

LXXXIV.—*The Constitution of the Anhydro-bases derived from Tetrahydroberberine Alkyl Hydroxides.*

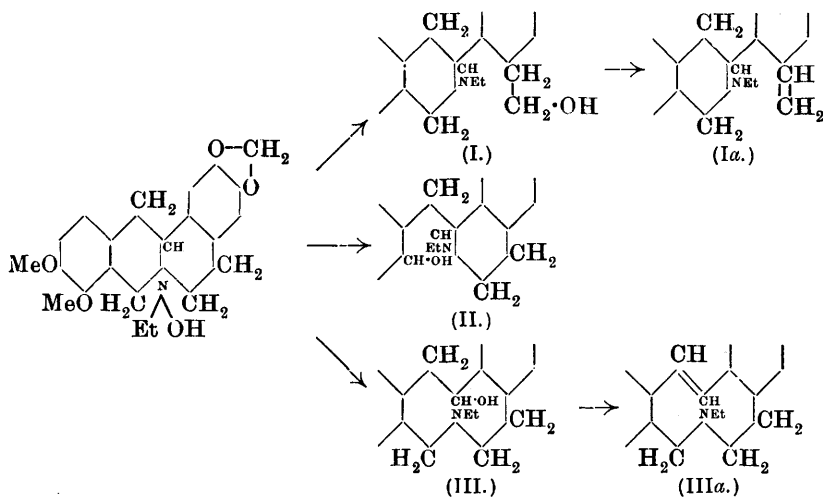
By FRANK LEE PYMAN.

THE degradation of tetrahydroberberine by Hofmann's method, that is, the removal of the elements of water from tetrahydroberberine alkyl hydroxides has been the subject of several previous investigations.

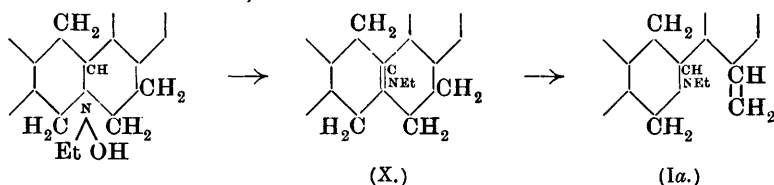
The point was first studied by E. Schmidt and his pupils, Court, Schreiber, Gaze, and Link (*Arch. Pharm.*, 1890, **228**, 596, 604; 1892, **230**, 287, 291; and *Dissertations*), the effect of heating the metho- and etho-hydroxides of tetrahydroberberine being examined. The resulting compounds, however, did not agree in their properties with those to be expected from true anhydro-bases, as E. Schmidt himself (*Arch. Pharm.*, 1892, **230**, 289) points out, since tetrahydroberberine alkyl iodides were regenerated from them by the action of alkyl iodides, whereas unsaturated alkyl iodide additive products should have been obtained.

Voss and Gadamer (*Arch. Pharm.*, 1910, **248**, 43), who next studied this subject, offered further evidence that the products obtained by the previous investigators were not the true anhydro-bases. These authors were the first to isolate a true anhydro-base derived from tetrahydroberberine. They dried tetrahydroberberine ethocarbonate in a vacuum on the water-bath to constant weight, and isolated from the product the ethyl anhydro-base, which melted at 132·5°. They also obtained the same base by evaporating *l*-canadine (*l*-tetrahydroberberine) ethohydroxide to dryness in a vacuum and working up the product so obtained; in this case, however, the presence of another product was observed, for the crude ether-soluble product (which would contain only tertiary bases, such as anhydro- and possibly carbinol bases) proved to be optically active, but the identity of this by-product was left to be cleared up later. The fact that the ethyl anhydro-base, melting at 132·5° was obtained from *l*-canadine as well as from tetrahydroberberine enabled Voss and Gadamer to deduce its constitution as follows.

Tetrahydroberberine ethohydroxide is capable of yielding three hypothetical carbinol bases, I, II, III, of which two, I and III, can lose water with formation of the corresponding anhydro-bases, Ia and IIIa respectively.

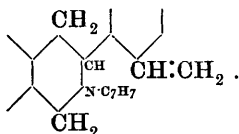


If the reaction proceeds according to the first scheme, the asymmetry of the asymmetric carbon atom is preserved, whereas according to the third scheme it is lost. Since therefore *l*-canadine ethohydroxide gave an optically inactive anhydro-base, the latter is to be formulated as IIIa. This conclusion has since been criticised by McDavid, Perkin, and Robinson (T., 1912, 101, 1218), who regarded this formula as improbable, since it contains a ten-membered ring, and in order to account for the production by Voss and Gadamer of an optically inactive anhydro-base from optically active *l*-canadine ethohydroxide by heat, suggested that the reactions involved were probably correctly represented in the scheme shown below, which was not further elaborated:



According to this view the reaction does not proceed through the hypothetical carbinol base, but the hydroxyl group attached to the nitrogen atom, together with a hydrogen atom from the asymmetric carbon atom, are together eliminated in the form of water, yielding the anhydro-base X, which then rearranges itself to the anhydro-base Ia. It may be pointed out that this method of representing the formation of an anhydro-base from its parent quaternary alkyl hydroxide is unusual, and is frankly designed to meet the particular case.

McDavid, Perkin and Robinson themselves actually studied experimentally the degradation of tetrahydroberberine benzyl chloride down to the nitrogen-free compound berberilene. The first step in this series was the conversion of the former compound into the corresponding anhydro-base, which was carried out by boiling with alcoholic potassium hydroxide. To the product, which was isolated in the form of its hydrochloride, they ascribed the constitution of *N*-benzylisotetrahydroberberine:



The views of Voss and Gadamer on the one hand, and of McDavid, Perkin, and Robinson on the other as to the constitution of their respective anhydro-bases are therefore divergent.

Quite recently, the present author, in collaboration with Jowett (this vol., p. 290), isolated *l*- α -canadine methochloride from *Xanthoxylum Brachyacanthum*. Before the identity of this compound was established a quantity was converted into the corresponding anhydro-base, and evidence was obtained that this was not a simple substance, but a mixture, since its optical activity gradually diminished on repeated crystallisations.

Now Voss and Gadamer had found, as has already been noted, that the crude product obtained by the action of heat on *l*-canadine ethohydroxide was optically active, whilst, after purification, an optically inactive anhydro-base identical with that obtained from tetrahydroberberine ethohydroxide was obtained, and had reserved the further study of this point for a later occasion. As it seemed probable that the study of the effect of heat on the methohydroxide of *l*-canadine would yield valuable information as to the nature of the anhydro-bases produced, Prof. Gadamer was communicated with, and he very kindly expressed his willingness that the present author should continue the work.

The investigation has shown that when *l*-canadine methohydroxide is evaporated to dryness in a vacuum, a mixture of no less than three isomeric anhydro-bases having the composition $C_{21}H_{23}O_4N$ results. The melting points, optical behaviour, and yields in percentages of the theoretical are as follows:

	M. p.		Yield, per cent.
Base <i>A</i>	135—136° (corr.)	optically inactive	53
„ <i>B</i>	114—115 „	„	4
„ <i>C</i>	101—102 „	$[\alpha]_D^{25} - 113.6^{\circ}$	12

The three bases behave as unsaturated compounds towards

bromine and permanganate, and each forms a characteristic hydrochloride and methiodide.

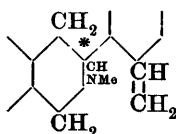
When the corresponding racemic compound, tetrahydroberberine methohydroxide, is similarly treated, the base *A* is obtained in 54 per cent. yield, and the base *B* in 19 per cent. yield. The yield of base *B* in this case is thus approximately equivalent to that of *B* + *C* in the case of *l*-canadine methohydroxide, and this suggests that *B* is the racemic form of *C*.

When, however, *l*-canadine methohydroxide is evaporated to dryness on the water-bath under atmospheric pressure, the base *A* is not found amongst the products of the reactions, but a mixture of *B* and *C* results.

Similarly, when tetrahydroberberine methohydroxide is evaporated to dryness on the water-bath, under atmospheric pressure, the base *A* is not found, and the only anhydro-base obtained is *B*. The yields in the two latter cases are only moderate owing to the neutralisation of a part of the methohydroxide by the carbonic acid of the atmosphere, for the carbonate so formed is not converted into anhydro-base by heating with water on the water-bath. This has been shown definitely by a separate experiment in which a quantity of tetrahydroberberine methohydroxide was saturated with carbonic acid and evaporated on the water-bath; as the evaporation proceeded, crystals of the carbonate separated, and even after concentration to a paste the product was completely soluble in hot water excepting a slight turbidity, and deposited crystals of the carbonate on cooling. The solutions of the carbonates resulting after the removal of the anhydro-bases *B* + *C* or *C* in the experiments described above can be caused to yield further quantities of these bases by the addition of alkali hydroxides which remove the carbonic acid. By this means, a yield of 71 per cent. of *B* and 11 per cent. of *C* has been obtained in the dehydration of *l*-canadine methohydroxide under atmospheric pressure, and a yield of 79 per cent. of *B* from tetrahydroberberine methohydroxide in similar circumstances.

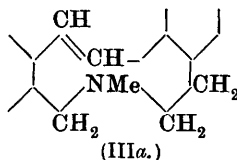
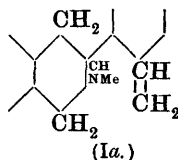
The preparation of the three bases having been described, it now remains to describe their properties and discuss their constitutions.

In the first place, the optically active base *C* can only have the constitution given below:



* An asterisk over the asymmetric carbon atom denotes that the compounds are optically active.

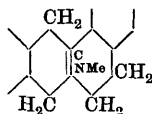
Now, a marked difference in behaviour is shown by the base *A* on the one hand, and the bases *B* and *C* on the other. In the first place, the hydrochloride of *A* is readily soluble in boiling water containing a little hydrochloric acid, whilst those of *B* and *C* are very sparingly soluble; secondly, whilst freshly prepared cold aqueous alcoholic solutions of the three bases are only faintly alkaline in their reaction to litmus, after short heating in the water-bath, the solution of *A* becomes very strongly alkaline, whilst the solutions of *B* and *C* are unchanged. Further, as has already been pointed out, when the optically inactive tetrahydroberberine methohydroxide is employed for the preparation of the anhydro-bases in the place of *l*-canadine methohydroxide, an additional quantity of *B* is found in the place of *C*. It follows that *B* is the racemic form of *C*, since there are only two* optically inactive anhydro-bases, namely, *Ia* and *IIIa*, theoretically derivable from tetrahydroberberine methohydroxide, and of these *Ia* is the racemic form corresponding with the optically active base *C*. There can be no doubt,



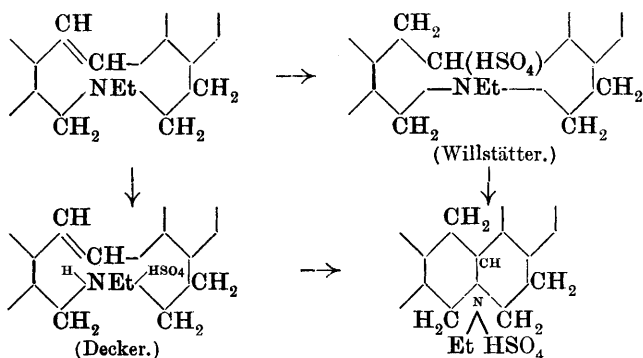
therefore, that *B* has the formula *Ia*, whilst *A* must then have the formula *IIIa*.

The behaviour of *A* with hot aqueous alcohol is entirely similar to that of Voss and Gadamer's anhydroethylcanadine, which, the latter authors showed, became converted into tetrahydroberberine ethohydroxide in similar circumstances. They also showed that the salts of their base underwent a similar change, and represented it according to the schemes shown on p. 822, which depend on the adoption of Willstätter's (*Annalen*, 1903, **326**, 4) and Decker's (*Ber.*, 1904, **37**, 520) methods of representing such a change respectively:

* The possibility that one of the anhydro-bases might have a formula analogous to McDavid, Perkin, and Robinson's intermediate product X (p. 818):



is eliminated by the fact that each of the anhydro-bases forms a distinct unsaturated hydrochloride from which it can be prepared by treatment with ammonia, whereas a base of the above formula could only yield with hydrochloric acid the saturated quaternary salt, tetrahydroberberine methochloride.

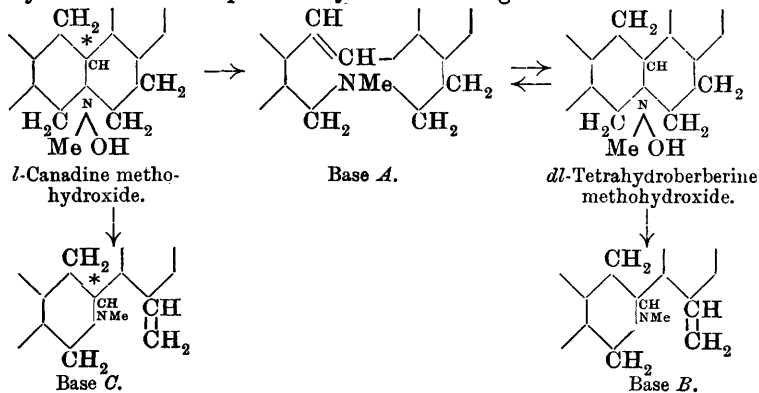


It has now been found that the change takes place in the case of anhydromethylcanadine base *A* with great readiness. After short boiling with aqueous alcohol, this base is converted into a solution of β -tetrahydroberberine methohydroxide, which, when acidified with hydrochloric acid, yields the corresponding methochloride in a yield amounting to 71 per cent. of the theoretical.

It has already been shown that tetrahydroberberine methohydroxide, when evaporated to dryness under atmospheric pressure, yields the base *B*, and it is consequently not surprising to find that the base *A*, when similarly evaporated several times with dilute alcohol, is converted into a mixture of base *B* and the quaternary carbonates.

The disappearance of base *A* when either *l*-canadine or tetrahydroberberine methohydroxides are evaporated on the water-bath under atmospheric pressure, and the formation of the optically inactive base *B* from *l*-canadine, are thus accounted for.

The whole course of the formation of the three anhydro-bases may therefore be explained by the following scheme:



* An asterisk over the asymmetric carbon atom denotes that the compounds are optically active.

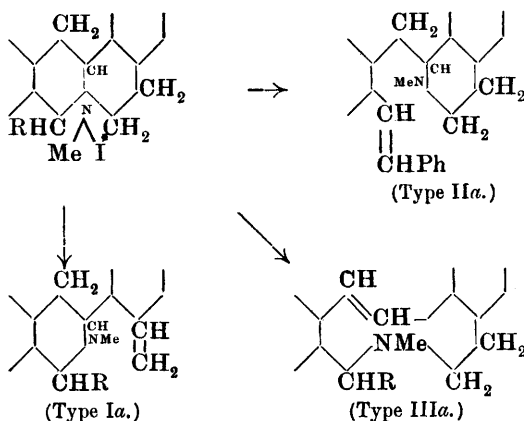
l-Canadine methohydroxide, when evaporated either in a vacuum or under atmospheric pressure on the water-bath, yields a small proportion of the optically active base *C* directly; in a vacuum, it yields a large amount of the base *A*, of which a small proportion is converted through tetrahydroberberine methohydroxide into base *B*; under atmospheric pressure, at the water-bath temperature, the whole of *A* is converted into tetrahydroberberine methohydroxide and transformed partly into base *B*, and partly into the quaternary carbonates.

Tetrahydroberberine methohydroxide shows a similar behaviour except that the base *C* cannot be here formed; in a vacuum, a mixture of *A* and *B* is obtained, whilst under atmospheric pressure the only anhydro-base in the final product is *B*. It may be inferred by analogy with the behaviour of *l*-canadine methohydroxide that in the case of tetrahydroberberine methohydroxide a small proportion of base *B* is produced directly in each case.

Applying these results to the work of former investigators, it is clear that Voss and Gadamer's anhydroethylcanadine has, in fact, the constitution which these authors assigned to it. The contention of McDavid, Perkin, and Robinson with respect to its constitution and mode of formation is consequently invalid. The constitution which the latter authors assigned to their anhydro-derivative of tetrahydroberberine benzyl chloride, namely, that of *N*-benzyl-isotetrahydroberberine, is, however, doubtless correct, for the conditions of its formation, namely, boiling with alcoholic potassium hydroxide, were such that even if a base of the type of base *A* were primarily produced, it would be converted into a base of the type of base *B*.

It is interesting to note that while these results were being written up for publication there appeared in the *Chemiker Zeitung* of the 4th of March (1913, **27**, 270) a report of a paper read by M. Freund before the *Chemische Gesellschaft zu Frankfurt a.M.*, on the 13th December, 1912, in which the degradation of the α -alkyltetrahydroberberine methiodides is recorded.

The full account of this research has since appeared in the *Annalen* (1913, **397**, 1). It is shown that the degradation of α -alkyl-, arylalkyl-, and aryl-tetrahydroberberine methiodides may take place in different ways:



Where R=benzyl, the anhydro-base was of type IIa, since it yielded hydrastinine on oxidation.

Where R=*iso*amyl, the main product was an anhydro-base, to which the constitution of the type IIIa was assigned, since it behaved similarly to Voss and Gadamers anhydroethylcanadine. This base was accompanied by small quantities of an isomeric base of type Ia, which could also be prepared by boiling the first base with alcohol. The presence of this second base amongst the products of the degradation appears to be regarded as due to transformation of some of the first base by manipulation.

Where R=phenyl or an alkyl radicle other than *iso*amyl, the single anhydro-base isolated was of type Ia, and the question as to whether this was produced directly or through the intermediate stages of an unstable base of type IIIa changing to the quaternary hydroxide and thence to the isomeride of type Ia, was left open, although it was pointed out that the latter view more readily accounts for the production of a single anhydro-base from the two stereoisomeric racemic forms of α -alkyltetrahydroberberine hydroxides.

In the light of the present communication it is not surprising that bases of the type of IIIa could not usually be isolated, for the degradation was carried out by boiling with aqueous potassium hydroxide, and it has now been shown that the anhydromethylcanadine of type IIIa is transformed into the base of type Ia at the temperature of boiling water.

It seems probable that the course of the degradation of the α -alkyltetrahydroberberine methohydroxides is entirely similar to that of tetrahydroberberine methohydroxide as described above, and that a quantitative study of their dehydration in a vacuum would confirm this view.

EXPERIMENTAL.

Tetrahydroberberine Methochlorides.

The methylation of *l*-canadine (Jowett and Pyman, T., 1913, 103, 296) gave a mixture of the α - and β -methochlorides, of which the latter more sparingly soluble salt was formed in the larger proportion. An experiment was described, showing that the latter was, in fact, the β -salt, that is, the more stable isomeride. Similarly, the methylation of tetrahydroberberine yields two isomeric salts, of which one, the more sparingly soluble, is formed in the larger proportion; the latter is therefore the racemic form of *l*- β -canadine methochloride.

Twenty-five grams of tetrahydroberberine and 30 c.c. of methyl iodide were heated for fifteen minutes on the water-bath under a reflux condenser; the excess of methyl iodide was then distilled off, and the residue dissolved in 1.2 litres of boiling water. The solution was then thoroughly agitated with an excess of silver chloride, filtered from the silver salts, and evaporated to a volume of about 120 c.c. On cooling, a large quantity of the β -methochloride separated, and this was crystallised from 200 c.c. of hot water, when 15.9 grams of the pure salt were obtained in the first crop. The original mother liquors deposited, after concentration and cooling, a quantity of crude α -salt, which was also purified by crystallisation from water. The two salts were separated without difficulty, and these were eventually obtained, 19.5 grams of the β -methochloride, and 6.5 grams of the α -methochloride, both in a pure state. These yields are respectively 60 and 21 per cent. of the theoretical, so that in all 81 per cent. was obtained in a pure state.

α -*Tetrahydroberberine methochloride* crystallises from water in clusters of colourless, prismatic needles, which contain $2\text{H}_2\text{O}$, all of which is lost at 100° . The air-dried salt sinters at 140° , and melts and effervesces at 144° (corr.). After drying at 100° , it melts and effervesces at 150° (corr.). It is soluble in about 30 parts of cold water, and very readily so in hot water:

0.2062 * lost 0.0184 at 100° . $\text{H}_2\text{O}=8.9$.

0.1622 * gave 0.3538 CO_2 and 0.0962 H_2O . $\text{C}=59.5$; $\text{H}=6.6$.

$\text{C}_{21}\text{H}_{24}\text{O}_4\text{NCl}\cdot 2\text{H}_2\text{O}$ requires $\text{C}=59.2$; $\text{H}=6.6$; $\text{H}_2\text{O}=8.5$ per cent.

0.1496 † gave 0.3520 CO_2 and 0.0888 H_2O . $\text{C}=64.2$; $\text{H}=6.6$.

$\text{C}_{21}\text{H}_{24}\text{O}_4\text{NCl}$ requires $\text{C}=64.7$; $\text{H}=6.2$ per cent.

α -*Tetrahydroberberine methiodide* was prepared from the methochloride by double decomposition with potassium iodide and recrystallisation from water. It forms warty clusters, which decom-

* Air-dried.

† Δ Dried at 100° .

pose at 251° (corr.). It is anhydrous, and is sparingly soluble in hot, very sparingly so in cold, water:

0.1430 gave 0.2742 CO_2 and 0.0642 H_2O . $\text{C}=52.3$; $\text{H}=5.0$.

$\text{C}_{21}\text{H}_{24}\text{O}_4\text{NI}$ requires $\text{C}=52.4$; $\text{H}=5.0$ per cent.

β -Tetrahydroberberine methochloride crystallises from water in colourless, well-defined, monoclinic prisms. The air-dried salt shows signs of sintering at about 180° , but does not melt and decompose until 288° (corr.). It contains $3\text{H}_2\text{O}$, of which two are lost at 100° , and the remaining one at 110 – 120° . It is soluble in about 80 parts of cold water, but readily so in hot water:

0.3828 * lost 0.0312 at 100 – 110° . $\text{H}_2\text{O}=8.2$.

0.3828 * „ 0.0448 „ 110 – 120° . $\text{H}_2\text{O}=11.7$.

0.1495 * gave 0.3105 CO_2 and 0.0885 H_2O . $\text{C}=56.6$; $\text{H}=6.6$.

$\text{C}_{21}\text{H}_{24}\text{O}_4\text{NCl}, 3\text{H}_2\text{O}$ requires $\text{C}=56.8$; $\text{H}=6.8$; $2\text{H}_2\text{O}=8.5$;
 $3\text{H}_2\text{O}=12.2$ per cent.

0.1440 † gave 0.3248 CO_2 and 0.0890 H_2O . $\text{C}=61.5$; $\text{H}=6.9$.

$\text{C}_{21}\text{H}_{24}\text{O}_4\text{NCl}, \text{H}_2\text{O}$ requires $\text{C}=61.8$; $\text{H}=6.4$ per cent.

β -Tetrahydroberberine methiodide was prepared from the methochloride by double decomposition with potassium iodide and recrystallisation from water. It forms quadrilateral plates, which decompose at 248° (corr.). It is anhydrous, and is sparingly soluble in hot, very sparingly so in cold, water:

0.1472 gave 0.2804 CO_2 and 0.0688 H_2O . $\text{C}=52.0$; $\text{H}=5.2$.

$\text{C}_{21}\text{H}_{24}\text{O}_4\text{NI}$ requires $\text{C}=52.4$; $\text{H}=5.0$ per cent.

Physiological Action of dl- α - and β -Tetrahydroberberine Methochlorides.

These two salts have been tested by Dr. P. P. Laidlaw, of the Wellcome Physiological Research Laboratories, in the same manner as *l- α -* and *l- β -canadine methochlorides* (T., 1913, 103, 294). The physiological activities of the two latter salts were previously found to be as 1:12. It has now been found that the ratio of activity of *dl- α -*: *dl- β -* salt is as 1:4, and of *l- α -*: *dl- α -* as 1:5. From these data, the activities of *d- α -* and *d- β -canadine methochlorides* can be calculated, and the relative activity of the four optically active isomerides is as follows: *l- α -*: *d- α -*: *l- β -*: *d- β -canadine methochloride* as 1:9:12:28.

Dehydration of Tetrahydroberberine Methohydroxide by Evaporation under Atmospheric Pressure: Formation of Base B.

(1) Ten grams of tetrahydroberberine and 15 c.c. of methyl iodide were boiled for fifteen minutes on the water-bath under a

* Air-dried.

† Dried at 100° .

reflux condenser. The crystalline mass was then heated to remove the excess of methyl iodide, and the residual methiodide dissolved in 500 c.c. of boiling water. The solution was agitated with an excess of silver hydroxide until all the iodide was removed from it and filtered from the silver salts. The resulting solution of the methohydroxide was then evaporated to dryness on the water-bath under atmospheric pressure, when the crude base *B* separated as an insoluble, grey varnish. This was collected and crystallised from alcohol. The alcoholic and aqueous mother liquors were then mixed, and again evaporated to dryness under the same conditions, when a further quantity of the base was obtained. In this way 5.0 grams of base *B*, melting at 111–112°, were obtained. The combined aqueous and alcoholic mother liquors, which no longer gave a separation of insoluble matter on evaporation, were extracted with chloroform, which, however, removed only a trace of material. The liquor was then acidified with hydrochloric acid, when considerable effervescence took place, and 3.2 grams of β -tetrahydroberberine methochloride separated.

(2) It seemed clear from the last experiment that the cause of the low yield of the anhydro-base lay in the combination of a part of the methohydroxide with the carbonic acid of the atmosphere, and this was proved by the following experiment.

Five grams of tetrahydroberberine were converted into a solution of the methohydroxide in 240 c.c. of water in the usual manner, and this solution was then saturated with carbonic acid and evaporated to low bulk. No insoluble, amorphous matter separated during concentration, but a quantity of crystals were obtained in its place, and even after evaporation of the liquor to a thick paste, no insoluble anhydro-base separated. The liquor was then somewhat diluted and set aside to crystallise, the crystals so obtained being again recrystallised from water, when they were found to consist of β -tetrahydroberberine methocarbonate (1.8 grams):

0.1532 * lost 0.0237 at 100°. $H_2O = 15.5$.

$C_{22}H_{25}O_7N, 4H_2O$ requires $H_2O = 14.8$ per cent.

0.1228 † gave 0.2849 CO_2 and 0.0702 H_2O . $C = 63.3$; $H = 6.4$.

$C_{22}H_{25}O_7N$ requires $C = 63.6$; $H = 6.1$ per cent.

This salt, after drying at 100°, melts and effervesces at 165–167° (corr.); it is readily soluble in hot, sparingly so in cold, water. The mother liquors from this salt, on evaporation to dryness with the addition of potassium hydroxide, readily furnished 1.6 grams of base *B*, melting at 112–113°.

(3) Tetrahydroberberine (25 grams) was then converted into a solution of methohydroxide, just as in the first experiment, but

* Air-dried.

† Dried at 100°.

when the aqueous mother liquors no longer gave a separation of insoluble material on evaporation, potassium hydroxide was added, and a further quantity of the anhydro-base was obtained. Under these conditions 15.7 grams of base *B*, melting at 111–112°, and 4.8 grams, melting at 110–111°, were obtained, the total quantity, 20.5 grams, representing 79 per cent. of the theoretical.

Dehydration of Tetrahydroberberine Methohydroxide by Evaporation in a Vacuum: Formation of Bases A and B.

Twenty-five grams of tetrahydroberberine were converted into a solution of the methohydroxide in 1200 c.c. of water, as in the preceding example. This was evaporated to dryness under the diminished pressure effected by a good water-pump, the bolt-head containing the solution being placed in a vigorously boiling water-bath. The product was heated under these conditions for a further thirty minutes after it appeared to be dry. The residue was then boiled with 100 c.c. of ethyl acetate, which had been well dried over anhydrous potassium carbonate, and filtered from a very small amount of insoluble matter. The filtrate deposited, on cooling, a large quantity of the base *A* in colourless, silky needles, melting at 132–133°; the mother liquor from these, on concentration to about half volume and cooling, gave a further crop of the same melting point. The two crops together amounted to 13.0 grams. The ultimate mother liquor was evaporated to dryness, and the residual mixture of bases separated by means of the different solubilities of the hydrochlorides.

The residue was ground with 100 c.c. of hot 3 per cent. aqueous hydrochloric acid, which separated the mixture into hydrochlorides easily soluble, and nearly insoluble in hot dilute hydrochloric acid. The acid solution was filtered from the insoluble hydrochlorides, and the latter well washed with hot aqueous 1 per cent. hydrochloric acid; the filtrate and washings were then combined, rendered alkaline with ammonia, and extracted with ether. The ethereal solution, after being dried and distilled to a volume of a few c.c., deposited on cooling 1.1 grams of base *A*, melting at 132–133°, whilst the filtrate from these crystals gave, on evaporation to dryness, 0.9 gram of partly crystalline material. The total yield of base *A*, 14.1 grams, is 54 per cent. of the theoretical.

The insoluble hydrochlorides were shaken with ammonia and ether, and the ethereal solution was evaporated to dryness and dissolved in a little alcohol. On keeping, 5.0 grams of base *B*, melting at 111–112°, were collected, and the mother liquor contained only 0.3 gram of amorphous substances.

The yield of base *B*, 5.0 grams, is 19 per cent. of the theoretical.

Dehydration of l-Canadine Methohydroxide by Evaporation under Atmospheric Pressure: Formation of Bases B and C.

(1) Ten grams of *l*-canadine were converted into a solution of the methohydroxides in water in the usual manner.* This solution, amounting in volume to about 500 c.c., was evaporated to dryness on the water-bath under atmospheric pressure; the residue was diluted with water, and the separated clear, grey varnish crystallised from a quantity of alcohol just sufficient to dissolve it when hot; on cooling, the first crop of crystals separated. The aqueous and alcoholic mother liquors were then combined, again evaporated to dryness, and subjected to the same treatment once more, yielding the second crop of crystals. The aqueous and alcoholic mother liquors from the second crop were then combined and again evaporated to dryness when very little insoluble matter separated, since the compound was now present in the form of methyl carbonate owing to combination with the carbonic acid of the atmosphere. A quantity of 10 per cent. aqueous potassium hydroxide was added, and evaporation to low bulk was repeated twice, when a further quantity of base insoluble in water was formed. After crystallisation from a little alcohol, this formed the third crop.

The amounts and properties of the three crops were as follows:

	Grams.	M. p.	$[\alpha]_D$.
1st crop	3.3	105—110°	-41.9°
2nd ,,	1.5	108—111	-19.8
3rd ,,	2.7	111—113	- 3.8

Fractional crystallisation from ethyl acetate of these crops, together with those of the second experiment described below, gradually effected a separation into substances of low and high rotation, the latter being more readily soluble. After repeated

* The mixture of α - and β -methohydroxides obtained in this way was always employed for the dehydration. The possibility that the two compounds might behave differently had been tested in the preliminary experiments in the case of evaporation on the water-bath (this vol., p. 299). It was there stated that 10 grams of *l*- α -canadine methiodide gave 4.1 grams of anhydro-base, melting at 111—112°, and having $[\alpha]_D$ -25.2° (after one crystallisation from alcohol). This yield is 56 per cent. of the theoretical. It was further stated that a similar result was obtained, starting from *l*- β -canadine methochloride; the details of the latter case are as follows:

Eight grams of hydrated *l*- β -canadine methochloride gave 2.8 grams of anhydro-base, melting at 111—112°, and having $[\alpha]_D$ -24.0° (after one crystallisation from alcohol). This yield is 49 per cent. of the theoretical.

The anhydro-base obtained in these experiments was, of course, a mixture of the anhydro-bases *B* and *C*; the above results indicate that they are produced in approximately the same proportion, whether the α - or β -metho-salts are employed.

crystallisations, the most sparingly soluble fraction was obtained almost free from optical activity ($[\alpha]_D -0.3^\circ$), when it melted at $114-115^\circ$ (corr.), and was found to represent the base *B* in a nearly pure state:

0.1526 gave 0.3994 CO_2 and 0.0890 H_2O . $\text{C}=71.4$; $\text{H}=6.5$.

$\text{C}_{21}\text{H}_{28}\text{O}_4\text{N}$ requires $\text{C}=71.4$; $\text{H}=6.6$ per cent.

The purification of the more readily soluble portion was more difficult, and the quantity of material was insufficient to admit of complete purification, but an end-fraction, melting at $99-101^\circ$ and having $[\alpha]_D -99^\circ$, was obtained, consisting mainly of base *C*, which it is subsequently shown melts at $101-102^\circ$ (corr.), and has $[\alpha]_D -113.6^\circ$ when pure. No evidence of the presence of a third constituent of the mixture was obtained, and it is therefore admissible to calculate the proportion of two bases in the mixture from the known specific rotations of *B* and *C*.

The yields thus calculated are 57 per cent. of the theoretical of *B*, and 15 per cent. of *C*.

(2) Twenty-five grams of *l*-canadine were then converted into the methohydroxide, but in order to avoid contact with the carbonic acid of the atmosphere as far as possible, the solution was evaporated on the water-bath in a vacuum to a volume of about 200 c.c. It was then transferred to an evaporating dish, the small amount of base that had separated on the sides of the vessel being washed in with a little alcohol, and the evaporation to dryness continued under atmospheric pressure. The resulting product was then treated as in the previous case, two crops being collected before, and one after, the addition of potassium hydroxide. They were:

	Grams.	M. p.	$[\alpha]_D$.
1st crop	16.6	109—111°	— 22°
2nd „	1.5	106—110	— 33
3rd „	4.2	111—112	— 8

The yields of the two bases calculated from these figures are: Base *B*, 71 per cent. of the theoretical; base *C*, 11 per cent. of the theoretical.

Dehydration of l-Canadine Methohydroxide by Evaporation in a Vacuum: Formation of Bases A, B, and C.

Thirty grams of *l*-canadine were converted into a solution of the methohydroxide in 1500 c.c. of boiling water in the usual manner. The solution was then evaporated to dryness under the diminished pressure effected by a good water-pump, the bolt-head containing the solution being placed in a vigorously boiling water-bath, and

the residue was heated under these conditions for a further thirty minutes after it appeared to be dry.

The residue was then boiled with about 100 c.c. of ethyl acetate, which had been well dried over anhydrous potassium carbonate, and filtered from a very small amount of insoluble matter. The filtrate, on cooling, deposited a large quantity of the base *A* in colourless, silky needles, melting at 133°; the mother liquor from these, on concentration to about half volume and cooling, gave a further crop, melting at 131°. The two crops together amounted to 14.8 grams.

The ultimate ethyl acetate mother liquor, after concentration to very low bulk, gave about 8 grams of a mixture of bases, melting at 85—95°, and a residue of 2.5 grams of gummy bases.

These last two fractions were ground with 100 c.c. hot 3 per cent. aqueous hydrochloric acid, which separated the mixture into hydrochlorides soluble and nearly insoluble in hot dilute hydrochloric acid.

The acid solution was filtered from the insoluble hydrochlorides, and the latter well washed with hot very dilute hydrochloric acid; the filtrate and washings were then combined, rendered alkaline with ammonia, and extracted with ether. The ethereal solution, after being dried and distilled to a volume of a few c.c., deposited, on cooling, 1.9 grams of the base *A*, melting at 133°, the filtrate from this on evaporation to dryness amounting to only 0.8 gram of partly crystalline material.

The total yield of the nearly pure base *A* thus amounts to 16.7 grams, that is, 53 per cent. of the theoretical.

The insoluble hydrochlorides were shaken with ammonia and ether, and the ethereal solution was evaporated to low bulk and kept, when crystals separated; the mother liquor, on concentration, deposited a further quantity of crystals, and eventually the following fractions were obtained in the order given:

Grams.	M. p.	$[\alpha]_D$.
3.0	105°	- 72°
1.5	102	- 98
0.6	98	- 101
0.2	residue	

In a second experiment, using 50 grams of *l*-canadine, the similar fractions obtained were:

Grams.	M. p.	$[\alpha]_D$.
5.7	102—106°	- 60°
3.9	100—102	- 83

The fractions from these two experiments and from a preliminary experiment, in all 18.9 grams, with specific rotatory power from

-30° to -101° , were suitably combined, and crystallised fractionally from ethyl acetate. By this means a gradual separation was effected, and at a certain stage, for instance, 8.0 grams, melting at $111-113^{\circ}$ and having $[\alpha]_D -18.6^{\circ}$, were obtained as the most sparingly soluble portion, and 5.7 grams in small fractions, melting at about 100° and having $[\alpha]_D$ from -103° to -108° as the most readily soluble portion.

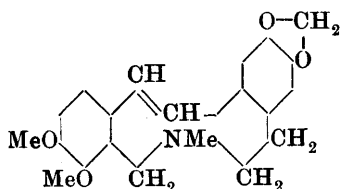
The first of these fractions after two crystallisations from 25 c.c. of alcohol amounted to 4.3 grams with $[\alpha]_D -11.3^{\circ}$, and after two further crystallisations from ethyl acetate to 2.0 grams with $[\alpha]_D -2.4^{\circ}$; after two further crystallisations from ethyl acetate, 0.6 gram with $[\alpha]_D -2.3^{\circ}$ was obtained. In spite of the constancy obtained in the specific rotatory power, there is little reason to doubt that this more sparingly soluble fraction consists mainly of the inactive base *B*. It melted at the same temperature, namely, $114-115^{\circ}$ (corr.), did not depress the melting point of the latter, and had the same general properties.

The later fraction, which was readily soluble in cold ethyl acetate, was crystallised from a mixture of this solvent (1 part) with alcohol (3 parts), when fractions of somewhat lower rotation separated at first; on concentrating the mother liquors and cooling, fractions of higher rotation crystallised. The latter were crystallised in a similar manner, until of almost constant specific rotatory power, and eventually furnished a small quantity of the base *C* with $[\alpha]_D -113.6^{\circ}$.

Whilst this product is regarded as very nearly pure, it must be pointed out that the purification of a substance which tends to remain in the mother liquors is necessarily difficult, and it may be that a repetition of this experiment with still larger quantities might result in the isolation of base *C* with a slightly higher specific rotatory power.

No evidence was obtained during the fractionation of the presence of a constituent other than *B* or *C*, and it is therefore admissible to calculate the proportion of the two bases in the original mixture, assuming that *B* is optically inactive, and that *C* has $[\alpha]_D -113.6^{\circ}$.

It is thus found that the crystalline fractions from the first experiment, 5.1 grams, amounted to 1.4 grams of *B*, that is, 4 per cent., and 3.7 grams of *C*, that is, 12 per cent. of the theoretical; whilst in the second experiment the total quantity (8.6 grams) represents 2.8 grams of *B*, that is, 5 per cent., and 5.8 grams of *C*, that is, 11 per cent. of the theoretical.

Anhydromethylcanadine (Base A).

This base is the chief product of the dehydration of *l*-canadine and tetrahydroberberine methohydroxide by evaporation to dryness in a vacuum, and is formed in a yield amounting to about 53 per cent. of the theoretical. It crystallises from anhydrous ethyl acetate in colourless, woolly needles, which melt at 135—136° (corr.). It suffers no loss at 100°, and is optically inactive:

0.1556 gave 0.4058 CO₂ and 0.0920 H₂O. C=71.1; H=6.6.

0.1676 „ 0.4370 CO₂ „ 0.0994 H₂O. C=71.1; H=6.6.

C₂₁H₂₃O₄N requires C=71.4; H=6.6 per cent.

Molecular-weight determination by the cryoscopic method:

0.2096 in 18.56 benzene gave Δt -0.170°. M.W.=332.

0.5624 „ 18.56 „ „ Δt -0.440°. M.W.=352.

C₂₁H₂₃O₄N requires M.W.=353.

It is insoluble in water, sparingly soluble in cold alcohol, ethyl acetate, or ether, and readily so in chloroform or hot ethyl acetate.

It is decomposed by hot alcohol. The cold alcoholic solution reacts faintly alkaline to litmus, but after heating this solution for a few minutes on the water-bath, the solution reacts strongly alkaline owing to the formation of tetrahydroberberine methohydroxide. The readiness with which this conversion takes place is illustrated by the following experiment.

Three grams of the pure base were dissolved in 30 c.c. of hot alcohol, and 30 c.c. of water were added; the alcohol was then distilled from the solution, leaving it slightly turbid. A further quantity of 10 c.c. of alcohol, followed by 20 c.c. of water, was next added, and the alcohol again removed by distillation. The solution was then filtered from a very small quantity of insoluble amorphous matter, and acidified with concentrated hydrochloric acid. On cooling, 2.8 grams of β -tetrahydroberberine methochloride separated in a pure state, that is, 71 per cent. of the theoretical yield. This salt was identified as such by its melting point, crystalline form, sparing solubility in water, and inability to decolorise potassium permanganate. The mother liquor from this salt did not appear to contain any of the α -methochloride.

Anhydromethylcanadine (Base A) is also decomposed on heating with chloroform. A solution of 1 gram in 25 c.c. of chloroform was evaporated to a syrup and kept, when the residue set to a

crystalline mass having a high melting point. After extracting this with a little hot water, the filtered extract deposited crystals, which were again recrystallised from water, and then represented 0.6 gram of pure β -tetrahydroberberine methochloride.

Base *A* decolorises bromine in chloroform, yielding a colourless solution, and decolorises potassium permanganate in aqueous acid solution.

The *hydrochloride* of base *A* was obtained as follows:

Two grams of the base were added to 10 c.c. of hot 5 per cent. hydrochloric acid, and the solution cooled, when the aqueous salt separated in rosettes of colourless plates. This salt sintered somewhat at 150–155° (corr.), but did not melt until 288° (corr.), being probably converted into β -tetrahydroberberine methochloride under the influence of heat:

0.1760 * lost 0.0176 at 100°. $H_2O = 10.0$.

0.1472 † „ 0.3356 CO_2 and 0.0860 H_2O . $C = 62.2$; $H = 6.5$.

$C_{21}H_{23}O_4N.HCl, 3\frac{1}{2}H_2O$ requires loss of $2\frac{1}{2}H_2O = 9.9$ per cent.

$C_{21}H_{23}O_4N.HCl, H_2O$ requires $C = 61.8$; $H = 6.4$ per cent.

This salt is readily soluble in hot, sparingly so in cold, water. Freshly made solutions of this salt in water gave with ammonia a white precipitate, at first amorphous, then crystalline, of the original base *A*, and decolorised aqueous potassium permanganate. An aqueous solution of the salt, after digestion for a short time in the water-bath, no longer gave a turbidity with ammonia nor decolorised potassium permanganate, owing to the conversion of the salt into β -tetrahydroberberine methochloride.

The *methiodide* of base *A* was prepared by heating the latter with methyl iodide for a few minutes on the water-bath. It crystallises from alcohol in colourless plates containing EtOH, which begin to turn brown at about 220°, and to sinter and effervesce at 225° (corr.). It is sparingly soluble in cold water or alcohol, but fairly readily so in hot water. It decolorises potassium permanganate in aqueous solution:

0.1721 lost 0.0045 at 120°. $EtOH = 2.6$.

0.1676 ‡ gave 0.3276 CO_2 and 0.0848 H_2O . $C = 53.3$; $H = 5.7$.

$C_{22}H_{26}O_4NI$ requires $C = 53.1$; $H = 5.3$ per cent.

Conversion of Base A into Base B.—Since the base *A* is easily converted into tetrahydroberberine methohydroxide, and this readily yields the base *B* on evaporation under atmospheric pressure, the conversion of base *A* into base *B* can be readily effected.

Two grams of base *A* were dissolved in 10 c.c. of hot alcohol, and 10 c.c. of water added. The liquor was evaporated nearly to dryness

* Air-dried.

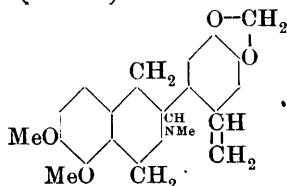
† Dried at 100°.

‡ Dried at 120°.

on the water-bath under atmospheric pressure, and the residue again dissolved in a little alcohol, diluted with water, and again evaporated to dryness. The residue was then mixed with a little hot water, and the insoluble varnish collected and crystallised from alcohol, when 0.75 gram of base *B*, melting at 111–112°, was obtained.

Anhydromethylcanadine (Base B).

dl-*N*-Methylisotetrahydroberberine,



This base is the sole anhydro-base produced by the evaporation of an aqueous solution of tetrahydroberberine methohydroxide under atmospheric pressure, the yield amounting to 79 per cent. of the theoretical, when potassium hydroxide is employed to decompose the methocarbonates formed at the same time. It is also formed in 19 per cent. yield, when the same compound is evaporated in a vacuum, and is further obtained mixed with the *lævo*-variety by the degradation of *l*-canadine methohydroxide. This base crystallises from alcohol in tufts of small, colourless needles, which melt at 114–115° (corr.). It is anhydrous, and is insoluble in water, sparingly soluble in cold, but readily so in hot, alcohol, fairly readily soluble in cold, and very readily so in hot, ethyl acetate, fairly readily soluble in ether, and readily so in chloroform:

0.1598 gave 0.4183 CO₂ and 0.0940 H₂O. C=71.4; H=6.6.

C₂₁H₂₃O₄N requires C=71.4; H=6.6 per cent.

Molecular-weight determination by the ebullioscopic method:

0.1824, in 23.28 chloroform, gave Δt 0.072°. M.W.=398.

0.4012, „ 23.28 „ „ Δt 0.185°. M.W.=341.

0.4978, „ 23.28 „ „ Δt 0.243°. M.W.=322.

C₂₁H₂₃O₄N requires M.W.=353.

This base is optically inactive. An alcoholic solution reacts faintly alkaline to moist litmus paper, and does not become more alkaline after boiling on the water-bath. It decolorises bromine in chloroform, yielding a nearly colourless solution with a faint green tinge, and decolorises potassium permanganate in aqueous acid solution. This base and its salts are not converted into tetrahydroberberine methohydroxide and metho-salts in the various circumstances in which base *A* and its salts are so converted.

The *hydrochloride* was prepared by adding dilute aqueous hydro-

chloric acid to an alcoholic solution of the base, when it separated in white, matted, woolly needles, which decompose at 258° (corr.). It is anhydrous, and is very sparingly soluble in cold water or alcohol, more readily so in these solvents when hot. It is very sparingly soluble in hot dilute hydrochloric acid:

0.1468 gave 0.3470 CO_2 and 0.0778 H_2O . $\text{C}=64.4$; $\text{H}=5.9$.

$\text{C}_{21}\text{H}_{25}\text{O}_4\text{N}$, HCl requires $\text{C}=64.7$; $\text{H}=6.2$ per cent.

The *methioidide* was prepared by heating the base with methyl iodide on the water-bath for a few minutes. It crystallised from alcohol in colourless, anhydrous plates, which melted sharply at 231° (corr.). It is very sparingly soluble in cold, more readily so in hot, water or alcohol. It decolorises potassium permanganate in aqueous solution:

0.1820 gave 0.3562 CO_2 and 0.0852 H_2O . $\text{C}=53.4$; $\text{H}=5.2$.

$\text{C}_{22}\text{H}_{26}\text{O}_4\text{N}$ requires $\text{C}=53.3$; $\text{H}=5.3$ per cent.

Anhydromethylcanadine (Base C).

l-N-Methylisotetrahydroberberine.

This base is produced in a yield of about 12 per cent. by the dehydration of *l*-canadine methohydroxide either under atmospheric pressure or in a vacuum. It crystallises from alcohol in clusters of clear, colourless prisms, which melt at $101\text{--}102^{\circ}$ (corr.). It is anhydrous and is insoluble in water, somewhat sparingly soluble in cold, but readily so in hot, alcohol, readily soluble in cold, and very readily so in hot, ethyl acetate, and readily soluble in ether or chloroform:

0.1517 gave 0.3986 CO_2 and 0.0913 H_2O . $\text{C}=71.6$; $\text{H}=6.7$.

$\text{C}_{21}\text{H}_{23}\text{O}_4\text{N}$ requires $\text{C}=71.4$; $\text{H}=6.6$ per cent.

The specific rotatory power was determined in chloroform solution:

$\alpha_D - 2.30^{\circ}$; $c=1.012$; $l=2$ dcm.; $[\alpha]_D - 113.6^{\circ}$.

An alcoholic solution reacts faintly alkaline to moist litmus paper, and does not become more alkaline after boiling on the water-bath. It decolorises bromine in chloroform, yielding a nearly colourless solution with a faint green tinge, and decolorises potassium permanganate in aqueous acid solution. This base and its salts are not converted into tetrahydroberberine methohydroxide and metho-salts in the various circumstances in which base *A* and its salts are so converted.

The *hydrochloride* was prepared in the same manner as the salt of the racemic base. It separated in tufts of woolly needles, which melted at 229° (corr.). It is very sparingly soluble in cold water,

sparingly so in hot water or cold alcohol, and fairly readily so in hot alcohol. It is very sparingly soluble in hot dilute hydrochloric acid:

0.1497 gave 0.3565 CO_2 and 0.0836 H_2O . $\text{C}=64.9$; $\text{H}=6.2$.

$\text{C}_{21}\text{H}_{23}\text{O}_4\text{N}, \text{HCl}$ requires $\text{C}=64.7$; $\text{H}=6.2$ per cent.

The *methiodide* crystallises from alcohol in colourless plates, which melt at 230° (corr.). It is anhydrous, and is sparingly soluble in cold water or alcohol. It decolorises potassium permanganate in aqueous solution:

0.1687 gave 0.3310 CO_2 and 0.0805 H_2O . $\text{C}=53.5$; $\text{H}=5.3$.

$\text{C}_{22}\text{H}_{26}\text{O}_4\text{NI}$ requires $\text{C}=53.4$; $\text{H}=5.3$ per cent.

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