2. Four stable, isomeric α-*p*-tolylethylamine camphorates have been prepared and found to illustrate Case 7 (or 10) and the solubility order *l*B*d*A < *l*B*dl*A < *dl*B*dl*A < *d*B*d*A.

NASHVILLE, TENNESSEE

[CONTRIBUTION NO. 99 FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

REDUCTIONS IN THE MORPHINE SERIES. I. DIHYDROPSEUDOCODEINE[1,2]

BY ROBERT E. LUTZ AND LYNDON F. SMALL

RECEIVED JULY 6, 1932 PUBLISHED DECEMBER 13, 1932

In respect to their behavior on catalytic hydrogenation, the alkaloids of the morphine series may be divided sharply into two classes. The one class includes all of those derivatives having an ethylenic double linkage in the 7,8-position of the hydroaromatic ring. Hydrogenation of such compounds in the presence of platinum or palladium under the ordinary conditions of temperature and pressure results in addition of one molecule of hydrogen at the hydroaromatic unsaturation, without disturbance of the 4,5-ether bridge.[3] This type of reduction, which we designate as normal (*i. e.*, in the sense, expected), is met in the cases of morphine,[4] codeine (I),[4a] isocodeine,[5] codeinone,[6] hydroxycodeinone[7] and α-[8] and γ-methylmorphimethines.[9,10]

The other class of morphine derivatives, in which the hydroaromatic unsaturation lies between carbon atoms 6 and 7, has heretofore been re-

[1] This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc.

[2] Presented in part at the New Orleans meeting of the American Chemical Society, March 30, 1932.

[3] The halogeno derivatives of morphine and codeine are exceptional in this respect, and the mechanism of their reduction is uncertain. Under some conditions, however, they also yield hydrogenation products in which the ether bridge is intact. See Mosettig, Cohen and Small, THIS JOURNAL, **54**, 793 (1932).

[4] (a) Oldenberg, *Ber.*, **44**, 1829 (1911); (b) German Patent 260,233 (1913); (c) Skita and Franck, *Ber.*, **44**, 2862 (1911).

[5] Speyer and Wieters, *ibid.*, **54**, 2647 (1921).

[6] Mannich and Löwenheim, *Arch. Pharm.*, **258**, 295 (1920).

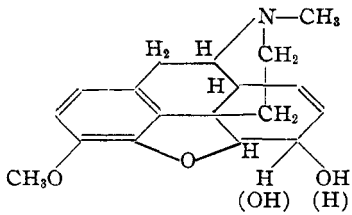
[7] Freund and Speyer, *J. prakt. Chem.*, **94**, 135 (1916); Freund and Speyer, German Patent 296,916 (1916); *Friedländer*, **13**, 880; U. S. Patent 1,468,805 (Sept. 25, 1923); Freund, U. S. Patent 1,485,673 (March 4, 1924).

[8] Von Braun and Cahn, *Ann.*, **451**, 55 (1927).

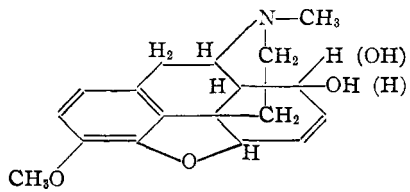
[9] Speyer and Koulen, *ibid.*, **438**, 34 (1924).

[10] The dimolecular oxidation product of morphine, pseudomorphine, also reduces normally (unpublished results, L. F. Small and F. L. Cohen) and this fact may be taken as evidence that the unsaturation in the two morphine nuclei still occupies the original 7,8-position.

ducible by the catalytic method always with addition of two molecules of hydrogen. One molecule of hydrogen is used in saturating the double linkage, and the second goes to open the 4,5-ether bridge, with formation of a phenolic hydroxyl at position 4. This behavior, which we shall refer to as abnormal reduction, is exhibited by the structural isomers of codeine and isocodeine, namely, pseudocodeine and allopseudocodeine (II),[11] as well as by other compounds which are known to be of the pseudocodeine type, as ϵ- and ζ-methylmorphimethines[9] and pseudocodeinone,[12] and has been accepted as evidence of the presence of a pseudocodeine type of structure.[13]



I. Codeine and Isocodeine



II. Pseudocodeine and Allopseudocodeine

In the course of the pharmacological experiments which are being carried out in connection with our morphine studies, pseudocodeine has been found to be of exceptional interest[14] and the preparation of a normal non-phenolic dihydropseudocodeine for comparative studies assumed considerable importance. From the theoretical standpoint there appears to be no reason why the catalytic addition of hydrogen to the allyl ether system present in pseudocodeine should proceed exclusively with scission of the ether grouping, whatever the mechanism of the reaction. Systematic experiments have, in fact, shown us that the mode of hydrogenation of pseudocodeine is not invariable, but rather is dependent upon several factors (Table IV). Under suitable conditions the reduction may be caused to proceed in the normal way to the extent of 85%, resulting in a new, non-phenolic dihydropseudocodeine. This substance, which still contains the 4,5-ether bridge, is the analog of the non-phenolic dihydrocodeine and dihydroisocodeine obtained by catalytic reduction of codeine

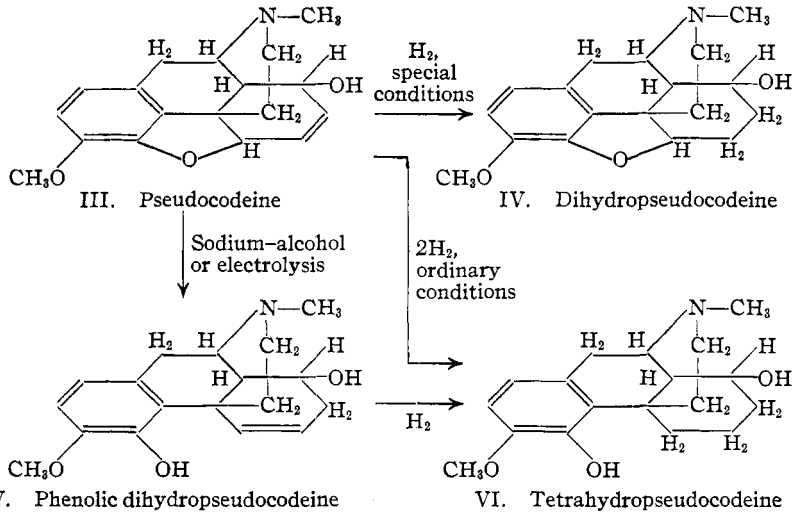
[11] (a) Speyer and Wieters, *Ber.*, **54**, 2647 (1921); (b) Speyer and Krauss, *Ann.*, **432**, 233 (1923).

[12] Karl A. T. Hill, Dissertation, Frankfurt a/M, 1925, p. 41. The position of the double linkage in the hydroaromatic ring III of pseudocodeinone is in doubt, for pseudocodeinone condenses with benzaldehyde [Knorr and Hörlein, *Ber.*, **40**, 3353 (1907)] and gives other reactions indicating the presence of the —CO—CH_2— grouping; *cf.* Schöpf, *Ann.*, **452**, 212, Note 2 (1927).

[13] (a) Schöpf and Winterhalder, *ibid.*, **452**, 237 (1927); (b) Schöpf and Hirsch, *ibid.*, **489**, 235, footnote (1931); (c) Small and Cohen, THIS JOURNAL, **53**, 2221 (1931).

[14] "Studies on Morphine, Codeine and their Derivatives. II. Isomers of Codeine," by Nathan B. Eddy, *J. Pharmacol.*, **45**, 361 (1932).

and isocodeine under ordinary conditions, and is also isomeric with the phenolic dihydropseudocodeine (V) which Speyer prepared by electrolytic or sodium and alcohol reduction of pseudocodeine.[15] In contrast to the new dihydropseudocodeine, Speyer's phenolic dihydropseudocodeine still contains an alicyclic double bond and may be hydrogenated (one mole of hydrogen) to the same tetrahydropseudocodeine (VI) as is obtained through the abnormal catalytic hydrogenation (two moles of hydrogen) of pseudocodeine itself.



Since the new non-phenolic dihydropseudocodeine (IV) represents the normal dihydro product and is comparable to other dihydro compounds in the morphine series, we shall refer to it simply as dihydropseudocodeine, and distinguish the previously known dihydropseudocodeine (V) with the qualification "phenolic." A similar convention will be observed in the case of the isomeric phenolic and non-phenolic degradation products.

The hydrogenation of pseudocodeine, as is evident from the data listed in Table IV, always produces both dihydropseudocodeine and tetrahydropseudocodeine in amounts which vary considerably with the experimental conditions. Dihydropseudocodeine undoubtedly escaped previous detection only because of its relatively high solubility, for we have found it present even in those hydrogenations which were formerly thought to yield tetrahydropseudocodeine exclusively. In addition to these two products, a phenolic dihydropseudocodeine, which is different from the above-mentioned phenolic dihydropseudocodeine of Speyer, can sometimes be detected, and is apparently formed as an intermediate step in that phase of the reduction which ultimately gives tetrahydropseudocodeine. This

[15] Speyer and Krauss, *Ann.*, **432**, 249 (1923).

phenolic dihydro product, which resembles tetrahydropseudocodeine closely in physical properties and can be separated from it only with difficulty, will be described in more detail in our next communication. It is present in the crystalline precipitate which often separates during the hydrogenation of pseudocodeine in concentrated solutions. This precipitate is completely soluble in alkali and can therefore contain no pseudocodeine; nevertheless, when it is brought into solution and subjected to further hydrogenation, a notable absorption takes place. The observed variation of hydrogen absorbed from absorption calculated on the basis of the dihydro- and tetrahydropseudocodeine isolated can thus be accounted for in several instances.

The variation in relative yields of phenolic and non-phenolic end-products with changing conditions shows that a number of factors are operative. Chief among these are solvent, nature of catalyst, and hydrogen-ion concentration. Amount of catalyst, rate of reduction and temperature seem to have little, if any, effect on the course of the reaction. When the free base pseudocodeine is used in alcohols (alkaline reducing conditions) the minimum yields of dihydropseudocodeine, 5 to 9%, are obtained. With ethyl acetate the yield rises to 15 or 20%, and in glacial acetic acid increases to about 40%. The effect of solvent, which is roughly parallel for different catalysts, is shown in Table I.

TABLE I

EFFECT OF SOLVENT AND CATALYST ON YIELD OF DIHYDROPSEUDOCODEINE

Solvent	PtO_2	Pd-$BaSO_4$	Pd-$CaCO_3$
Methyl alcohol	5%	....	.....
Ethyl alcohol	7- 9%	9.5%	6%
Ethyl acetate	24–27%	15%	16–20%
Gl. acetic acid	35–40%	28%	.....

The most marked influence upon the course of pseudocodeine hydrogenation seems to be exerted through changes in hydrogen-ion concentration, a fact which we have further verified by extension of the reduction process in acid media to other pseudocodeine types. Our results are not consistent enough to permit of a reasonable theoretical explanation, but they have proved very useful as a practical solution of the difficulties met in obtaining normal reduction products from all pseudocodeine types. As will be seen from Table II, the yield of dihydropseudocodeine in aqueous medium is highest when a strong acid, as hydrochloric or sulfuric, is present in some excess, but is relatively low in very weakly acid solutions, as in the case of pseudocodeine hydrochloride in water, or pseudocodeine base in excess of dilute acetic acid. With a palladium catalyst, excess of strong acid beyond a certain limit lowers the yield of dihydro product sharply. Inexplicably, the best yields of dihydropseudocodeine were obtained when pseudocodeine hydrochloride was hydrogenated in glacial acetic acid. In this medium an

excess of strong base (the alkaloid itself, or sodium acetate)[16] or of strong acid lowers the yield, in some cases very considerably. For the normal reduction, platinum is more favorable than palladium; yields in strongly acid aqueous solution approach those obtained with the salt in glacial acetic acid.

TABLE II

EFFECT OF HYDROGEN-ION CONCENTRATION. PERCENTAGE YIELD OF DIHYDROPSEUDOCODEINE

Substance	Solvent	PtO_2	$Pd-BaSO_4$
Base	5–8% Acetic acid	9.5	10
Hydrochloride	Water	11–23	28–31
Base	Excess 1–3% HCl	68–70	44
Base	Excess 7% H_2SO_4	76	66
Base	Excess 10% HCl	65	7
Base	Gl. AcOH + 10% NaOAc	39	45
Base	Gl. AcOH	35–40	28
Hydrochloride	Gl. AcOH	71–85	51–59
Base	Gl. AcOH + 2% HCl	49	18–20

Very few observations upon the effect of hydrogen ion on the course of hydrogenation of alkaloids belonging to the morphine series have been reported previously. An investigation carried out by Schöpf and Winterhalder[17] on the effect of P_H on the hydrogenation of thebaine is to a certain extent in agreement with our results. Thebaine, which contains a system somewhat similar to pseudocodeine, although complicated by the presence of an enol-ether group and another double bond, was found to give the nonphenolic dihydrothebaine in yields which increased from 11 to 22% when the medium was changed progressively from P_H 7 to 2, although the yield of the phenolic substance, dihydrothebainone, was not notably decreased. Studies on the reduction of thebaine and certain of its degradation products in absolutely acid-free medium were made by Wieland and Kotake,[18] who found that under these conditions the result was a reductive scission of the ether ring without hydrolysis of the enol ether grouping.

The new dihydropseudocodeine (IV) crystallizes in thin rectangular scales melting (when anhydrous) at 155°.[19] It forms well-crystallized salts and methiodide. The latter was degraded by boiling with dilute alkali, and yielded the oily dihydro-ε-methylmorphimethine (XI),[20] an isomer of the phenolic dihydro-ε-methylmorphimethine (VII) which Speyer obtained by degradation of phenolic dihydropseudocodeine meth-

[16] Hall and Conant, THIS JOURNAL, **49**, 3047, 3062 (1927), have shown that sodium acetate or amines function in acetic acid as relatively strong bases. Thus the hydrochloride of the alkaloid, as a salt, is probably nearly neutral in character in glacial acetic acid solution.

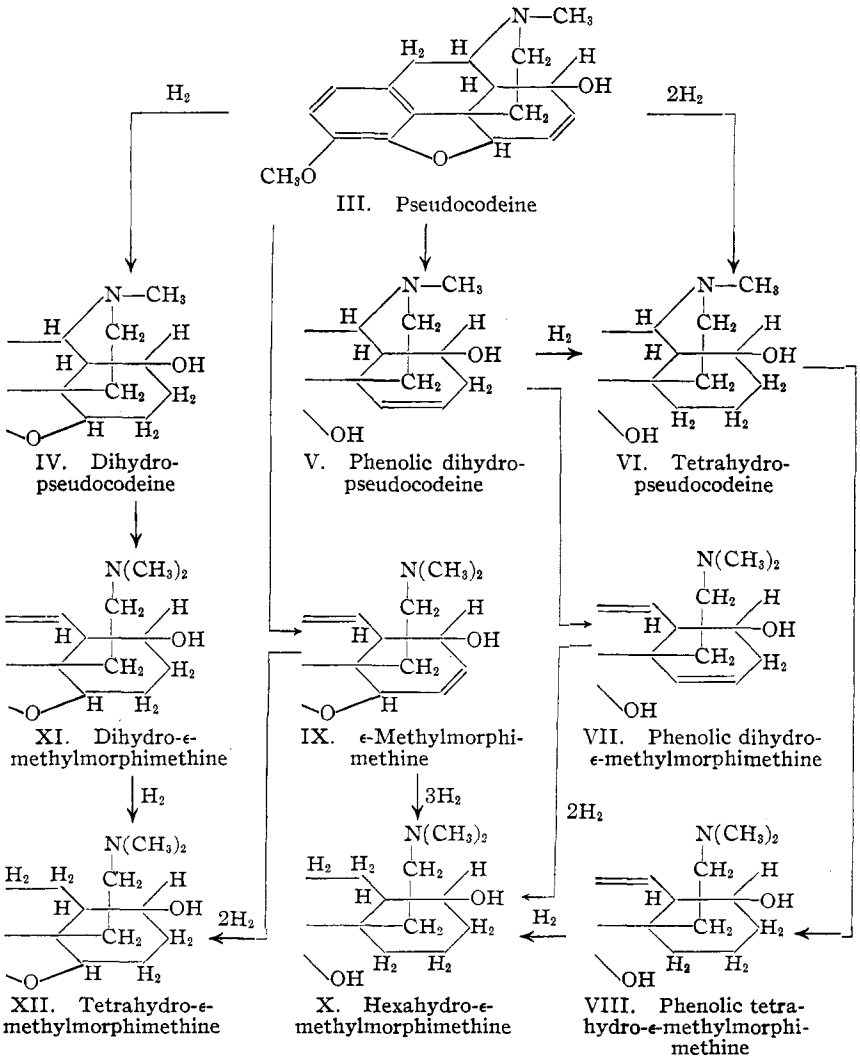
[17] Schöpf and Winterhalder, *Ann.*, **452**, 244 (1927).

[18] Wieland and Kotake, *Ber.*, **58**, 2009 (1925).

[19] The phenolic dihydropseudocodeine of Speyer melts at 128°.

[20] In view of the fact that the term ε-methylmorphimethine is firmly established in the literature it seems advisable to adhere to the "methine" nomenclature in this series instead of using the more flexible and exact "des-N-methyl-" [Willstätter, *Ann.*, **317**, 268 (1901)] system. Thus, dihydro-ε-methylmorphimethine instead of des-N-methyldihydropseudocodeine, hexahydro-ε-methylmorphimethine instead of dihydro-des-N-methyltetrahydropseudocodeine, etc.

iodide. Dihydro-ϵ-methylmorphimethine could not be induced to crystallize, but formed crystalline salts, and reduced with absorption of one molecule of hydrogen to give (non-phenolic) tetrahydro-ϵ-methylmorphimethine (XII), a substance which we were likewise able to prepare directly by application of our special hydrogenation conditions to ϵ-methylmorphimethine (IX).



The catalytic reduction of ϵ-methylmorphimethine under the ordinary conditions of hydrogenation was first carried out by Speyer and Koulen,[9] who observed absorption of three molecules of hydrogen with formation of

hexahydro-ϵ-methylmorphimethine. Our hydrogenation studies have necessitated a repetition of the Speyer and Koulen experiment, in which under comparable conditions we obtain results agreeing essentially with those of Speyer. When, however, the hydrogenation is conducted in the manner which we have found to favor normal reduction of pseudocodeine, an absorption of less than three molecules of hydrogen is observed. The products obtained are hexahydro-ϵ-methylmorphimethine (X) and a non-phenolic tetrahydro-ϵ-methylmorphimethine (XII). The latter results from normal hydrogenation and is identical with the new tetrahydro-ϵ-methylmorphimethine mentioned above. Its appearance proves that the hydrogenation of ϵ-methylmorphimethine under special conditions actually takes a course parallel to that observed for pseudocodeine itself. Table III summarizes the effect of varying conditions upon the relative yields of tetrahydro- and hexahydro-ϵ-methylmorphimethine. These results are roughly parallel to those given in Table II for pseudocodeine. In no case could the hydrogenation of ϵ-methylmorphimethine be so conducted that normal reduction was the principal reaction.

TABLE III

HYDROGENATION OF ϵ-METHYLMORPHIMETHINE. EFFECT OF CONDITIONS ON YIELD OF PRODUCTS

Substance	Solvent	Catalyst	% Tetrahydro	% Hexahydro
Hydrochloride	Gl. AcOH	PtO_2	29	45
Hydrochloride	0.7% HCl	PtO_2	39	39
Hydrochloride	H_2O	Pd-$BaSO_4$	25	Main product
Hydrochloride	H_2O	PtO_2	Trace	Main product
Base	Alcohol	Pd-$CaCO_3$	..	Main product

Hexahydro-ϵ-methylmorphimethine crystallizes from ethyl acetate in hair-like needles or thick prisms, depending upon the speed of crystallization, and melts at 168° (Speyer, 155°). Although phenolic in nature[21] the base is soluble in alkali only with difficulty. The solid crystalline base dissolves slowly and in but slight degree in aqueous sodium hydroxide. If a solution of hexahydro-ϵ-methylmorphimethine in acid is made alkaline, a momentary precipitate is observed at the isoelectric point; this precipitate dissolves in the excess alkali, but separation of crystalline hexahydro-ϵ-methylmorphimethine begins almost immediately. A small amount of base remains in the alkaline solution and separates when ammonium chloride is added. The base is almost completely removed from its very dilute solution in alkali by a few extractions with ether. The peculiar alkali-insolubility often shown by similar substances which carry a phenolic hydroxyl group at C-4 and which are completely hydrogenated in ring III has been discussed in a previous paper.[22]

[21] Speyer and Koulen, Ref. 9, were able to prepare a diacetyl derivative.

[22] Small and Cohen, THIS JOURNAL, **54**, 802 (1932). A reasonable explanation of

In the pseudocodeine series the weakening in acidity of the phenolic hydroxyl appears with scission of the nitrogen-containing ring. Tetrahydropseudocodeine (VI), which was prepared by abnormal hydrogenation of pseudocodeine and which is typically phenolic in alkali solubility, was converted to the methiodide and degraded by heating with potassium hydroxide. The oily material which precipitates in this degradation was found to be the phenolic tetrahydro-ε-methylmorphimethine base (VIII) and not its potassium salt as claimed by Speyer.[23] The crystalline methine base thus obtained proved to be practically alkali-insoluble, although derived directly from the alkali-soluble tetrahydropseudocodeine,[24] and reduced readily with absorption of one molecule of hydrogen to the same hexahydro-ε-methylmorphimethine described above.

The assumption seems justified that the mechanism of the hydrogenation of pseudocodeine, ε-methylmorphimethine, and other pseudocodeine types under the special conditions described is in each case the same. The simultaneous formation of dihydropseudocodeine and tetrahydropseudocodeine must involve at least two competing processes. Dihydropseudocodeine results from normal addition of one molecule of hydrogen to an ethylenic bond, and, having ring III completely saturated, is as stable as dihydrocodeine or dihydroisocodeine toward further reduction. Tetrahydropseudocodeine, on the other hand, must result either from a primary 1,4-addition of hydrogen, beginning on oxygen and carbon atom 7, *i. e.*, the ends of the allyl ether system, as postulated by Schöpf,[13a,25] or from a direct reductive scission of the ether bridge, a reaction which must be attributed to the activating influence of the adjacent allylic double bond. If the latter hypothesis is correct, the 6,7-double linkage of pseudocodeine does not take a direct part in the addition of the first molecule of hydrogen, but is saturated in the second stage of the reduction.

Dihydropseudocodeine can be demethylated with boiling hydriodic acid to give directly the hydriodide of the new dihydro-γ-isomorphine. Attempts at the normal hydrogenation of the isomers of morphine as well as

this phenomenon cannot be advanced. Tetrahydropseudocodeine (VI) is an exception to this general rule.

[23] The melting point 162–163° was given by Speyer and Krauss for phenolic tetrahydro-ε-methylmorphimethine. We find the melting point to lie at 197°. From our analysis of this base and through its smooth hydrogenation to hexahydro-ε-methylmorphimethine we are certain that we actually have phenolic tetrahydro-ε-methylmorphimethine under examination.

[24] A closure of the 4,5-ether bridge by a rearrangement during the degradation is so improbable that it hardly merits discussion. Such a rearrangement, involving a shift of 2H to the newly-formed double bond at C—9, C—10, must in any case lead to the nonphenolic tetrahydro-ε-methylmorphimethine (XII), which cannot be hydrogenated to hexahydro-ε-methylmorphimethine.

[25] This point will be elaborated in a paper dealing with the isomeric phenolic dihydropseudocodeines.

of allopseudocodeine and other pseudocodeine types will be described in later papers.

In its physiological action, dihydropseudocodeine resembles pseudocodeine. Like the latter it is entirely non-convulsant; it is more analgesic and more emetic, and appears to be slightly more active in its effect on respiration. In these respects pseudocodeine and dihydropseudocodeine show the same differences as do the pairs codeine–dihydrocodeine and isocodeine–dihydroisocodeine. Further particulars on the physiological action will appear in publications by Dr. N. B. Eddy from the Pharmacological Laboratory of the University of Michigan.

TABLE IV

EFFECT OF CONDITIONS ON HYDROGENATION OF PSEUDOCODEINE

The yields given represent the maximum and minimum obtained in a number of experiments. The platinum catalyst used was in every case platinum oxide; the palladium catalyst was palladium on barium sulfate, excepting in the first two experiments listed, which include reductions using both palladium on calcium carbonate and palladium on barium sulfate.

Catalyst	Conditions	Yield in % Dihydro	Tetrahydro
Pd or Pt	Base in EtOH or MeOH	5–10	72–90
Pd	Base in EtOAc	15–20	75–79
Pt	Base in EtOAc	24–27	65–72
Pd	Hydrochloride in H_2O	28–31	62
Pt	Hydrochloride in H_2O	11–23	69–88
Pd or Pt	Base in dilute AcOH	10	87–90
Pd	Base in 1% HCl	44	45
Pd	Base in 10% HCl	7	62
Pd	Base in 15% H_2SO_4	66	32
Pt	Base in HCl or H_2SO_4 (1–15%)	65–77	19–28
Pd or Pt	Base in glacial AcOH	30–40	58–64
Pd or Pt	Base in glacial AcOH with NaOAc	39–45	54–63
Pd	Hydrochloride in glacial AcOH	51–59	41–44
Pt	Hydrochloride in glacial AcOH with wide variation in temp. up to 60°	76–85	5–15
Pd	Hydrochloride in glacial AcOH + 0.3 cc. concd. HCl	19–20	66–70
Pt	Hydrochloride in glacial AcOH + 0.5 cc. concd. HCl or 1 g. concd. H_2SO_4	49–52	41–50

Experimental

Pseudocodeine.—The pseudocodeine used in these experiments was prepared according to the method of Knorr[26] and Speyer[27] by the hydrolysis of α-chlorocodide. In large-scale runs (500 to 1000 g. of α-chlorocodide) it was found advantageous, after the hydrolysis with dilute acetic acid, to precipitate the mixture of isomeric bases under ether with sodium hydroxide. The bases which first precipitated separated in the form of an oil, which dissolved in the ether layer; as more alkali was added, the concentration in the ether reached the point where crystallization started (the codeine isomers are only sparingly soluble in ether) and practically the entire yield of the mixed isomers

[26] Knorr, *Ber.*, **41**, 972 (1908).

[27] Speyer, *Ann.*, **432**, 246 (1923).

crystallized in the aqueous layer and could be filtered off and washed with water. The oil obtained from the ether layer contained practically no pseudocodeine, but some isocodeine and allopseudocodeine, and was added to the mixture of these bases which remained after pseudocodeine had been removed as the hydrochloride. The oily residue from the purification of pseudocodeine hydrochloride likewise contained some isocodeine and allopseudocodeine, which were separated by the Speyer procedure. The hydrolysis of α-chlorocodide in 580-g. portions gave yields of crude crystalline salts as follows: pseudocodeine hydrochloride, 215 to 277 g.; allopseudocodeine hydriodide, 86 to 96 g.; isocodeine binoxalate, 160 to 190 g. A small amount of oily material was always obtained at the end of the separation of the isomers.

Attempted reductions of pseudocodeine with sodium hydrosulfite, aluminum amalgam in moist ether, or by electrolysis with prepared (Tafel) or unprepared lead electrodes yielded only unchanged starting material. Sodium amalgam in acetic acid reduced part of the material to phenolic dihydropseudocodeine. Zinc in acetic or hydrochloric acid effected no reduction.

Isocodeine Acid Tartrate.—This salt was prepared for pharmacological study. The calculated amounts of isocodeine and tartaric acid were dissolved in methyl alcohol and the solution concentrated. The salt crystallized very slowly as diamond-shaped plates, exceedingly soluble in water. It was purified from methyl alcohol, and melted at 185–186° (corr.) with foaming. In aqueous solution it showed $[\alpha]_D^{24}$ −99.4°, c = 1.60.

Anal. Calcd. for $C_{22}H_{27}O_9N$: C, 58.77; H, 6.05. Found: C, 59.04; H, 6.18.

Dihydroisocodeine Acid Tartrate.—The hydrogenation of isocodeine was carried out according to the directions of Speyer and Wieters[11a] using palladium–barium sulfate as catalyst. The reduction proceeds equally well in dilute acetic acid, hydrochloric acid or oxalic acid solution. The most convenient procedure consisted in direct hydrogenation of the purified isocodeine binoxalate (from the separation of the codeine isomers) in water solution. The hydrogenated base was thrown out by strong alkali and crystallized from alcohol. A solution of 8.7 g. of dihydroisocodeine with 4.4 g. of *d*-tartaric acid in 60 cc. of water, when cooled slowly, yielded 11.6 g. of crystals, m. p. about 180°. The salt is soluble to the extent of 4.5 g. in 100 cc. of water at 24°. It contains three molecules of hydrate water, part of which is lost in the vacuum desiccator; in aqueous solution, $[\alpha]_D^{26}$ −62.4°, c = 1.94.

Anal. Calcd. for $C_{22}H_{29}O_9N + 3H_2O$: H_2O, 10.69. Found: H_2O, 10.28. Calcd. for $C_{22}H_{29}O_9N$: C, 58.50; H, 6.47. Found: C, 58.68; H, 6.79.

Hydrogenation of Pseudocodeine: Dihydropseudocodeine.—The catalysts used in the hydrogenation experiments listed in Table IV were prepared by the usual methods[28] and whenever possible the same batch of catalyst was used throughout a series of comparative reductions.

The solution of pseudocodeine base or salt was shaken with catalyst and hydrogen until absorption stopped. In many cases a fresh portion of catalyst was added to make sure that reduction was complete. The pseudocodeine reduced rapidly and completely excepting in those hydrogenations which were carried out in concentrated solution, from which the products of hydrogenation often crystallized during the experiment. This crystalline precipitate usually carried down some phenolic dihydropseudocodeine, and could be slowly reduced further, or more rapidly if sufficient solvent was added. The method of isolation of the reduction products in all experiments was practically the same.

[28] Platinum oxide, Adams and Shriner, THIS JOURNAL, **45**, 2171 (1923); palladium on barium sulfate, Schmidt, *Ber.*, **52**, 409 (1919); palladium on calcium carbonate, Busch and Stöve, *ibid.*, **49**, 1064 (1916).

After complete reduction, the catalyst was filtered off, the solution being warmed if necessary to dissolve any crystalline precipitate. Organic solvents, where used, were removed by adding water and distilling under diminished pressure. Glacial acetic acid solutions were first concentrated under vacuum and diluted with water. The aqueous suspension or solution was acidified, if necessary, to bring all material into solution, and an excess of sodium hydroxide solution added, with stirring. The flocculent amorphous precipitate which first formed redissolved, and the dihydropseudocodeine (non-phenolic) immediately separated in crystalline form. After the solution was cooled this base could be filtered off in nearly pure form; a small second fraction (contaminated by a little tetrahydropseudocodeine) could be obtained by extracting the alkaline filtrate with ether. This ethereal solution was evaporated to dryness, digested with sodium hydroxide, and the insoluble portion, crude dihydropseudocodeine, filtered off. The alkaline filtrate, containing some tetrahydropseudocodeine, was added to the original alkaline solution, the further treatment of which is described under tetrahydropseudocodeine. The crude dihydropseudocodeine from ether was purified by crystallization from 60% alcohol or from ethyl acetate; thin rectangular scales or plates of m. p. 121–122° (corr.). After drying at 100° it melted at 155° (corr.); $[\alpha]_D^{28}$ −41.4°, c = 1.59 (alcohol).

Anal. Calcd. for $C_{18}H_{23}O_3N + H_2O$: C, 67.67; H, 7.89; H_2O, 5.64. Found: C, 67.62; H, 7.97; H_2O, 5.74. Sample dried at 100°. Calcd. for $C_{18}H_{23}O_3N$: C, 71.71; H, 7.70. Found: C, 71.67; H, 7.80.

A solution of 0.5 g. of the base in 30 cc. of absolute alcohol was treated with 4 g. of sodium, with occasional addition of more alcohol, over a period of two hours. The base, 0.44 g., was recovered unchanged.

Dihydropseudocodeine Hydrochloride.—Prepared in absolute alcohol with alcoholic hydrogen chloride; it crystallizes from alcohol in thin rectangular scales melting at 239–241° (corr.) with decomp. and red color. In aqueous solution $[\alpha]_D^{28}$ −24°, c = 1.46.

Anal. Calcd. for $C_{18}H_{24}O_3NCl + 0.5H_2O$: H_2O, 2.66. Found: H_2O, 2.60, 2.63.

Anal. (Subs. dried at 155°) Calcd. for $C_{18}H_{24}O_3NCl$: C, 63.86; H, 7.16; Cl, 10.50. Found: C, 63.86; H, 7.05; Cl, 10.45, 10.40.

Dihydropseudocodeine Hydriodide.—Prepared in methyl alcohol and recrystallized from water. It showed the m. p. 287° (corr.) when heated rapidly, 268–269° (corr.), decomposing, when heated slowly. In aqueous solution, $[\alpha]_D^{28}$ −22.5°, c = 1.11.

Anal. (Sample dried at 155°) Calcd. for $C_{18}H_{24}O_3NI$: I, 29.55. Found: I, 29.54.

Dihydropseudocodeine Methiodide.—Prepared from methyl alcohol, crystallizes from water as octahedra melting at 190–195° (corr.) when heated rapidly, at 241–243° (corr.) with decomposition when heated slowly. In water it showed $[\alpha]_D^{28}$ −22.1°, c = 1.23.

Anal. Calcd. for $C_{19}H_{26}O_3NI + H_2O$: H_2O, 4.06. Found: H_2O, 3.68, 3.31.

Anal. (Subs. dried at 155°) Calcd. for $C_{19}H_{26}O_3NI$: I, 28.63. Found: I, 28.33.

Dihydro-e-methylmorphimethine (Des-N-methyldihydropseudocodeine).—A solution of 12 g. of dihydropseudocodeine methiodide in 200 cc. of 12% sodium hydroxide was boiled for five minutes. The oily methine base was extracted from the cooled mixture with ether, from which it was obtained as an oil, not crystallizable even after purification through its salts. The oil was dissolved in 15 cc. of 25% acetic acid and treated with 6 g. of sodium iodide, yielding 10.3 g. of nearly pure hydriodide (decomp. 202–204°). This salt crystallized from water or alcohol as short hexagonal prisms of m. p. 232–235° (corr.) with decomp., turning red. In water it showed $[\alpha]_D^{28}$ +99.0, +100°, c = 1.66.

Anal. (Subs. dried at 155°) Calcd. for $C_{19}H_{26}O_3NI$: I, 28.63. Found: I, 28.57.

The hydrochloride was prepared from the oily base in acetone by addition of alcoholic hydrogen chloride, and was purified from absolute alcohol or acetone. It crystallized in long rectangular prisms of m. p. 222–224° (corr.) and showed the rotation $[\alpha]_D^{25}$ +123.0°, c = 1.21 (water).

Anal. Calcd. for $C_{19}H_{26}O_3NCl$: C, 64.80; H, 7.44. Found: C, 64.87; H, 7.57.

Tetrahydro-ε-methylmorphimethine (Dihydro-des-N-methyldihydropseudocodeine).—A solution of 2.14 g. of dihydro-ε-methylmorphimethine in 15 cc. of alcohol was hydrogenated in the presence of palladium–calcium carbonate. In one hour 147 cc. (standard conditions) or 1.0 mole of hydrogen was absorbed. The product obtained after evaporation of the solvent was an oil which yielded 2.25 g. of crystalline hydriodide when dissolved in dilute acetic acid and treated with sodium iodide; the base was not obtained in crystalline form even after purification through its hydriodide. The salt crystallizes from water as bundles of flat prisms, and has the m. p. 225–226° (corr.) with decomp.; in aqueous solution, $[\alpha]_D^{28}$ +17.4, 16.5, 18.6°, c = 1.3 to 1.7.

Anal. (Subs. dried at 155°) Calcd. for $C_{19}H_{28}O_3NI$: I, 28.50. Found: I, 28.28.

The hydrochloride, prepared in acetone with alcoholic hydrogen chloride, crystallized as needles from ethyl acetate or as long rectangular scales from methyl ethyl ketone, alcohol–acetone mixtures or from small volumes of water. It is very soluble in alcohol. It showed the m. p. 187° (corr.) and $[\alpha]_D^{28}$ +18.6, +20°, c = 1.11 (water). Under some conditions the salt apparently forms a trihydrate as well as a hemihydrate. Direct determinations of water were difficult as the salt sublimes slightly.

Anal. Calcd. for $C_{19}H_{28}O_3NCl + 0.5H_2O$: C, 62.69; H, 8.02. Found: C, 62.60, 62.63; H, 7.88, 8.06. Calcd. for $C_{19}H_{28}O_3NCl + 3H_2O$: H_2O, 13.2. Found (at 140°): H_2O, 13.02. Calcd. for $C_{19}H_{28}O_3NCl$: C, 64.43; H, 7.97. Found: C, 64.02; H, 8.16.

The salicylate, which was prepared in ether with ethereal salicylic acid, could be recrystallized from water as thin prismatic needles, melting at 198° (corr.); $[\alpha]_D^{27}$ −18.1°, c = 1.08 (water).

Anal. (Subs. dried at 100°) Calcd. for $C_{19}H_{27}O_3N \cdot C_7H_6O_3$: C, 68.54; H, 7.29. Found: C, 68.40; H, 7.27.

Tetrahydro-ε-methylmorphimethine acid tartrate crystallizes from water in thin square twinned scales of m. p. 195.5° (corr.) with frothing. In aqueous solution it shows $[\alpha]_D^{27}$ +27°, c = 1.29.

Anal. (Subs. dried at 100°) Calcd. for $C_{19}H_{27}O_3N \cdot C_4H_6O_6$: C, 59.08; H, 7.10. Found: C, 59.05; H, 7.19.

Tetrahydropseudocodeine.—The sodium hydroxide solution remaining after the separation of dihydropseudocodeine (usually a pink or red color developed) was cooled by adding ice, acidified with concd. hydrochloric acid, and made ammoniacal under ether. After two more ether extractions, the combined ethereal layers, containing all of the tetrahydropseudocodeine, were evaporated to dryness and the oily residue crystallized from 60% alcohol. Tetrahydropseudocodeine is soluble with difficulty in cold alcohol, and separates fairly pure and quite completely. The principal impurity present was a new phenolic dihydropseudocodeine, which could often be isolated in an amount roughly proportional to the difference in hydrogen absorption observed, from that which was calculated on the basis of the dihydropseudocodeine (non-phenolic) and tetrahydropseudocodeine isolated. Those reductions which were carried out in concentrated alcoholic solution yielded tetrahydropseudocodeine samples which, even after numerous crystallizations from alcohol, melted over the range 112–115°, and contained as much as 15% of the new phenolic dihydropseudocodeine. Mixtures of the phenolic dihydro-

pseudocodeine and tetrahydropseudocodeine all melt over approximately the same temperature range. The specific rotation of tetrahydropseudocodeine or its derivatives, containing traces of the above-mentioned impurities was generally 5–7° more positive than the rotation of the corresponding products in a state of purity.

Tetrahydropseudocodeine, freed from unsaturated material through prolonged hydrogenation, was purified by several crystallizations from alcohol, two crystallizations as the hydrochloride, and two more crystallizations as the base. The physical properties agree approximately with those reported by Speyer. It forms rhombic prisms or plates melting over a wide range; it begins to sinter at about 100°, and melts from 115–120° (corr.), even after long drying in vacuum. Frothing occurs above the melting point, apparently with loss of hydrate water. Heated slowly in a vacuum the base sinters to a glass below 100°, and distils easily at 160° (0.2 mm.). The hydrated base crystallizes unchanged from ethyl acetate, but if boiled in this solvent for a short time apparently loses its hydrate water and can be obtained only as an oil; the oil is converted to the crystalline hydrated base by dilute alcohol. For the specific rotation of the hydrated base we find $[\alpha]_D^{25}$ −9.9°, c = 1.08 (alcohol). The crystal form, melting points, rotations, and solubilities of the two phenolic dihydropseudocodeines and most of their salts are very similar to those of tetrahydropseudocodeine and its salts and cannot be used for identification. Tetrahydropseudocodeine gives two characteristic derivatives, a low-melting salicylate (the phenolic dihydropseudocodeine salicylates melt about 70° higher, and a high-melting methine which is soluble with difficulty in alkali and is extracted completely from alkaline solution with ether. Tetrahydropseudocodeine does not give a crystalline acid tartrate.

Tetrahydropseudocodeine hydrochloride melts at 263° (corr.) with darkening and subsequent decomposition. It is weakly dextrorotatory, in aqueous solution $[\alpha]_D^{25}$ +0.25, +1.9°, c = 1.01, 1.33.

Tetrahydropseudocodeine salicylate, prepared in ether with ethereal salicylic acid, crystallizes hydrated from alcohol as hexagonal plates or elongated prisms containing two molecules of water and melting at 135–136°. When the dihydrate is boiled in ethyl acetate solution or dried in a vacuum oven it is changed to a crystalline monohydrate of m. p. 165–166°. The monohydrate goes back to the dihydrate on crystallization from alcohol. The monohydrate shows the specific rotation in alcohol $[\alpha]_D^{24}$ −1.7°, c = 0.58.

Anal. Calcd. for $C_{25}H_{31}O_6N + 2H_2O$: H_2O, 7.54. Found: H_2O, 7.80. Calcd. for $C_{25}H_{31}O_6N + H_2O$: C, 65.32; H, 7.24; H_2O, 3.92. Found: C, 65.49; H, 7.51; H_2O, 3.90.

Tetrahydropseudocodeine methiodide has the specific rotation $[\alpha]_D^{26}$ −0.9°, c = 1.15 (water).

Phenolic Tetrahydro-ε-methylmorphimethine (Des-N-methyltetrahydropseudocodeine).—Twelve and eight-tenths grams of tetrahydropseudocodeine methiodide in 120 cc. of water was treated with 100 g. of solid potassium hydroxide and the solution boiled for fifteen minutes. The brown oil which separated solidified to a glass on cooling and was extracted into ether (difficultly soluble) or chloroform. Upon evaporation of the solvent an oily residue remained, which crystallized when dissolved in ethyl acetate and seeded; yield, 7.4 g. of nearly pure base. Purification from ethyl acetate gave prisms of m. p. 196–197° (corr.) with decomposition.[29] In alcohol, $[\alpha]_D^{28}$ +192°, c = 1.09; in chloroform, $[\alpha]_D^{26}$ +156.5°, c = 1.10.

Anal. (Subs. dried at 100°) Calcd. for $C_{19}H_{27}O_3N$: C, 71.88; H, 8.57. Found: C, 71.66; H, 8.48.

[29] Speyer and Krauss, *Ann.*, **432**, 254 (1923), found the m. p. 162–163° and reported the base alkali-soluble.

Solutions of the base in alcohol turn dark orange rapidly. In ethyl acetate or chloroform it is stable for a considerable time. A solution in hydrochloric acid turns deep red on standing for several days; the color is discharged by ammonia but reappears on acidification.

Phenolic tetrahydro-ϵ-methylmorphimethine is precipitated amorphous from its solutions in acids by addition of sodium hydroxide. It redissolves in excess of alkali, but crystallizes immediately from the alkaline solution, even in considerable dilutions. The crystalline precipitate was identified as phenolic tetrahydro-ϵ-methylmorphimethine; the separation is quite complete, for the alkaline filtrate gave no further precipitate with ammonium chloride. If the solution of phenolic tetrahydro-ϵ-methylmorphimethine in acid is diluted to a very large volume before addition of alkali, no precipitation takes place; three extractions of the alkaline solution with ether resulted in recovery of 90–95% of the base. The base in such an extremely dilute alkaline solution is apparently in loose combination with the alkali. It is probably not water-soluble, for addition of ammonium chloride precipitates the crystalline base.

Phenolic tetrahydro-ϵ-methylmorphimethine did not yield a crystalline hydrochloride, acid tartrate nor salicylate. The hydriodide, prepared in water, crystallized from acetone as thin truncated rectangular scales, m. p. 123–124° (corr.). The solid salt is not very stable, and the aqueous solution turns dark rapidly.

Anal. Calcd. for $C_{19}H_{28}O_3NI + 0.5H_2O$: H_2O, 2.02. Found: H_2O, 1.98. Calcd. for $C_{19}H_{28}O_3NI$: I, 28.50. Found: (sample dried at 110°) I, 28.50.

Hydrogenation of Phenolic Tetrahydro-ϵ-methylmorphimethine.—A solution of 1.0 g. of the base in 25 cc. of alcohol with 0.1 g. of palladium–calcium carbonate catalyst absorbed 70 cc. (stand. cond.) of hydrogen, or one mole, in one hour. The residue obtained after filtering and evaporating off the solvent was crystallized from ethyl acetate, and yielded 0.75 g. of hexahydro-ϵ-methylmorphimethine which was identified by mixed melting point and by comparison of the hydrochloride and hydriodide with known samples.

Normal Hydrogenation of ϵ-Methylmorphimethine: Tetrahydro-ϵ-methylmorphimethine (Non-phenolic).—The ϵ-methylmorphimethine for these experiments was prepared by the method of Knorr[30] and was used in the form of an oil, since it did not crystallize even after purification through the crystalline hydrochloride. In our first preparations of ϵ-methylmorphimethine hydrochloride we obtained the low-melting hydrated salt described by Knorr as melting at 150° and having the specific rotation $[\alpha]_D^{15}$ −154°. We observed as constants m. p. 149–150° and $[\alpha]_D$ −151°. When the hydrochloride was prepared in absolute alcohol with alcoholic hydrogen chloride, an anhydrous form was obtained, which melted at 211–212° (corr.) and showed in water $[\alpha]_D^{22}$ −154.5°, c = 1.19. An examination of the hydrated samples previously prepared showed that they had also become anhydrous. After the anhydrous form appeared we were no longer able to prepare the hydrated hydrochloride.

Anal. Calcd. for $C_{19}H_{23}O_3N \cdot HCl$: C, 65.20; H, 6.92. Found: C, 65.10; H, 6.98.

Two grams of ϵ-methylmorphimethine hydrochloride in 10 cc. of glacial acetic acid was shaken under hydrogen in the presence of 0.15 g. of platinum oxide. In one-half hour the reduction was complete, with an absorption of 363 cc. (standard) of hydrogen, or 2.72 moles (corrected for the catalyst). The solution was filtered, made alkaline with ammonia and extracted with ether, which yielded a mass of needle crystals on evaporation. Crystallization from ethyl acetate gave 0.8 g. of the sparingly soluble hexahydro-ϵ-methylmorphimethine of m. p. 161–163° (identification by mixed melting point and specific rotation). The ethyl acetate mother liquors, on evaporation, gave an oily base

[30] Knorr, Butler and Hörlein, *Ann.*, **368**, 305 (1909).

which was dissolved in acetone and converted to the crystalline hydrochloride by addition of alcoholic hydrogen chloride. A yield of 0.65 g. of tetrahydro-ϵ-methylmorphimethine hydrochloride was obtained. This was identified by its melting point, specific rotation $[\alpha]_D^{25}$ +19°, c = 1.14 (water), and by conversion through the oily base to the two characteristic salts—salicylate and acid tartrate. These salts were checked by melting point, rotation and mixed melting points with the corresponding salts of tetrahydro-ϵ-methylmorphimethine prepared via dihydropseudocodeine.

Two grams of ϵ-methylmorphimethine hydrochloride in 10 cc. of water containing 0.2 cc. of concd. hydrochloric acid and 0.1 g. of platinum oxide absorbed 344 cc. or 2.52 moles (corr. for catalyst) and yielded 0.7 g. of hexahydro-ϵ-methylmorphimethine and 0.87 g. of tetrahydro-ϵ-methylmorphimethine hydrochloride.

Two grams of ϵ-methylmorphimethine hydrochloride in water with palladium on barium sulfate gave 0.55 g. of tetrahydro-ϵ-methylmorphimethine hydrochloride. With platinum, under these conditions, the hexahydro derivative was practically the sole product.

A reduction of ϵ-methylmorphimethine base in alcohol with palladium–calcium carbonate gave chiefly hexahydro-ϵ-methylmorphimethine, and a small amount of oil which yielded an unidentified hydrochloride of specific rotation $[\alpha]_D^{29}$ +94°, c = 1.33 (water).

Hexahydro-ϵ-methylmorphimethine.—This base, prepared and purified as described in the above reductions, crystallized from ethyl acetate as fine hairs or granular prisms, depending upon the rate of cooling. It melts at 166.5–167.5° and has the specific rotation $[\alpha]_D^{28}$ +28°, c = 1.08 (alcohol).[31]

Anal. Calcd. for $C_{19}H_{29}O_3N$: C, 71.43; H, 9.14. Found: C, 71.22; H, 9.12.

In the solid state, or when freshly precipitated, the base dissolves very reluctantly in alkali. When a moderately dilute acid solution of the base is made alkaline (NaOH) an amorphous precipitate appears and redissolves; in a short time the base crystallizes from the alkaline solution. The filtrate still contains a small amount of the sodium salt, from which ammonium chloride precipitates the base. Extremely dilute solutions of the base in sodium hydroxide remain clear, but two extractions with ether remove practically all of the alkaloid.

The hydrochloride of hexahydro-ϵ-methylmorphimethine was prepared in acetone with alcoholic hydrogen chloride, and crystallizes as plates from absolute alcohol. It melts at 250–254° (corr.) with decomposition[32] and shows $[\alpha]_D^{28}$ +8.1°, c = 1.53 (water).

Anal. Calcd. for $C_{19}H_{30}O_3NCl$: Cl, 10.08. Found: (dried at 155°) Cl, 10.06.

The acid tartrate was prepared by dissolving the calculated amounts of hexahydro-ϵ-methylmorphimethine and *d*-tartaric acid in methanol, adding methyl ethyl ketone, boiling off a portion of the solvent and seeding. After long standing the salt crystallized very slowly; it is exceedingly soluble in cold alcohol or water. It melts at 114–115° (corr.) with frothing, and shows $[\alpha]_D^{27}$ +15.6°, c = 1.16 (water).

Anal. Calcd. for $C_{23}H_{35}O_9N + H_2O$: H_2O, 3.69. Found: H_2O, 3.69. Calcd. for $C_{23}H_{35}O_9N$: C, 58.81; H, 7.52. Found: (dried at 100°) C, 58.74; H, 7.54.

Summary

1. The catalytic hydrogenation of morphine derivatives of the pseudocodeine type, which usually proceeds with addition of two molecules of hydrogen and results in phenolic products, can be greatly influenced by

[31] Speyer and Koulen, *Ann.*, **438**, 55 (1924), found m. p. 155° and could detect no rotation.

[32] Speyer and Koulen give the m. p. 213°.

solvent, nature of catalyst, and especially by hydrogen-ion concentration. Pseudocodeine can thus be reduced in excellent yield to a new non-phenolic dihydropseudocodeine.

2. The degradation of dihydropseudocodeine to dihydro-ϵ-methylmorphimethine, and conversion of the latter to tetrahydro-ϵ-methylmorphimethine is described. The preparation of tetrahydro-ϵ-methyl-morphimethine through extension of the special hydrogenation method to ϵ-methylmorphimethine has been accomplished.

3. The degradation product from tetrahydropseudocodeine is correctly described and its relationship to hexahydro-ϵ-methylmorphimethine established.

UNIVERSITY, VIRGINIA

[CONTRIBUTION FROM THE LABORATORY OF PHYSICAL CHEMISTRY OF THE UNIVERSITY OF UPSALA]

THE MOLECULAR WEIGHT OF THE HEMOCYANIN OF OCTOPUS VULGARIS

BY THE SVEDBERG AND INGA-BRITTA ERIKSSON

RECEIVED JULY 8, 1932 PUBLISHED DECEMBER 13, 1932

In three previous papers[1,2,3] reports have been given of the determination of the molecular weights and the sedimentation constants of hemocyanin from *Helix pomatia* and *Limulus polyphemus* by means of the ultracentrifugal methods developed in this Laboratory. Both of these hemocyanins (called *h*-hemocyanin and *l*-hemocyanin) differ markedly from all other proteins by having molecular weights of the order of millions. It seemed desirable to extend this study to other members of the hemocyanin group. The chemical and physico-chemical properties of the hemocyanin of *Octopus vulgaris* (*o*-hemocyanin) are well known, the protein having been the object of a great number of investigations.[4] The blood of octopus is comparatively easy to obtain in sufficient quantities and the protein is very stable. It was therefore chosen as a proper object for a detailed ultracentrifugal investigation.

Material.—The *o*-hemocyanin was prepared by one of us (T. S.) during a stay at the Stazione Zoologica of Naples, Italy.[5] To 50 cc. of octopus blood drawn in the manner described by Henze[6] was added 50 cc. of

[1] Svedberg and Chirnoaga, THIS JOURNAL, **50**, 1399 (1928).

[2] Svedberg and Heyroth, *ibid.*, **51**, 539 (1929).

[3] Svedberg and Heyroth, *ibid.*, **51**, 550 (1929).

[4] *E. g.*, Dhéré, Thèse, Fribourg, 1909; Dhéré, *J. physiol. path. gén.*, 1915–1922; Quagliariello, in Wintersteins "Handb. d. vergl. Physiolog.," Jena, 1922; Schmitz, *Z. physiol. Chem.*, **194**, 232 (1931); **196**, 71 (1931).

[5] For the interest and help shown him on this occasion by the director of the Station, Prof. R. Dohrn, and by Prof. L. Califano, sincere thanks are expressed.

[6] Henze, *Z. physiol. Chem.*, **33**, 370 (1901).