caustic potash, exposed to the air for an hour, acidified, and agitated with ether.

By evaporation of the ether, an indigo blue-black deposit is left, exhibiting faint traces of crystalline structure. This deposit mainly consists of a colouring matter, which is soluble in alcohol, chloroform, benzene, carbon disulphide, ether, alkaline liquids, and water containing much ammoniacal salts, although insoluble in pure water or dilute acids. The tint communicated to a given bulk of solvent by a given weight of material varies with each solvent, being cerulean blue with solutions of ammoniacal salts, grass-green with dilute sodium carbonate, and of different shades varying from blue to violet and almost crimson with the other solvents above named. The absorption-spectra of solutions of equal strengths but with different solvents are now under investigation by Dr. Gladstone.

To obtain this colouring matter in as pure a state as possible, the crude ethereal solutions were agitated with sodium carbonate solution, and the bright green aqueous liquid thus obtained was acidified with hydrochloric acid. Indigo-blue flakes were thus precipitated, which dissolve, all but traces, in ether. This process was repeated several times, the product finally obtained being wholly soluble in ether, the solubility, however, not being very great, a litre of ether taking up only a few decigrams of substance. Neither the precipitated flakes nor the residue left on evaporation of the solution in ether, chloroform, &c., exhibited any very well defined crystals, although traces of crystalline structure were usually visible, one specimen being distinctly crystalline. The following numbers were obtained :—

A. Precipitated flakes prepared as above—

0.2430 gram gave 0.653 CO₂ and 0.118 H₂O.

0.2880 „ 0.0885 Pt (burnt with soda-lime).

B. Another specimen of flakes from another preparation—

0.2125 gram gave 0.5715 CO_2 and 0.1040 H_2O .

C. Residue left on evaporating ethereal solution of purified flakes—

0.2390 gram gave 0.6470 CO_2 and 0.1170 H_2O .

0.2470 „ 0.0730 Pt.

	Calculated.		A.	Found. B.	C.
C_{40}	480	73.40	73.27	73.35	73.82
H_{34}	34	5.20	5.39	5.44	5.44
N_2	28	4.28	4.37	—	4.20
O_7	112	17.12	—	—	—
<hr/> $\text{C}_{40}\text{H}_{34}\text{N}_2\text{O}_7$..	<hr/> 654	<hr/> 100.00			

Attempts to obtain derivatives from this substance so as to fix its formula proved abortive. The solubility in alkalis and insolubility in acids appear to indicate that the body is a weak acid or a kind of phenol. Its solution in alkalis takes up oxygen slowly, and deposits green or black flakes, but no crystals; the solution in ammonia parts with all the ammonia present at 100° , and slowly loses it over sulphuric acid. No barium, silver, or lead salt could be obtained by double decomposition or treatment with the oxide. A mercury compound, however, is obtainable as a chocolate precipitate when the perfectly neutral solution of the substance in ammonia (obtained by leaving the ammoniacal solution over sulphuric acid for some days) is added to corrosive sublimate solution. A specimen of this substance gave the following numbers :—

A. 0.189 gram gave 0.1280 HgS . $\text{Hg} = 58.40$ per cent.
 B. 0.2105 „ 0.049 AgCl . $\text{Cl} = 5.76$ „

From these numbers it appears probable that the chocolate precipitate is a mixture of calomel (formed by the reduction of the corrosive sublimate) and the mercury salt of some oxidation-product of the blue compound. The quantity of this chocolate substance obtained was too small for further examination.

When kept for two years in a sealed tube, the ethereal solution of the blue compound deposits black flakes, apparently arising from decomposition. Simultaneously with the blue compound, black flakes insoluble in ether are formed by the action of air on a solution of apomorphine in caustic potash. These are insoluble in acids, but somewhat soluble in dilute alkalis, and are probably identical with the flakes above mentioned formed by the further oxidation of an alkaline solution of the blue compound. Nothing fit for analysis could be obtained from these black flakes.

Admitting the accuracy of the empirical formula $C_{40}H_{34}N_2O_7$, the formation of this product from apomorphine may be taken as confirming the view deduced by one of us from previous researches, viz., that apomorphine is a derivative of the *di*-polymeride of morphine, and has consequently a formula containing more carbon than C_{34} .

Apomorphine is not the only body that is capable of giving rise to this colouring matter, deoxymorphine and diapo-dimorphine being both capable of producing it by the same treatment. It is noteworthy, however, that no "tetra" polymeride of morphine or codeine, no derivative from these polymerides, and no body of the class viewed in previous papers as derived from monomorphine or monocodeine is capable of yielding it, at least if the substance operated upon be perfectly free from apomorphine (tetrapo-dimorphine), deoxy-morphine, or diapo-dimorphine. It would therefore appear that the process which, for want of a better term, has been referred to under the name of "polymerisation," exerts a marked action on the chemical character of the substance operated on, as well as on the physical and physiological properties.

§ 2. *Action of Heat on Morphine Derivatives.*

When the aqueous hydrochloride of the base having the composition $(\bar{M} + HCl - H_2O)$, or the mixture of hydrochlorides of bases $(\bar{M} + HCl)$ and $(\bar{M} + 2HCl - 2H_2O)$, &c., described in a former communication (this Journal, 1873, p. 215), is gently heated, the water evaporates, but the mass never solidifies, inasmuch as the gummy, anhydrous hydrochloride melts at a little above 100° ; on continuing to heat, the mass darkens in colour, and at 150° — 180° swells up, and gives off a powerful and peculiar odour; on dissolving the resulting mass in water, adding potash and distilling, a distillate containing *pyridine* is obtained. If the heating be interrupted before the temperature rises to 150° , little pyridine, or none at all, is formed; whence it appears probable that the monomorphine derivatives split up on heating into pyridine and some other substance (probably destroyed by the temperature employed), just as narcotine under analogous circumstances splits up into cotarnine and meconin (Matthiessen and Wright, *Phil. Trans.*, 1869, 667).

The pyridine obtained appears to be mixed with more or less methylaniline, probably from the polymerisation by heat of the base employed (*vide infra*). The purest specimen obtained gave these numbers:—

0.1520 gram of platinum salt gave 0.0539 Pt. = 35.46 per cent.

Calculated for pyridine platinochloride, 34.67 per cent.

Other specimens gave 37—39 per cent. of platinum, and contained

so much methylamine, that the fishy smell of this base overpowered the tarry odour of pyridine, when potash was added to the mixture.

To prove that pyridine was really present in these mixtures, the platinochlorides were boiled with a large bulk of water for some days, when the characteristic platino-pyridine salt of Anderson was precipitated. Of this

0.3000 gram gave 0.1175 Pt.	Pt. = 39.17 per cent.
Calculated for $C_{10}H_6Pt.N_24HCl$.	= 39.75 „

In one experiment a product was obtained, which appeared to contain a higher homologue of pyridine (picoline, lutidine, &c.) but this portion was unfortunately lost, and the presence of these bodies could not be proved in any other specimen.

In a former communication (*loc. cit.*) it has been shown that by the prolonged action of hydrochloric acid on morphine, the monomorphine derivatives first produced become "polymerised," a tetra-base, $(\bar{M}_4 + 2HCl)8HCl = C_{136}H_{154}Cl_2N_8O_{24}, 8HCl$, being formed, together with apomorphine (tetrapodimorphine). Through the kindness of Messrs. Macfarlane, of Edinburgh, we have been enabled to examine the action of heat on the hydrochloride of this tetra-base, which is produced in some little quantity during the manufacture of apomorphine for pharmaceutical use. When it is treated in the same way as the monomorphine derivative above described, quantities of methylamine are obtained, but no trace of pyridine could be found by long-continued boiling of the platino-chloride. No appreciable quantity of ammonia appeared to be produced, the hydrochloride of the volatile base distilled off being wholly soluble in absolute alcohol. The platinum salt made from this gave these numbers:—

0.4500 gram gave 0.1890 Pt.	= 42.00 per cent.
Methylamine platinochloride requires	41.68 per cent.

It is evident from these numbers, that no appreciable amount of pyridine could have been present, pyridine platinochloride requiring 34.67 per cent. of Pt.

On treating apomorphine (tetrapo-dimorphine) hydrochloride in precisely the same way, a just perceptible trace of methylamine was evolved, but no pyridine.

It hence appears that the three series of morphine derivatives, viz., the mono-, di-, and tetra-morphine series, differ in the way in which their hydrochlorides split up by the action of heat, the mono- series eliminating nitrogen in the form of pyridine; the di- series giving no appreciable quantity of any volatile base (at 150°—180°); and the tetra-series giving methylamine under the same circumstances.

In conclusion, we are desirous of expressing our obligations to

Messrs. Macfarlane and Co., of Edinburgh, for their kindness in furnishing us gratuitously, not only with the original morphine requisite for the preparations of the derivatives, &c., obtained by us, but also with a considerable quantity of apomorphine hydrochloride, and various bye-products obtained during its manufacture.

§ 3. By C. R. A. WRIGHT, D.Sc.

Action of Silver Nitrate and Nitric Acid on certain Morphine and Codeine Derivatives.

It has been shown in previous papers that when certain bodies derived from polymerides of morphine or codeine are treated with silver nitrate and nitric acid, a *blood-red* liquid is formed; whilst when similar derivatives containing more hydrogen than that present in the normal morphine polymeride derivatives are treated in the same way, a bright *yellow* liquid is obtained; in some instances the amount of derivative at the operator's disposal was sufficient to enable him to isolate the colouring principles formed.

The derivative was dissolved in about 40 times its weight of boiling water, silver nitrate solution added in excess, and strong nitric acid in small quantity gently dropped into the hot liquid. Carbon dioxide and oxides of nitrogen were evolved with effervescence; all chlorine, bromine, or iodine associated with the compound examined was precipitated as silver salt, and a liquid was obtained, from which amorphous flakes deposited on cooling (after filtration whilst boiling). These flakes were almost insoluble in water in each case, but dissolved in boiling water acidulated with nitric acid, separating again as the liquids cooled; no trace of crystalline structure was noticeable in any instance, the flakes presenting under the microscope the appearance of strings of coalesced globules. Although the products obtained varied much in colour, yet comparatively little difference was noticed in the composition of the flakes. Neither treatment with ammonium sulphate nor with zinc and hydrochloric acid appeared to alter the substances in any way, nor did caustic alkalis produce any change other than solution of small quantities; from which it may be inferred that the substances are neither nitrates nor nitro-compounds. The following numbers were obtained:—

A. *Product from Chlorotetramorphine*.—This product, when purified by recrystallisation (if this term can be used in the case of a non-crystalline substance) from boiling dilute nitric acid, was of a bright scarlet colour, its concentrated solution being blood-red.

0.4760 gram gave 0.901 CO₂ and 0.159 H₂O.

0.4255 „ 0.803 „ 0.141 „

0.3805 „ 0.2015 platinum.

B. *Product from Tetramorphine*.—The purified flakes obtained in this case were brick-red, the solution being of a brownish red colour.

0.4250 gram gave 0.847 CO₂ and 0.162 H₂O.
 0.2415 " 0.4785 " 0.099 "
 0.2845 " 0.1380 Pt.

C. *Product from Tetracodeine*.—This much resembled that from tetramorphine.

0.4510 gram gave 0.8750 CO₂ and 0.179 H₂O.
 0.5405 " 1.049 " 0.216 "
 0.4200 " 0.1900 Pt.

D. *Product from the Base produced by action of Hydriodic Acid and Phosphorus on Codeine, at 135°, viz. [(M̄ + H₈)₄ + 4HI - 12H₂O].*—This was of a yellow tint, with a slight shade of orange; the solution was of a deep yellow colour, slightly inclining to orange.

0.2490 gram gave 0.4800 CO₂ and 0.0980 H₂O.
 0.3305 " 0.1545 Pt.

	A.		B.		C.		D.
Carbon ..	51.62	51.45	54.36	54.04	52.90	52.93	52.57
Hydrogen	3.71	3.68	4.23	4.55	4.41	4.44	4.37
Nitrogen.	7.51		6.89		6.43		6.65

A agrees with the formula, C₂₄H₂₀N₃O₁₃; B approximates to C₉H₈NO₄; C is represented by C₁₉H₁₈N₂O₁₀; whilst D agrees with C₁₈H₁₇N₂O₉. All attempts to obtain derivatives by means of which these formulæ might be controlled proved abortive; fractional separation from hot dilute nitric acid did not cause the substances to separate into two dissimilar portions.

The mother-liquors from which the crude coloured flakes separated in these experiments were distilled with excess of caustic potash. No trace of pyridine was liberated, but ammonia and methylamine came over in some little quantity. The hydrochlorides of these two bases were separated by absolute alcohol, and the platinum salts made and analysed with the following results; contrary to what might have been expected, only traces of methylamine were formed in the case of specimen C from tetracodeine (from which the methyl groups originally present had not been eliminated), whilst larger amounts were produced in all the other instances where the original methyl groups had been expelled by the previous treatments to which the original alkaloid had been submitted.

Specimen A (from chlorotetramorphine).

0.4765 gram gave 0.2005 Pt.

B (from tetramorphine).

0·4520 gram gave 0·1915 Pt.

C (from tetracodeine). Only just sufficient platinum salt was obtained for analysis, a considerable quantity of ammonium chloride being produced; the numbers indicate that the portion taken up by the alcohol was little but ammonium chloride.

0·5260 gram gave 0·2295 Pt.

D (from mother-liquors of D above).

0·4725 gram gave 0·1995 Pt.

E. The product of the action of hydriodic acid on morphine gave a deep yellow liquid, from which flakes separated, precisely resembling those from D above; through an accident, the quantity obtained of these flakes was too small for examination. The mother-liquors treated as the other specimens gave a platinum salt, of which

0·4415 gram gave 0·1875 Pt.

Calculated.		Found.				
		A.	B.	C.	D.	E.
For ammonium platinochloride	Pt=44·27	—	—	43·63	—	—
For methylammonium „	Pt=41·68	42·07	42·36	—	42·22	42·47

The brown product obtained during the extraction of morphine by the Robertson-Gregory process, and referred to on page 218 of this volume, when treated with silver nitrate and nitric acid, yielded flakes of a chocolate-red colour, which contained

Carbon	37·76	36·91
Hydrogen	3·20	2·92

The mother-liquors from which these flakes separated yielded much methylamine; the platinum salt obtained as above gave Pt. = 42·28 per cent.