X.—*Researches on the Polymerides of Morphine and their Derivatives.*

By E. LUDWIG MAYER of Glasgow, and C. R. A. WRIGHT, D.Sc.,
Lecturer on Chemistry in St. Mary's Hospital Medical School.

THE experiments detailed in the several papers united together below were originally commenced by us separately, the first named of us examining the action of zinc chloride on morphine, and the other the actions of hydrochloric and sulphuric acids on the same alkaloid; inasmuch, however, as circumstances have prevented one of us from continuing his investigations, and as the products formed by these different reagents exhibit close family relationships, we think it best to amalgamate our results, and publish them conjointly.

I. *On the action of Zinc Chloride on Morphine.*

When zinc chloride solution of such strength as to boil at about 200° is heated to 120°, a strong solution of morphine hydrochloride then dropped in, and the whole kept at 120°—125° for twenty minutes, a change is produced, inasmuch as the liquid ceases to yield the usual *blue* coloration with ferric chloride, but gives instead a *red* tint with ferric chloride and hydrochloric acid together. When it was poured into water acidulated with hydrochloric acid, a brown amorphous precipitate was obtained on cooling; the filtrate from this gave, on dilution with water, a further amount of amorphous precipitate less coloured than the first; and on standing for some days, crystals formed, fusible at 100° after drying in blotting paper, and solidifying to a crystalline mass; these appeared to be a loose compound of zinc chloride and morphine hydrochloride;* on recrystallisation, crystals containing less zinc we obtained: and, finally, after several recrystallisa-

* Graefinghoff has described (*Jahresbericht*, 1865, 446) a crystalline compound of morphine and zinc chloride, having the formula $C_{34}H_{38}N_2O_6 \cdot 2ZnCl_2 \cdot 4H_2O$.

tions ordinary morphine hydrochloride nearly free from zinc was obtained, the quantity of zinc diminishing at each successive recrystallisation. This hydrochloride gave the usual blue colour with ferric chloride, and yielded on analysis numbers agreeing with those required for morphine hydrochloride :—

Found	Carbon 63·10	Hydrogen 6·28	Chlorine 10·84
Calculated. .	„ 63·46	„ 6·22	„ 11·04

Up to this point no appreciable quantity of anything different from morphine has been formed; but if the action be allowed to proceed further, tetrapodimorphine (“apomorphine”) is formed amounting to 30—40 per cent. of the morphine used: the yield of this base is larger the lower the temperature and the more concentrated the zinc chloride solution, a longer time, however, being required for the conversion. On precipitation of the product with sodium carbonate and treatment with ether, &c., a crystalline hydrochloride was obtained apparently identical in all respects with that produced by the action of hydrochloric acid.

0·4110 gram gave 1·0115 CO₂ and 0·231 H₂O :—

	Calculated.		Found.
C ₆₈	816	67·22	67·12
H ₇₂	72	5·93	6·24
N ₄	56	4·61	—
O ₈	128	10·54	—
Cl ₄	142	11·70	—
<hr/>			
C ₆₈ H ₆₈ N ₄ O ₈ ·4HCl ..	1214	100·00	

When higher temperatures are employed, other products appear to be also formed; thus, after treatment for one hour at 170°, the product obtained, after precipitation with sodium carbonate, treatment with ether, &c., was black and viscid instead of crystalline; this product was digested with animal charcoal, which almost wholly decolourised it, so that a nearly colourless, viscid hydrochloride was obtained after another treatment with sodium carbonate and ether and agitation with hydrochloric acid; a small quantity of flakes formed in the viscid solution; these were separated by a funnel and dissolved in water; on cooling, crystals were obtained, which at first resembled tetrapodimorphine hydrochloride in appearance, but, after standing over sulphuric acid, lost their transparency and communicated a violet tint to water; finally, they became a violet-coloured mass which gave the following numbers :—

0·3576 gram gave 0·8816 CO₂ and 0·2162 of H₂O, which was strongly acid from presence of HCl.

Found	Carbon 67·24	Hydrogen 6·71
Calculated for tetrapodimorphine hy-	,, 67·22	,, 5·93
drochloride.....		

It hence appears, that this substance is either isomeric with tetrapodimorphine, or actually is that substance contaminated with a small quantity of some foreign body which causes the crystals to become violet. The physiological action of the substance was examined by Dr. Reginald Stocker, careful comparison being made between this sample and a specimen of tetrapodimorphine hydrochloride of known purity; no material difference was noticeable between the two. On the other hand, this substance formed a platinum salt which decomposed slowly *in vacuo*, and more quickly in the air, and turned first green and then black at 100°; pure tetrapodimorphine platino-chloride is much more stable. The small amount of the substance formed prevented a more minute examination of its properties.

The viscid hydrochloride from which these flakes had separated gave the following numbers after drying at 100°:—

0·3056 gram gave 0·6915 CO₂ and 0·1676 H₂O

0·2881 „ „ 0·1868 AgCl

0·2489 „ „ 0·1615 „

	Calculated.		Found.	
C ₃₄	408	61·68	61·71	—
H ₃₉	39	5·90	6·09	—
N ₂	28	4·23	—	—
O ₅	80	12·09	—	—
Cl ₃	106·5	16·10	16·04	16·06
<hr/>				
C ₃₄ H ₃₇ ClN ₂ O ₅ ·2HCl ..	661·5	100·00		

It would hence appear that the base was formed from morphine by the nascent hydrogen chloride produced by the tendency of the zinc chloride to become basic, in accordance with the reaction—

as will be shown hereafter, this base (along with small quantities of others) is formed by the action of hydrochloric acid on morphine at 100°.

It would hence appear that the dehydrating action of zinc chloride is more marked than its polymerising action; in order to see what is the end-product of its action, approximately equal volumes of solid zinc chloride, strong hydrochloric acid, and morphine were heated together in sealed tubes to 180°—220° for 24 hours; no pressure was observed on opening the tubes; on dissolving the product in water (in which it dissolves very slowly) and precipitating by strong hydrochloric acid, a non-crystalline hydrochloride was finally obtained,

insoluble in absolute alcohol, soluble in weak alcohol: this substance much resembled salts of chlorotetramorphine and bromotetramorphine, but had a much darker colour; with nitric acid it gave a dirty-red colour, and with sodium carbonate an amorphous precipitate, almost insoluble in ether; on analysis the following numbers were obtained, from which, together with its properties, it appears evident that the body was the "tetra" polymeride of "apomorphine," and hence that it may fairly be called *octapo-tetramorphine*.

0.2720 gram gave 0.673 CO₂ and 0.160 H₂O

0.2880 " " 0.1380 AgCl.

	Calculated.	Found.
C ₁₃₆	67.22	67.47
H ₁₄₄	5.93	6.54
N ₈	4.61	—
O ₁₆	10.54	—
Cl ₈	11.70	11.85
C ₁₃₆ H ₁₃₆ N ₈ O ₁₆ .8HCl ..	100.00	

The physiological action of this base has been examined by Dr. J. G. Blackley, who finds that it is *destitute of emetic properties*; doses up to 0.13 gram subcutaneously injected into an adult cat produced neither salivation nor vomiting, but simply slight narcotism; the difference between this substance and its isomeride tetrapodimorphine (apomorphine) is very marked.

When a longer exposure to a lower temperature (36—48 hours at 100°) was tried, the resulting product was a compound of zinc chloride and a base (or mixture of bases) belonging to the "tetra" series, but different from octapo-tetramorphine, and apparently containing chlorine: it was not found practicable to remove all the associated zinc by repeated solution in hot water and separation of the hydrochloride by cooling or by addition of strong hydrochloric acid; finally a product was obtained which yielded the following numbers after drying at 100° (the still adherent zinc chloride being carefully estimated and subtracted from the original numbers):—

0.8249 gram gave 1.9352 CO₂ and 0.4836 H₂O

0.2577 " " 0.6043 CO₂ (H₂O lost)

0.3053 " " 0.1518 AgCl

0.2568 " " 0.0320 Cl.

	Calculated.		Found.	
C ₁₃₆	1632	64.34	63.97	63.95
H ₁₅₃	153	6.03	6.51	—
Cl ₉	319.5	12.59	12.43	12.46
N ₄	112	4.41	—	—
O ₂₀	320	12.63	—	—
C ₁₃₆ H ₁₄₅ ClN ₄ O ₂₀ .8HCl ..	2536.5	100.00		

This product yielded with sodium carbonate a precipitate insoluble in ether and but sparingly soluble in chloroform; assuming it to be a single substance, it may be regarded as formed from the base $C_{34}H_{37}ClN_2O_5 \cdot 2HCl$ (which, as just shown, is formed by the action of zinc chloride on morphine) by polymerisation and subtraction of the elements of hydrogen chloride:

a reaction perfectly parallel with others found to take place with other morphine derivatives, as will be shown in a subsequent paper (*vide* page 218).

II. On the Action of Hydrochloric Acid on Morphine.

It has been shown by the author, in conjunction with the late A. Matthiessen (*Proc. Roy. Soc.*, xvii, 455 and 460), that when hydrochloric acid acts on morphine in sealed tubes at 140° — 150° , "apomorphine" is produced, the same product being also obtainable from codeine by similar treatment; inasmuch, however, as it was further shown (*Proc. Roy. Soc.*, xviii, 83) that other reactions take place intermediately in the latter case, it becomes desirable to examine the intermediate reactions that take place in the case of morphine.

(A.) Morphine was heated in a flask on the water-bath for six hours, with 5—6 times its weight of strong hydrochloric acid, too little product for successful examination being formed by a shorter time of treatment; the liquid being diluted with water, and nearly neutralised with caustic soda, yielded an amorphous white precipitate with sodium carbonate; this precipitate almost wholly dissolved in ether (morphine solutions do not precipitate instantaneously with sodium carbonate; the precipitate, when it does appear, is made up of crystals, and the base is practically insoluble in ether). The ethereal solution agitated with a few drops of hydrochloric acid, yielded a viscid hydrochloride, which refused to crystallise, and gave the following numbers after drying at 100° :—

0.4085 grm. gave 0.9065 CO_2 and 0.229 H_2O .

0.3160 ,, 0.2075 $AgCl$.

(B.) Morphine was treated as in (A) for five hours; the acid liquid was then evaporated on the water-bath in an open basin for four hours more, being nearly dry at the end of that time; finally a hydrochloride precisely resembling (A) was obtained, after precipitation with sodium carbonate and solution in ether, &c.:—

0.337 gram gave 0.739 CO_2 and 0.188 H_2O .

0.3215 ,, 0.711 ,, (H_2O was lost).

0.3565 ,, 0.244 $AgCl$.

(C.) Morphine was gently boiled with about 6 parts of hydrochloric acid for four hours, the product being treated as in (A); a precisely similar hydrochloride was obtained—

0·311 grm. gave 0·694 CO₂ and 0·165 H₂O.

0·308 „ 0·212 AgCl.

When the action of the hydrochloric acid is pushed further than the point reached in (C), the precipitate thrown down by sodium carbonate fails to dissolve wholly, or nearly so, in ether; but in each of the three cases A, B, C, the amount of insoluble substance was very small.

The numbers obtained above approximate in each case to the composition of the base described in the previous paper on the action of zinc chloride on morphine, viz., C₃₄H₃₇ClN₂O₅·2HCl, which requires

$$C = 61·68 \quad H = 5·90 \quad Cl = 16·10,$$

but the discrepancy is in each case sufficiently marked to indicate that other products are also present; the nearest compositions deducible from the analyses are the following :—

which require the following numbers :—

	A.		B.		C.	
	Calculated.	Found.	Calculated.	Found.	Calculated.	Found.
Carbon . . .	60·44	60·51	60·03	59·79 60·31	60·84	60·85
Hydrogen . .	5·94	6·23	5·92	6·20 —	5·85	5·90
Chlorine ..	16·43	16·25	16·98	— 16·94	17·20	17·03

These compositions are those required for mixtures of bases denoted by the formulæ—

where—

whence it is considered probable that the following reactions take place :—

i.e., that the elements of HCl become added on to morphine *previously* to the abstraction of the elements of H₂O, a reaction similar to that already shown to take place in the case of several iodine derivatives. Experiments now in progress indicate that similar results are produced with codeine.

The last formed base (R) is homologous with the "chlorocodide" of Matthiessen and the author, the reactions which express the formation of the two bases from morphine and codeine respectively being precisely similar—

Inasmuch as "chlorocodide" reproduces ordinary codeine by the action of water, it is evident that no polymerisation has taken place during its formation; and as its formation appears to be *preceded* by the formation of a base homologous with base (P), it is evident that the formula of codeine must be written C₃₆H₄₂N₂O₆, instead of the half of this, as formerly, while by analogy morphine must be written C₃₄H₃₈N₂O₆.

Base (Q) is no doubt identical with the body of the same composition obtained by the action of zinc chloride on morphine, as described in the previous paper.

(D.) When the action of hydrochloric acid on morphine is pushed further than the point reached in (C), the precipitate thrown down by sodium carbonate fails to dissolve entirely, or nearly so, in ether; considerable quantities of an amorphous insoluble base, much resembling the tetra bases, are produced by gently boiling morphine and 5—6 parts of strong hydrochloric acid for about five hours (boiling point about 208°, rather higher towards the end). The portion soluble in ether yields a crystalline hydrochloride on agitation with hydrochloric acid; these crystals are tetrapodimorphine (apomorphine) hydrochloride—

0.2565 grm. gave 0.633 CO₂ and 0.145 H₂O.

0.1185 ,, 0.2905 ,, 0.067 ,,

0.3205 ,, 0.1570 AgCl.

	Calculated.		Found.	
C ₆₈	816	67.22	67.30	66.83
H ₇₂	72	5.93	6.28	6.28
N ₄	56	4.61	—	—
O ₈	128	10.54	—	—
Cl ₄	142	11.70	12.12	
C ₆₈ H ₆₈ N ₄ O ₈ .4HCl ..	1214	100.00		

The portion insoluble in ether was dissolved in hydrochloric acid, precipitated by sodium carbonate, and rapidly filtered to remove morphine (which is not immediately precipitated by sodium carbonate, but appears as crystals on standing); this process was repeated, and the final precipitate dissolved in hydrochloric acid, and fractionally precipitated by sodium carbonate to remove colouring matter; the last precipitate dissolved in hydrochloric acid, forming a brownish solution, from which a brownish tar was deposited on evaporation. This was very soluble in water, and was not precipitated by addition of strong hydrochloric acid, differing in this respect from chlorotetramorphine, which in all other respects it much resembles: after drying at 100°—

0.2795 grm. gave 0.6350 CO₂ and 0.163 H₂O.

0.2845 ,, 0.1480 AgCl.

	Calculated.	Found.
C ₁₃₆	61.70	61.95
H ₁₆₂	6.13	6.48
Cl ₁₀	13.45	12.87
N ₈	4.24	—
O ₂₄	14.52	—
C ₁₃₆ H ₁₅₄ Cl ₂ N ₈ O ₂₄ .8HCl..	100.00	

Like "apomorphine," this base gave a deep purple colour with ferric chloride. From the *simultaneous* formation of "apomorphine" and this chlorinated tetra base, it appears probable that both are produced by the polymerisation of, and subsequent elimination of the elements of hydrogen chloride from, the above-mentioned bases (P) and (R); thus:—

This view is corroborated by the circumstance that when the mixture of (P) and (R) obtained in Experiment B was gently boiled with hydrochloric acid for two hours, tetrapodimorphine and this chlorinated tetra base were actually produced in quantity.

In the manufacture of morphine by the Robertson-Gregory process, during the working up of the mother-liquors of the crude morphine hydrochloride, a substance is obtained as an amorphous, brown, pulverulent mass, which appears to have the composition of a much oxidised "base (Q)", or more probably of a tetra polymeride of that base. When dissolved in dilute hydrochloric acid, dirty flakes were thrown down on the addition of stronger acid; purified thus as far as

possible, and dried at 100°, a gummy, amorphous brittle mass was obtained, which gave the following numbers on analysis:—

0.3320 grm. gave 0.5890 CO₂ and 0.146 H₂O.

0.4075 ,, 0.2150 AgCl.

	Calculated.		Found.
C ₃₄	408	48.71	48.37
H ₃₉	39	4.66	4.88
Cl ₃	106.5	12.72	13.05
N ₂	28	3.34	—
O ₁₆	256	30.57	—

(C₃₄H₃₇ClN₂O₅.2HCl)_n + O₁₁ × n.. 837.5 100.00

Nitric acid and silver nitrate give a dirty red coloration with this body; sodium carbonate throws down a dirty-brown precipitate, insoluble in ether; not improbably, therefore, it belongs to the tetra series, its formula being C₁₃₆H₁₄₈Cl₄N₈O₂₀.8HCl + O₄₄.

The physiological action of the mixture of bases obtained in Experiment A has been examined by Dr. Reginald Stocker, and found to be utterly different from that of tetrapodimorphine. Doses of from 0.020 to 0.220 gram injected subcutaneously into adult cats, produced in a short time a condition of extreme excitement, almost amounting to frenzy; neither vomiting, nor purging, nor hypnotism was produced in any instance, whether smaller, medium, or larger doses were given; quantities of 0.1 gram and upwards produced ultimately paralysis for some hours; whilst doses of 0.2 gram brought on convulsions, terminating in death. In these instances salivation was noticed as one of the earlier symptoms; this did not occur with doses smaller than 0.2 gram. Evidently, therefore, it is necessary to purify crude apomorphine hydrochloride by repeated recrystallisation before using it in medicine; otherwise the effects of the drug may be complicated by those due to the presence of the other bases P, Q, R: specimens of apomorphine hydrochloride manufactured by Messrs. Macfarlan were found to be quite white and *absolutely pure*.

The difference between the action of morphine and this mixture of bases is much less than that between this mixture and tetrapodimorphine, which circumstance would appear to corroborate the conclusions previously arrived at, viz., that bases (P), (Q), and (R) are derivatives of ordinary or *non-polymerised* morphine, whilst the base formerly termed "apomorphine," is a derivative of a polymeride, dimorphine, and hence may be appropriately termed tetrapo-dimorphine.

Dr. J. G. Blackley has examined the nature of the action of the tetra base, C₁₃₆H₁₅₄Cl₂N₈O₂₄.8HCl produced simultaneously with tetrapodimorphine, and finds that it is entirely unlike tetramorphine, no vomiting being produced by doses of 0.05 gram, subcutaneously injected into adult cats; hypersensitiveness and great excitement with salivation are the most marked symptoms.

III. *On the Action of Sulphuric Acid on Morphine.*

By C. R. A. WRIGHT, D.Sc.

By heating morphine sulphate with excess of sulphuric acid to 150° — 160° , Arppe obtained (*Ann. Chem. Pharm.*, 55, 96) a brown liquid, which yielded a white precipitate on addition of water; this precipitate dissolved in boiling water acidulated with sulphuric acid, separating again in amorphous flakes as the liquid cooled; after washing with cold water, Arppe obtained the following percentages:—

Carbon	61.12	61.22
Hydrogen	5.58	5.88
Nitrogen.....	3.96	
Sulphur.....	(a) 5.86 (b) 5.66 (c) 3.56	2.62

sulphur determination (a) being made by oxidising the substance with potassium chlorate and hydrochloric acid; (b) by heating with lime and saltpetre; (c) by solution in water acidulated with hydrochloric acid, and direct precipitation by barium chloride. From these numbers Arppe deduced the formula ($C = 6$, $O = 8$) $4(C_{35}H_{20}NO_6) + 5SO_3$, which requires—

$$C = 61.4 \quad H = 5.8 \quad S = 5.8.$$

Laurent and Gerhardt (*Ann. Chim. Phys.*, xxiv, 112) repeated Arppe's experiments, and obtained a body of similar characters, which gave as percentages

$$C = 63.0 \quad H = 5.8 \quad S = 5.4.$$

Hence these chemists attributed to it the formula $C_{34}H_{36}N_2O_8S$ ($C = 12$, $O = 16$), which would require $C = 64.5$, $H = 5.7$, $S = 5.1$; and considered it to be a kind of amide related to morphine, as sulphamide is to ammonia.

The late A. Matthiessen and the author (*Proc. Roy. Soc.*, xvii, 455), on repeating Arppe's experiments, succeeded in isolating a small quantity of a base soluble in ether and yielding a crystalline hydrochloride, which furnished the "apomorphine" qualitative reactions; and hence concluded that not impossibly the so-called sulphomorphide was impure apomorphine sulphate. No numbers were, however, at that time obtained.

That the body in question is not a kind of amide was rendered probable by Armstrong (*Chem. Soc. J.*, [2], ix, 56), who found that the so-called "sulphonarcotide," of Laurent and Gerhardt (formed from narcotine as sulphomorphide from morphine), was really the sulphate of a narcotine derivative, viz., of dimethyl-nornarcotine.

The results obtained by E. L. Mayer, and detailed in the previous paper, render it probable that "sulphomorphide" might be the sul-

phate, not of ordinary "apomorphine," but of the *tetra-polymeride* termed octapotetramorphine. To throw some light on this subject, the action of sulphuric acid on morphine was carefully examined. The result of the action of this substance on codeine has been shown to be polymerisation without dehydration, bodies of the same percentage composition as codeine being formed, whose reactions and properties lead to the ascription of formulæ respecting double, treble, and quadruple of the formula of codeine.

(A.) Morphine was dissolved in a considerable excess of sulphuric acid diluted with its own bulk of water (morphine, 30 grams; SO_4H_2 , 30 cc.'s; H_2O , 30 cc.'s), and the whole kept at 100° in the water-bath for three hours; less time was found to give rise to too little product for successful examination. The acid liquid was largely diluted with water, and nearly neutralised by caustic soda; sodium carbonate then threw down a white amorphous precipitate, which was quickly separated by filtration. On agitation with ether, this precipitate dissolved, and the ethereal solution yielded, on agitation with a few drops of hydrochloric acid, a viscid hydrochloride, which utterly refused to crystallise on standing for weeks over sulphuric acid. (Morphine is not instantaneously precipitated by sodium carbonate, and the base, when it does separate, is in the form of crystals practically insoluble in ether.) After drying at 100° this product gave the following numbers:—

0.3005 gram gave 0.7000 CO_2 , and 0.188 H_2O .

0.3815 ,, 0.8840 ,, ,, 0.229.

0.532 ,, 0.2445 AgCl .

(B.) Morphine was treated as in (A) for ten hours, at the end of which time a product was formed, which, on adding sodium carbonate, gave an amorphous precipitate insoluble in ether. This precipitate, dissolved in the least possible quantity of dilute hydrochloric acid, gave a precipitate of flakes on adding stronger acid; these flakes became tarry when heated to 100° while moist, but remained solid at 100° , if previously dried over sulphuric acid.

0.4245 gram of substance obtained thus by fractional precipitation to remove colouring matters, gave 0.1820 AgCl .

0.3885 gram gave 0.9090 CO_2 and 0.228 H_2O .

Both the product obtained in (A) and this substance have the composition of morphine hydrochloride.

	Calculated.		Found.		(B.)
			(A)		
C_{34}	408	63.46	63.53	63.19	63.81
H_{40}	40	6.22	6.95	6.67	6.52
N_2	28	4.35	—	—	—
O_6	96	14.93	—	—	—
Cl_2	71	11.04	11.37		10.61
$(\text{C}_{34}\text{H}_{38}\text{N}_2\text{O}_6 \cdot 2\text{HCl})_n$..	643	100.00			

Product (B) appears to lose a small quantity of HCl at 100° , becoming slightly basic.

Both these bodies yield purple colorations with ferric chloride, and a blood-red tint with nitric acid; their physical and other properties indicate that (A) is the true homologue of tricodeine, while (B) corresponds to tetracodeine. The following names and formulæ may therefore be appropriately bestowed on them:—

Codeine Series.		Morphine Series.	
Codeine.	$C_{36}H_{42}N_2O_6$	Morphine.	$C_{34}H_{38}N_2O_6$
Dicodeine. . . .	$C_{72}H_{84}N_4O_{12}$		
Tricodeine . . .	$C_{108}H_{126}N_6O_{18}$	Trimorphine . .	$C_{102}H_{114}N_6O_{15}$
Tetracodeine. .	$C_{144}H_{168}N_8O_{24}$	Tetramorphine .	$C_{130}H_{152}N_8O_{24}$

Attempts to obtain the missing polymeride corresponding to dicodeine have as yet proved fruitless; the non-formation of crystals in the viscid trimorphine hydrochloride solution does not prove that there is no dimorphine present, only that the trimorphine is formed in much larger quantity. It is curious that with codeine the reverse is the case, dicodeine being produced to a much larger extent than tricodeine.

(C.) The acid morphine solution employed in (A) and (B) was heated to boiling and allowed to evaporate slowly, until the boiling point rose to 140° , at which temperature a slight smell of sulphur dioxide became perceptible. On pouring the product into water, a substance was obtained, presenting all the properties and appearances of the product obtained by Arppe, the sulphomorphide of Laurent and Gerhardt. After several purifications by dissolving in very dilute hot sulphuric acid, allowing part to separate by cooling, and filtering while still warm, so as to obtain on complete cooling a second batch of deposit much more free from colouring matter, and finally washing copiously with cold water, a perfectly white product was obtained, agreeing in every respect with the description of sulphomorphide. After drying at 100° , the following numbers were obtained:—

0.2885 gram gave 0.649 CO, and 0.155 H₂O.

(a.) 0.2435 gram heated with potassium chlorate and hydrochloric acid, gave 0.1015 gram of ignited precipitate with barium chloride; but on treating this with hot dilute hydrochloric acid after ignition, only 0.0765 BaSO₄ was left, the weight of which did not diminish by another similar treatment.

(b.) 0.2705 gram dissolved in hot dilute hydrochloric acid, and precipitated by barium chloride directly, gave 0.086 BaSO₄.

These numbers agree fairly with those required for tetramorphine sulphate, the percentage of sulphur being rather below the theoretical amount, indicating that the salt had become slightly basic by the washing with water.

POLYMERIDES OF MORPHINE AND THEIR DERIVATIVES. 223

	Calculated.		Found.	
			(a.)	(b.)
C ₁₃₆	1632	61.08		61.33
H ₁₆₀	160	5.99		5.97
N ₈	112	4.19		—
O ₄₀	640	23.95		—
S ₄	128	4.79	4.31	4.36
<hr/>				
C ₁₃₆ H ₁₅₂ N ₈ O ₂₄ .4H ₂ SO ₄ ..	2672	100.00		

The percentage of carbon here found is almost exactly that obtained by Arppe (61.12 and 61.22); the variable percentages of sulphur obtained by this chemist may perhaps be explained by the greater or lesser basicity or acidity in the product examined, according to the amount of washing. The apparently larger percentage of sulphur obtained by Arppe on oxidising with potassium chlorate and hydrochloric acid, evidently arose from the precipitation of some other barium salt, besides sulphate (perchlorate?); the above determination (a) would indicate 5.72 per cent. of sulphur if the weight of ignited precipitate were reckoned as being wholly BaSO₄. Arppe found 5.86 by this process.

Laurent and Gerhardt's analysis was probably made with an insufficiently washed impure product.

From these results it is evident that "sulphomorphide" is not an amide at all, nor has it the composition of n morphine + n H₂SO₄ - $2n$ H₂O, as Laurent and Gerhardt's formula would indicate; but that it is simply the sulphate of the "tetra" polymeride of morphine. In order to render the evidence on this point quite conclusive, pure "sulphomorphide" was dissolved in hot dilute hydrochloric acid, and precipitated again by adding excess of cold concentrated hydrochloric acid; the precipitate was similarly treated several times, and finally flakes were obtained exactly resembling the hydrochloride of tetramorphine obtained in (B), and containing no sulphur at all. After drying at 100° for several hours, till constant in weight, the following numbers were obtained:—

0.3495 gram gave 0.8280 CO₂ and 0.201 H₂O.

0.4405 „ „ 0.1740 AgCl.

These numbers indicate that the substance had become basic by long-continued heating to 100°, nearly one-eighth of the HCl being driven off.

	Calculated.		Found.	
C ₁₃₆	1632		64.36	64.62
H ₁₅₉	159		6.27	6.39
N ₈	112		4.41	—
O ₂₄ ..	384		15.16	—
Cl ₇	248.5		9.80	9.77
<hr/>				
C ₁₃₆ H ₁₅₉ N ₈ O ₂ .7HCl ..	2535.5		100.00	

It is hence manifest that the sulphate of tetramorphine had become transformed into the hydrochloride: the product was found to contain no sulphur.

(D.) The mother-liquors from which the "sulphomorphide" had separated during the purification described in (C), were nearly neutralised by caustic soda, precipitated by sodium carbonate, and exhausted with ether: on shaking up the ethereal extract with a drop of hydrochloric acid, a crystalline hydrochloride was obtained in small quantity (not more than 1.0 or 1.5 per cent. of the morphine used). After recrystallisation and drying at 100° , this gave the following numbers:—

0.2220 gram gave 0.5480 CO_2 and 0.122 H_2O .

	Calculated.	Found.	
C_{68}	816	67.22	67.32
H_{72}	72	5.93	6.10
N_4	56	4.61	—
O_8	128	10.54	—
Cl_4	142	11.70	—
<hr/>			
$\text{C}_{68}\text{H}_{68}\text{N}_4\text{O}_8.4\text{HCl}..$	1214	100.00	

Dr. Reginald Stocker has examined the physiological action of the above-described morphine polymerides with the following general results:—

Trimorphine.—Doses of from 0.025 to 0.1 gram subcutaneously injected into adult cats produced a state of excitement accompanied with salivation (slight with the smaller doses, but very marked with the larger ones). Hypnotism more or less marked followed the excitement. In each of two experiments, where 0.1 gram was given, the cat gradually sank and died in a few hours, death being preceded by convulsions of a tetanic character; in another case, with the same dose, the cat became slightly hypnotised, but entirely recovered in a few hours.

Tetramorphine.—Doses of from 0.01 to 0.10 gram of the hydrochloride of this base were subcutaneously injected into adult cats; profuse salivation and vomiting were in every instance produced in the course of a few minutes. Dilatation of pupils and cerebral congestion (determined by the ophthalmoscope) were noticed in some experiments.

It is noteworthy that the action of tetramorphine appears to be almost exactly the same as that of diapotetramorphine; both of these bases appear (as far as experiments on cats enable one to form an opinion) to be much more powerful emetics than "apomorphine:" doses of 0.01 gram or less of either of the tetra bases injected into cats produced vomiting in every instance; on the other hand, many

experiments with cats were made with specimens of "apomorphine" hydrochloride prepared in various ways (action on morphine of zinc chloride, of hydrochloric acid at 100°, of the same under pressure at 140°, of sulphuric acid, and of phosphoric acid); in all these cases it was found that vomiting was not produced in a cat with a less dose than 0·025 gram subcutaneously injected; smaller doses than this only produced more or less salivation and excitement: from 0·003 to 0·006 gram is, however, sufficient to produce vomiting in a healthy man.

For the sake of comparison, doses of 0·065 gram of morphine hydrochloride were injected into two cats; some amount of excitement was produced, but no salivation nor vomiting: the pupils were dilated in each case, and cerebral congestion was indicated in one instance by the ophthalmoscope. Contrary to expectation, no marked hypnotism was produced in either case.

It would hence appear that morphine, its non-polymerised derivatives, and trimorphine, are chiefly characterised by producing more or less excitement, sometimes followed by hypnotism; whilst diapotetramorphine, tetramorphine, and tetrapodimorphine (apomorphine) are distinguished by their emetic action, this symptom being produced, in the case of the last substance, only by doses of not less than 0·025 gram (these results referring to the physiological action on *cats*, which in some respects appears not to be comparable with that produced on the human subject). Much further research, however, is needed before any theory can be offered of the connection between the chemical composition and physiological action of these and other analogous bodies; the circumstance that the action of "apomorphine" on cats is by no means the same as that on man, whilst that on rodents is again different, tends to show that experiments made on one class of animal do not necessarily give a clue to the action which the drug used may exert on an animal of another kind.

When trimorphine hydrochloride is dissolved in strong hydrochloric acid, and the whole kept at 100° for eight hours, a change is produced in the substance indicated by the reaction—

On diluting the acid liquid with water, neutralising with caustic soda, and precipitating with sodium carbonate, a white precipitate is obtained; this is for the most part soluble in ether; the ethereal solution agitated with a few drops of hydrochloric acid gives a viscid liquid, which wholly refuses to crystallise, and accordingly does not appear to contain any appreciable quantity of "apomorphine." On standing over sulphuric acid, a brittle gum was obtained, which yielded the following numbers after heating to 100°:—

0·3355 gram gave 0·7705 CO₂ and 0·190 H₂O

0·2680 „ „ 0·1540 AgCl.

	Calculated.		Found.
C ₁₀₂	1224	62·26	62·63
H ₁₁₈	118	6·00	6·29
Cl ₈	284	14·45	14·22
N ₆	84	4·27	—
O ₁₆	256	13·02	—
C ₁₀₂ H ₁₁₂ Cl ₂ N ₆ O ₁₆ ·6HCl ..	1966	100·00	

The occurrence of this reaction in the substance, which evidently corresponds in the morphine series to the polymeride provisionally viewed as *tricodeine* (*Proc. Roy. Soc.*, xx, 278) in the codeine series, corroborates the view that these substances are actually the threefold polymerides of morphine and codeine respectively; it is noteworthy that the action of hydrochloric acid on tricodeine is simply of a dehydrating character, thus—

Tricodeine.

whilst that on trimorphine is of an entirely different character, the elements of HCl being added on, as well as those of H₂O subtracted; thus—

The non-formation of “apomorphine” which might not improbably have been anticipated from the nature of the reaction with codeine, corroborates, therefore, the view that this base is really a derivative of the missing dimorphine, and that its probable formula is, therefore, the one ascribed to it throughout this paper, viz., that of *tetrapodimorphine*, C₆₈H₆₈N₄O₈.

When tetramorphine is gently boiled with several times its weight of hydrochloric acid for five hours, and then evaporated down to dryness on the water-bath, a product is obtained which, after solution in water and fractional precipitation with hydrochloric acid to free it from colouring matters, gave the following numbers:—

0·3080 gram gave 0·7190 CO₂ and 0·190 H₂O

0·3840 „ „ 0·1780 AgCl.

	Calculated.		Found.
C ₁₃₆	1632	63·46	63·66
H ₁₆₀	160	6·22	6·85
N ₈	112	4·35	—
O ₂₄	384	14·93	—
Cl ₈	284	11·04	11·47
C ₁₃₆ H ₁₅₂ N ₈ O ₂₄ ·8HCl ..	2572	100·00	

It hence appears that the hydrochloric acid had no action on the tetramorphine. In this respect, therefore, tetramorphine resembles tetracodeine, but differs from diapotetramorphine, which undergoes the following reaction when treated with hydrochloric acid—

in physiological action, however, tetramorphine closely resembles diapotetramorphine, and differs considerably from tetracodeine.

IV. Conclusions.

The following table exhibits the relations to morphine and its polymerides of the derivatives described in these and previous papers*, such derivatives being actually derived *from morphine as starting point*; as will be shown in a future paper, numerous bodies derived from codeine as starting point also belong to one or other of these series. In designating in brief the relationships which exist between the morphine polymerides and their derivatives, the symbols $\overline{\text{M}}$, $\overline{\text{M}}_2$, $\overline{\text{M}}_3$, $\overline{\text{M}}_4$ are applied respectively to morphine, dimorphine (hypothetical), trimorphine, and tetramorphine. Each of these bases forms a hydrochloride (and probably other analogous salts) where the number of equivalents of HCl associated in the salt with the base is equal to the number of nitrogen-symbols in the formula of the base, *i.e.*, two for derivatives from morphine, four for those from dimorphine, six from trimorphine, and eight from tetramorphine.

Another class of base included in the table and designated as the *tetrahydro-series*, is formed by the derivatives obtained by the joint action of hydriodic acid and phosphorus on morphine; these may be all viewed as derived from a hypothetical base related to tetramorphine, and containing H_{16} more in its formula than that substance; or, what amounts to the same thing, from the tetra-polymeride of a base containing H_4 more than morphine, *i.e.*, having the formula $(\text{C}_{32}\text{H}_{42}\text{N}_2\text{O}_6)_4 = (\overline{\text{M}} + \text{H}_4)_4$.

* Matthiessen and Wright, Proc. Roy. Soc., xvii, 455 and 460; xviii, 83.
Wright, ditto, xx, 203. Wright, Chem. Soc. Journal [2], x, 652.
Meyer and Wright, Chem. Soc. Journal [2], xi, 211.

Name.	Origin.	Formula.	Relation to Morphine or polymerides thereof.
<i>Mono-Series.</i>			
Morphine		$C_{34}H_{38}N_2O_6$	$\bar{M}$.
"Base P"	Morphine and hydrochloric acid	$C_{34}H_{38}ClN_2O_6$..	$\bar{M} + HCl$.
"Base Q"	Ditto; also morphine and zinc chloride	$C_{34}H_{37}ClN_2O_5$..	$\bar{M} + HCl - H_2O$.
"Base R"	Morphine and hydrochloric acid (homologous to "chlorocodide")	$C_{34}H_{38}Cl_2N_2O_4$..	$\bar{M} + 2HCl - 2H_2O$.
<i>Di-Series.</i>			
Dimorphine (hypothetical)		$C_{68}H_{76}N_4O_{12}$	$\bar{M}_2$.
"Apomorphine" (tetrapodimorphine)	Morphine and hydrochloric acid	$C_{68}H_{63}N_4O_8$	$\bar{M}_2 - 4H_2O$.
<i>Tri-Series.</i>			
Trimorphine	Morphine and sulphuric acid	$C_{102}H_{114}N_6O_{18}$..	$\bar{M}_3$.
.....	Trimorphine and hydrochloric acid	$C_{102}H_{112}Cl_2N_6O_{16}$	$\bar{M}_3 + 2HCl - 2H_2O$.
<i>Tetra-Series.</i>			
Tetramorphine	Morphine and sulphuric acid	$C_{136}H_{152}N_8O_{24}$..	$\bar{M}_4$.
.....	Ditto and hydrochloric acid	$C_{136}H_{154}Cl_2N_8O_{24}$	$\bar{M}_4 + 2HCl$.
Diapotetramorphine	Ditto and phosphoric acid	$C_{136}H_{148}N_8O_{22}$..	$\bar{M}_4 - 2H_2O$.
.....	Ditto and zinc chloride	$C_{136}H_{145}ClN_8O_{20}$	$\bar{M}_4 + HCl - 4H_2O$.
.....	Ditto ditto	$C_{136}H_{138}N_8O_{16}$..	$\bar{M}_4 - 8H_2O$.
Octapotetramorphine	Diapotetramorphine and hydrochloric acid	$C_{136}H_{146}Cl_3N_8O_{20}$	$\bar{M}_4 + 2HCl - 4H_2O$.
.....	Ditto and hydriodic acid	$C_{136}H_{146}I_2N_8O_{20}$..	$\bar{M}_4 + 2HI - 4H_2O$.
<i>Tetra-hydro-Series.</i>			
Hypothetical tetrapolymeride of $\bar{M} + H_4$..		$C_{136}H_{168}N_8O_{24}$..	$(\bar{M} + H_4)_4$.
.....	Morphine, hydriodic acid, and phosphorus	$C_{136}H_{164}I_4N_8O_{20}$	$(\bar{M} + H_4)_4 + 4HI - 4H_2O$.
.....	Action of water on above	$C_{136}H_{162}I_2N_8O_{20}$	$(\bar{M} + H_4)_4 + 2HI - 4H_2O$.
.....	Further ditto ditto	$C_{136}H_{161}IN_8O_{20}$..	$(\bar{M} + H_4)_4 + HI - 4H_2O$.

It is noticeable that all the derivatives of the morphine polymerides can be included in one general formula, viz. :—

where x stands for 1, 2, 3, or 4 in the mono-, di-, tri-, and tetra-polymerides respectively.

m is either 0, 1, or 2.

X is either Cl or I (not improbably Br, &c.).

And n varies from 0 up to 8.

The "tetra-hydro-series" is expressed by the same formula, if $(\bar{M} + H_4)_4$ be substituted for $\bar{M}_x$.

In a future paper it will be shown that similar or identical formulæ apply to the numerous codeine derivatives hitherto investigated.

In conclusion the authors desire to return most cordial thanks to Messrs. Macfarlan and Co., of Edinburgh, whose great kindness in furnishing gratuitously considerable quantities of pure morphine, has contributed in no slight degree to the success of the experiments undertaken, it being impossible in many cases to obtain a sufficient quantity of derivative for examination without the sacrifice of a large quantity of morphine, the instability of the products necessitating great loss in fractional precipitation, &c., to get rid of oxidised products, colouring matters, &c., simultaneously formed, or produced during the process of extraction.