[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

STEREOCHEMICAL STUDIES IN THE MORPHINE SERIES. THE RELATIVE CONFIGURATION AT CARBONS FIVE AND SIX

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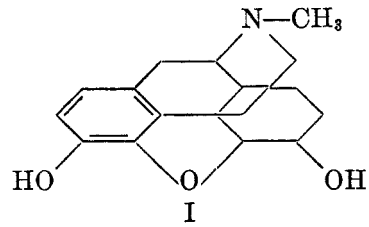
The morphine molecule (I) presents an interesting and important stereochemical problem with its five asymmetric carbons (positions 5, 6, 9, 13, 14) and multiple ring systems. Previous work on the spatial orientation at these asymmetric centers has been confined to some speculative deductions by Schöpf. With the aid of models, Schöpf and Pfeifer (1) interpreted the exclusive formation of dihydrocodeinone from dihydrothebainone by oxide ring-closure at carbon 5 as indicating that the oxygen bond to carbon 5 was *trans* to the ethanamine bond at carbon 13. The hydrogen at carbon 14 was inferred to be *cis* to the ethanamine bond at carbon 13 by analogy with the 14-hydroxy compound. Since degradation of dihydrohydroxycodeinone to nitrogen-free material resulted in a cyclic ether involving the 14-hydroxyl group, this group and the ethanamine chain must be *cis* (2). If one assumes the 14-hydroxyl and 14-hydrogen have the same configuration, then the 14-hydrogen is also *cis*. These conclusions have been supported in a recent re-examination of the evidence (3). The only other data on the subject are the assignments of rotational contributions (plus or minus) to the various asymmetric centers by Emde (4). This, of course, provides no information as to the actual configurations.



I

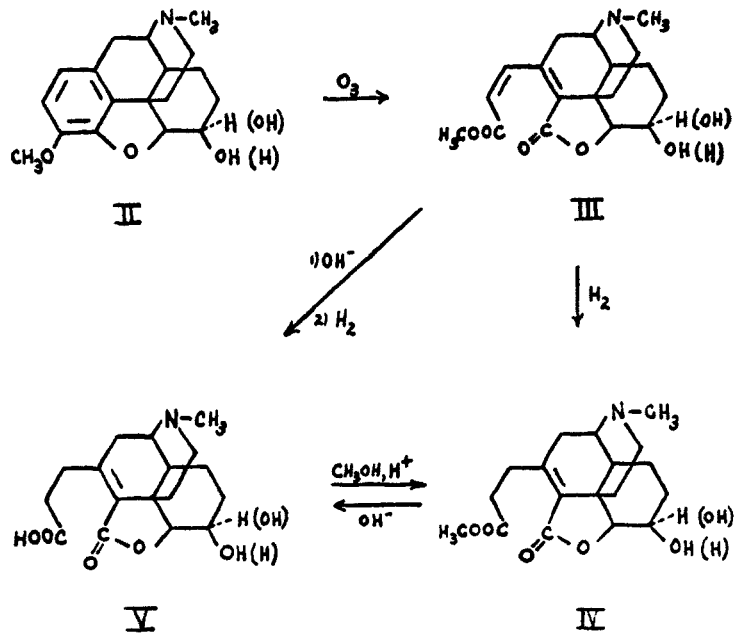
The current studies were undertaken with the objective of determining, by absolute methods, the relative configurations among the various asymmetric centers. This communication is concerned with establishing the relative configuration at carbons 5 and 6.

The epimeric alcohols, dihydrocodeine and dihydroisocodeine (II) constitute the isomeric pair needed for configurational studies at carbons 5 and 6. If the oxide bridge could be opened at carbon 4 instead of at carbon 5, as usually occurs, then a pair of cyclic vicinal diols would result, and their configuration could be determined with the usual reagents (5). Since the requisite opening of the aromatic ring has been achieved by ozonolysis (6), this appeared to be a feasible scheme.

Dihydrocodeine was easily prepared by hydrogenating codeine. However, the preparation of a reasonable quantity of dihydroisocodeine was much more

difficult. The path proceeding from codeine to α-chlorocodide (7), separation of the codeine isomers resulting from hydrolysis of the α-chlorocodide (8), and hydrogenation of the crude isocodeine (8), thus converting any residual pseudocodeine and allopseudocodeine to more easily removed phenolic substances (9), gave only a 6% over-all yield of dihydroisocodeine.

While pseudocodeine is the dominant isomer from the hydrolysis of α-chlorocodide, isocodeine predominates when bromocodide is hydrolyzed (10). Therefore, the preparation and hydrolysis of bromocodide was investigated. Conversion of codeine to bromocodide using thionyl bromide gave a more easily isolated product and in better yield (74%) than the previous phosphorus tribromide procedure (11). A large excess of thionyl bromide should be avoided since



this leads to an appreciable amount of a dibromo compound whose structure was shown to be 1-bromobromocodide by independent synthesis from 1-bromocodeine and thionyl bromide. Hydrolysis of the bromocodide and hydrogenation of the crude isocodeine resulted in a 35% yield (based on codeine) of dihydroisocodeine.

The ozonolysis of dihydrocodeine (II) to ozodihydrocodeine (III) and the characterisation of the latter has been reported by Speyer (6). By substituting aqueous acetic acid for the aqueous formic acid originally used and discontinuing the ozonolysis after the consumption of one mole of ozone, the yield of ozodihydrocodeine was increased from 40% to 75%. Hydrolysis of both the

[1] This nomenclature is based on dihydromorphinic acid (III, methyl ester and lactone hydrolyzed) as the fundamental compound of the series.

methyl ester and lactone groups of ozodihydrocodeine gave dihydromorphinic acid, but it proved too unstable to be used further.

If, however, the ozodihydrocodeine was hydrolyzed and the hydrolysate hydrogenated, the stable tetrahydromorphilactonic acid[1] (V) was isolated. The same compound was also obtained by hydrogenating first to methyl tetrahydromorphilactonate (IV) and saponifying the latter to (V); the methyl ester (IV) was regained by esterifying compound (V).

Speyer (6) has represented the hydrogenation of ozodihydrocodeine (III) as proceeding through hydrogenolysis of the carbon-oxygen bond at carbon 5 to the amino acid (VI) and the saponification of (VI) to give the dibasic acid (VII). The compounds obtained in the present work are identical with those reported previously and are assigned the structures (IV) and (V) instead of the isomeric structures (VI) and (VII) for the following reasons:

A. The hydrogenation product is readily soluble in ether. This would be expected of structure (IV) but not the amino acid (VI).

B. Esterification of the saponified material gives back the original ester with one methoxyl group. This is consistent with structure (V). If the structure of the saponified material was (VII), a dimethyl ester would be expected. Lactone formation conceivably might have occurred with the 6-hydroxyl to give only a monomethyl ester, but the product would then differ from the original ester due to loss of a molecule of water.

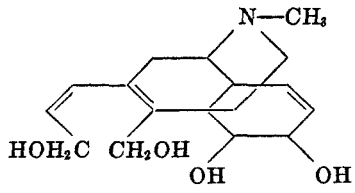
C. Potentiometric titration of the hydrogenation product indicates the absence of any carboxyl group.

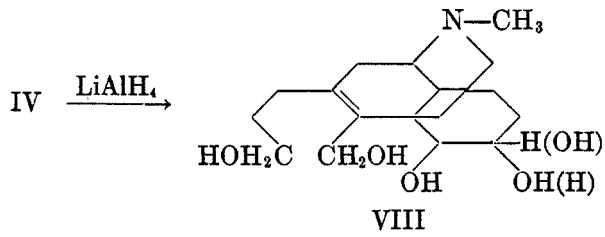
D. Potentiometric titration of the hydrogenated and saponified material shows the presence of one carboxyl and an equivalent weight of 319. This is consistent with structure (V), equivalent weight, 321.

The above evidence clearly eliminates structures (VI) and (VII) and supports the alternative formulations, (IV) and (V). The position of the double bond in these compounds has not been proved but is assumed to be as shown since only one mole of hydrogen is absorbed at atmospheric pressure and room temperature. The endocyclic double bond would be more likely to be resistant to hydrogenation.

A compound suitable for stereochemical examination was obtained by reducing methyl tetrahydromorphilactonate (IV) with lithium aluminum hydride (12). The resulting compound, tetrahydromorphitetrol[2] (VIII), although not

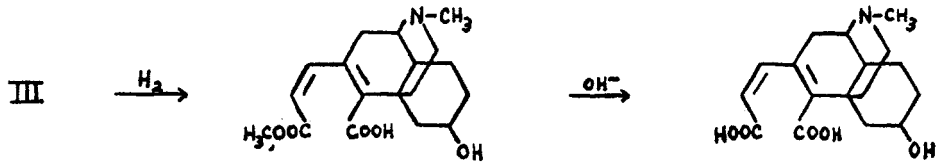
[2] In analogy with already established nomenclature in this series, the parent compound would be morphitetrol with the structure





VIII

obtainable crystalline, was characterized through derivatives and tetraacetate formation. Since the oxygen-carbon bond at carbon 5 is not broken, the configuration at this center remains unaffected (13), and a compound is formed containing a vicinal pair of hydroxyls at carbons 5 and 6 with the original configuration retained.



VI VII

To prepare the epimeric tetrol, dihydroisocodeine (II), differing from dihydrocodeine only in the configuration at carbon 6, was subjected to exactly the same sequence of reactions. Ozonolysis gave ozodihydroisocodeine (III), which was hydrogenated to methyl tetrahydro-α-isomorphilactonate[3] (IV) and the latter saponified to tetrahydro-α-isomorphilactonic acid (V). Lithium aluminum hydride reduction of the ester (IV) then gave tetrahydro-α-isomorphitetrol (VIII).

Of the several methods available for determining the relative configuration of the hydroxyls in a cyclic 1,2-diol (5), the rate of oxidation by lead tetraacetate appeared to be the most suitable. Recent work, especially with cyclic sugar derivatives, has firmly established the original observation (14) that *cis*-1,2-diols are oxidized more rapidly than *trans*.

Oxidation by lead tetraacetate in glacial acetic acid at 15° was applied to the crystalline picrates of both tetrols (VIII), after ascertaining that the presence of picric acid had no effect. The curves obtained are shown in Figure 1. In both cases, only one mole of lead tetraacetate was consumed per mole of tetrol. However, this consumption was complete after two hours with tetrahydromorphitetrol, and required over six hours with tetrahydro-α-isomorphitetrol. An examination of the curves also shows that the rate of oxidation of the one isomer was about three times as rapid as that of the other.

[3] Since the compounds in which the aromatic nucleus has been opened already have the "morphi" designation, the morphine nomenclature has been retained throughout. The alcohol epimeric with morphine is α-isomorphine, therefore all the compounds in this epimeric series have the "α-isomorphi" nomenclature.

From this we may conclude that the hydroxyl pair at carbons 5 and 6 are *cis* in tetrahydromorphitetrol and *trans* in tetrahydro-α-isomorphitetrol. Since the former is derivable from morphine and the latter from α-isomorphine, it follows that the carbon-oxygen bonds at carbons 5 and 6 are *cis* in morphine and *trans* in α-isomorphine.

EXPERIMENTAL

All melting points are corrected, and those above 200° were taken in evacuated tubes. Microanalyses were performed by the Micro Chemical Laboratory, University of California.

Dihydroisocodeine (II). *A. From α-chlorocodide.* Codeine was converted to α-chlorocodide (7) and the codeine isomers were obtained from the latter by the method of Speyer and Krauss (8). The crude isocodeine binoxalate (22.3 g., 21%) thus resulting from the hydrolysis

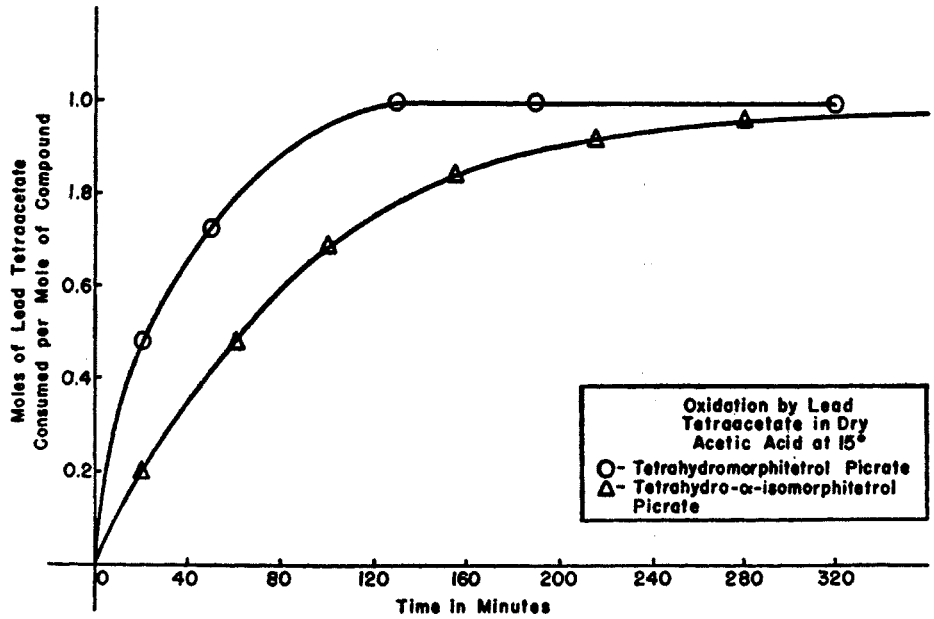


FIGURE 1.

of 88.0 g. of α-chlorocodide was dissolved in 200 ml. of warm water. Basifying with 6 *N* potassium hydroxide liberated an oil which was extracted into 300 ml. of ether, and the aqueous layer was further extracted with two 100-ml. portions of ether. After washing the combined ether solutions with water, drying over potassium carbonate, and evaporating, there was obtained about 16 g. of crude isocodeine. This was dissolved in 70 ml. of hot ethyl acetate and allowed to cool to room temperature. Once crystallization had begun, the solution was cooled overnight at 0°. Filtration gave 7.5 g. of isocodeine melting from 157–164° [reported (15) m.p. 171–172°]. This material, dissolved in 60 ml. of water and 2 ml. of glacial acetic acid, absorbed 1.3 moles of hydrogen when hydrogenated at room temperature and atmospheric pressure in the presence of 1.5 g. of 5% palladium on barium sulfate. Filter aid was added, the mixture was filtered, and the filtrate was basified with excess 6 *N* potassium hydroxide to give a white solid which was washed well with water. The weight of dihydroisocodeine melting from 190–200° was 6.2 g. (6% over-all from codeine). One recrystallization from ethanol gave material melting at 198–200° [reported (8)

m.p. 199–200°] but it was found that this was not necessary, since the crude material was satisfactory for subsequent work.

B. From bromocodide. In an apparatus with stirrer, condenser, dropping-funnel, and protection from moisture, a solution of 17.4 g. (0.084 mole, 6.5 ml.) of thionyl bromide (16) was added dropwise with stirring to a solution of 25 g. (0.084 mole) of dry codeine in 50 ml. of chloroform. A water-bath was used for cooling and the addition was made over a period of two hours. After the addition was complete, the reaction mixture was refluxed gently for three hours and then cooled. The reaction mixture was treated with 100 ml. of water followed by a saturated sodium carbonate solution, and the free base was extracted as an oil into 150 ml. of a 1:1 mixture (by volume) of ether and chloroform. Two additional 50-ml. extractions were made and the combined extracts were washed with 50 ml. of water, dried, and evaporated to give a solid residue of 28–30 g. Recrystallization from 225 ml. of absolute ethanol gave 21.2 g. of pure bromocodide, m.p. 159–160° [reported (11) m.p. 162°]. An additional 1.1 g. was recovered from the mother liquors; total yield, 22.3 g., 74%.

Twenty-five grams (0.069 mole) of bromocodide was suspended in 200 ml. of water and, after adding sufficient glacial acetic acid to bring the base into solution, the mixture was heated under reflux vigorously for four hours and then cooled. The free base was liberated as an oil by the action of excess 6 *N* potassium hydroxide, and this oil was immediately extracted into 150 ml. of a 1:1 mixture of ether and chloroform. The aqueous phase was extracted twice more with 50-ml. portions of ether-chloroform, and then the combined organic layer was washed with two 25-ml. portions of water and evaporated on the steam-bath to give 20 g. of white solid. Recrystallization from about 50 ml. of ethyl acetate gave 14 g. of a solid mixture of isocodeine, pseudocodeine, and allopseudocodeine which was dissolved in 150 ml. of water by adding the necessary amount of glacial acetic acid and hydrogenated at room temperature and 30 p.s.i., using 2.9 g. of a 5% palladium on barium sulfate catalyst. After four hours, hydrogen uptake ceased with a total absorption of 1.3 moles. The catalyst was filtered, washed with warm water, and the filtrate was basified with excess 6 *N* potassium hydroxide to precipitate an oil which solidified on standing. It was filtered, washed with water, and the filtrate and washings were extracted three times with 50-ml. portions of 1:1 ether-chloroform solution. The combined extracts after washing with water, were evaporated to give about 2 g. of solid residue which was added to the 8 g. from the original filtration. Total yield of dihydroisocodeine melting at 190–200° was 10 g. (48% from bromocodide, 35% from codeine). It was sufficiently pure for use in subsequent reactions.

Dihydrocodeine (II) was purified by the method of Homeyer and Shilling (17).

Ozodihydrocodeine (III). A solution of 15 g. (0.05 mole) of dihydrocodeine in 100 ml. of 4.5 *N* acetic acid was ozonized at 0° with a stream of oxygen containing 4% ozone (by volume) at a flow of about 17 liters per hour using the apparatus of Henne and Perilstein (18) and the procedure as described in Organic Syntheses (19). In about five hours, one mole of ozone had been consumed and the ozonolysis was stopped. During the course of the reaction, the solution turned bright yellow and faded to a pale yellow just before the reaction was over. The reaction mixture was brought to about *p*H 6 by the addition of solid sodium bicarbonate, concentrated ammonia was added carefully to *p*H 8 or 9 and the solution extracted five times with 50-ml. portions of chloroform. The combined extracts were washed with 50 ml. of water and evaporated on the steam-bath to a thick oil, which was converted to the hydrochloride by dissolving it in 75 ml. of absolute ethanol and adding 4 *N* alcoholic hydrochloric acid until the solution was acid to Congo Red. Cooling gave 13.5 g. (74%) of hydrochloride decomposing at 235–236°, and recrystallization did not alter the melting point; $[\alpha]_D^{20}$ +78.8° (water, *c*, 2.26); reported (6) m.p. 242°, $[\alpha]_D^{17}$ +78.6° (water, *c*, 5.0).

Ozodihydroisocodeine (III). A solution of 14 g. (0.046 mole) of dihydroisocodeine in 120 ml. of 4.5 *N* acetic acid was ozonized at room temperature as above. At the end of 16 hours about 1.1 moles of ozone had been absorbed and the solution had turned from dark to pale yellow. At that time the reaction was stopped and the product isolated in the same manner as the epimeric compound above. The oily free base was dissolved in 75 ml. of absolute

ethanol and treated with 1 *N* alcoholic perchloric acid until acid to Congo Red. Cooling gave 9.0 g. (45%) of ozodihydroisocodeine perchlorate melting at 203–205°, suitable for use in subsequent reactions without further purification. Recrystallization from ethanol gave material melting with decomposition at 206–208°; $[\alpha]_D^{20}$ +22.6° (water, *c*, 1.106).

Anal. Calc'd for $C_{18}H_{24}ClNO_9$: C, 49.8; H, 5.6; OCH_3, 7.2.

Found: C, 49.8; H, 5.4; OCH_3, 7.4.

Tetrahydromorphilactonic acid (V). A solution of 8.88 g. (24.0 millimoles) of ozodihydrocodeine hydrochloride in 200.0 ml. of 0.59 *N* alcoholic sodium hydroxide (118 millimoles) was heated under reflux in a nitrogen atmosphere for 1½ hours. After cooling, 45.0 ml. of 1 *N* hydrochloric acid was added to give a slightly basic solution. To this was added 1.8 g. of 5% palladium on charcoal, and the solution was hydrogenated at room temperature and 25 p.s.i. After 2 hours, hydrogenation ceased with an uptake of one mole of hydrogen. Filter aid was added, the solution was filtered, and to the filtrate was added 49.0 ml. of 1 *N* hydrochloric acid to liberate the amino acid from its sodium salt. Evaporation of the resulting solution *in vacuo* gave a solid mixture of sodium chloride and the amino acid which was digested for two hours with 200 ml. of absolute ethanol. Filtration and concentration (to about 75 ml.) of the resulting solution gave, on cooling, 6.5 g. (84%) of tetrahydromorphilactonic acid melting at 240–243° with decomposition. Recrystallization from ethanol gave m.p. 245–246°, $[\alpha]_D^{22}$ +29.0° (water, *c*, 2.38); reported (6) m.p. 245–248°, $[\alpha]_D^{17}$ +28.5°.

Anal. Calc'd for $C_{17}H_{23}NO_5$: C, 63.6; H, 7.2.

Found: C, 63.4; H, 7.3.

By potentiometric titration, the equivalent weight was found to be 319; calc'd 321.

The same compound was obtained by reversing the above procedure, *i.e.*, by first hydrogenating ozodihydrocodeine to methyl tetrahydromorphilactonate (below) and then saponifying the latter. The resulting amino acid melted at 245–246° and showed no depression on admixture with a sample of tetrahydromorphilactonic acid prepared above.

Methyl tetrahydromorphilactonate (IV). A solution of 14 g. (0.038 mole) of ozodihydrocodeine hydrochloride in 250 ml. of water containing 3.3 g. of 5% palladium on barium sulfate was hydrogenated at room temperature and 30 p.s.i. At the end of an hour hydrogenation ceased with an uptake of one mole of hydrogen. Filter aid was added and the solution filtered and basified with saturated potassium carbonate solution to *p*H 8 or 9. The solution was then extracted five times with 100-ml. portions of ethyl acetate, and the combined extracts were washed with water and dried over magnesium sulfate. On concentration of the solution, crystallization occurred when the volume was reduced to about 50 ml., at which point the solution was cooled and filtered to yield 9.2 g. (73%) of methyl tetrahydromorphilactonate, m.p. 147–148°, $[\alpha]_D^{19}$ +6.3° (ethanol, *c*, 1.026); [reported (6) m.p. 150–151°]. Recrystallization from either ethyl acetate or benzene did not alter the melting point.

Anal. Calc'd for $C_{18}H_{25}NO_5$: C, 64.4; H, 7.5; OCH_3, 9.3.

Found: C, 64.4; H, 7.2; OCH_3, 9.3.

Potentiometric titration indicated the absence of any acidic group.

The *picrate*, prepared in and purified from ethanol, melted at 228–229°, as reported (6).

Methyl tetrahydromorphilactonate could also be prepared by esterification of tetrahydromorphilactonic acid with methanol and sulfuric acid. The product was identical with that prepared above by hydrogenation of ozodihydrocodeine.

Tetrahydromorphilactonic acid amide. A solution of 600 mg. (1.8 millimoles) of methyl tetrahydromorphilactonate in 10 ml. of liquid ammonia was heated overnight at 100° in a bomb. Evaporation of the excess ammonia gave a solid which was twice crystallized from propanol to give 400 mg. of lactonic acid amide melting with decomposition at 226–228°, $[\alpha]_D^{19}$ −3.4° (ethanol, *c*, 1.102).

Anal. Calc'd for $C_{17}H_{24}N_2O_4$: C, 63.8; H, 7.6; N, 8.7.

Found: C, 63.6; H, 7.7; N, 8.4.

Methyl tetrahydro-α-isomorphilactonate (IV). A solution of 6.6 g. (0.015 mole) of ozodihydroisocodeine perchlorate in 150 ml. of 50% aqueous ethanol containing 2.0 g. of 5% palladium on barium sulfate was hydrogenated at room temperature and 20 p.s.i. Within

half an hour the hydrogenation ceased with an uptake of one mole of hydrogen. Filter aid was added, the solution filtered, and the filtrate concentrated to 50 ml. It was then brought to *p*H 8 by the addition of saturated sodium carbonate solution and extracted with six equal volumes of chloroform. The combined extracts were washed with water and evaporated to give 5 g. of residue which could not be induced to crystallize. For analytical purposes the *picrate* was made in and recrystallized from ethanol. It sintered from 213–218° and melted with decomposition at 218°, $[\alpha]_D^{23}$ +2.4° (water, *c*, 0.810).

Anal. Calc'd for $C_{24}H_{28}N_4O_{12}$: C, 51.1; H, 5.0; N, 9.9.

Found: C, 51.1; H, 5.0; N, 9.3.

Tetrahydro-α-isomorphilactonic acid (V). A solution of 560 mg. (1.67 millimoles) of methyl tetrahydro-α-isomorphilactonate in 15.0 ml. of 0.584 *N* alcoholic sodium hydroxide (8.75 millimoles) was heated under reflux in a nitrogen atmosphere for two hours. After adding 8.75 ml. of 1 *N* hydrochloric acid to the cooled solution, it was concentrated to dryness *in vacuo* and the residue of sodium chloride and lactonic acid was digested for two hours with 150 ml. of absolute ethanol. The sodium chloride was removed and the filtrate was concentrated to 25 ml. Thorough cooling precipitated 410 mg. (78%) of tetrahydro-α-isomorphilactonic acid decomposing at 240°. Crystallization from ethanol gave material decomposing at 243–245°, $[\alpha]_D^{19}$ 0.0° (water, *c*, 0.982).

Anal. Calc'd for $C_{17}H_{23}NO_5$: C, 63.6; H, 7.2.

Found: C, 63.3; H, 7.1.

Preparation of a standarizied solution of lithium aluminum hydride in tetrahydrofuran. Fifteen grams of lithium aluminum hydride were crushed into small pieces and added, with cooling, to 250 ml. of pure tetrahydrofuran. The solution was protected from moisture and allowed to reflux for three hours on the steam-bath. After cooling, it was filtered through a plug of glass wool into a 250-ml. graduated cylinder and allowed to stand for several hours at room temperature to settle the suspended material. The solution was standardized before each use by adding a 2-ml. aliquot to 10 ml. of ice-water. Addition of 15.0 ml. of 1 *N* HCl gave a clear solution when warmed on the steam-bath for a few minutes, and back-titration of excess acid was accomplished with 1 *N* sodium hydroxide to a Thymol Blue end-point. The freshly prepared solution contained 1.2 millimoles of lithium aluminum hydride per ml. Blank runs, carried out by titrating known volumes of standard hydrochloric acid with standard base in the presence of aluminum chloride, indicated that this procedure gave results accurate to about 2%.

Tetrahydromorphitetrol (VIII). In a flask equipped with stirrer, condenser, and dropping-funnel, and in a nitrogen atmosphere, was placed a solution of 2.0 g. (6.0 millimoles) of methyl tetrahydromorphilactonate in 50 ml. of pure tetrahydrofuran. To this was added with stirring, over a five-minute period, a standardized solution of 30 millimoles of lithium aluminum hydride in 25 ml. of tetrahydrofuran, and the reaction mixture was heated under reflux overnight. It was then cooled thoroughly before carefully decomposing with water. Sulfuric acid (10%) was added to dissolve the solid hydroxides and render the aqueous solution acidic. To the two-phase mixture was added 50 ml. of ether to effect a better separation, and the lower aqueous phase was separated. The organic layer was extracted with a 50-ml. portion of water and then the combined aqueous solutions were washed twice with 25-ml. portions of ether. After basification with saturated sodium carbonate solution, the aqueous portion was evaporated to dryness *in vacuo* and the resulting solid was digested for two hours by boiling with 200 ml. of ethyl acetate. After filtration, the solution was evaporated to an oily residue of 1.5 g. To remove any lactone-containing impurity, the oil was dissolved in 20 ml. of 0.5 *N* sodium hydroxide and warmed on the steam-bath for two hours. Carbon dioxide was then bubbled in until the basicity was lowered to *p*H 9. Concentration to dryness, followed by repetition of the above isolation procedure gave 1.3 g. (70%) of tetrahydromorphitetrol as an amorphous hygroscopic solid melting from 50–80° when thoroughly dry. All attempts at crystallization failed.

The *picrate* was formed in and recrystallized twice from absolute ethanol. It decomposed at 179–180°, $[\alpha]_D^{20}$ +25.0° (50% acetone-water, *c*, 0.792).

Anal. Calc'd for $C_{23}H_{32}N_4O_{11}$: C, 51.1; H, 6.0.
Found: C, 51.2; H, 5.8.

The *methiodide* was prepared by warming on the steam-bath an ethanolic solution of the tetrol with excess methyl iodide. Two recrystallizations from absolute ethanol gave material melting at 192–194°, $[\alpha]_D^{19}$ +36.7° (water, *c* 1.118).

Anal. Calc'd for $C_{18}H_{32}INO_4$: C, 47.7; H, 7.1.
Found: C, 47.6; H, 7.1.

Tetrahydromorphitetrol tetraacetate methiodide. A solution of 200 mg. (0.65 millimole) of tetrol in a mixture of 1 ml. of pyridine and 1 ml. (10.6 millimoles) of acetic anhydride was warmed on the steam-bath for 15 minutes and allowed to stand at room temperature overnight. The solution was then poured into 10 ml. of water and extracted three times with 10-ml. portions of chloroform. The combined extracts were washed first with a dilute sodium carbonate solution and then with water before evaporation to an oily residue which was dissolved in 3 ml. of absolute ethanol and warmed on the steam-bath for a half-hour with excess methyl iodide. Cooling gave a solid methiodide which was recrystallized from absolute ethanol, m.p. 236–237°, $[\alpha]_D^{19}$ +4.5° (water, *c*, 1.013).

Anal. Calc'd for $C_{26}H_{40}INO_8$: C, 50.2; H, 6.5; I, 20.4.
Found: C, 50.6; H, 6.4; I, 20.5.

Tetrahydro-α-isomorphitetrol (VIII). The preparation of this compound from 2 g. of methyl tetrahydro-α-isomorphilactonate was carried out exactly as described above for tetrahydromorphitetrol except that the saponification to remove lactone-containing material was continued under reflux overnight with 1 *N* potassium hydroxide. The yield of α-isotetrol was 1.3 g. (70%). It is a hygroscopic, amorphous solid that could not be induced to crystallize.

The *picrate* was formed by combining a solution of 200 mg. (0.64 millimole) of the α-isotetrol in 1 ml. of absolute ethanol with a solution of 172 mg. (0.75 millimole) of anhydrous picric acid in 2 ml. of benzene. One recrystallization from 50% ethanol-benzene solution gave material melting at 168–169°, $[\alpha]_D^{22}$ −4.5° (water, *c*, 0.837).

Anal. Calc'd for $C_{23}H_{32}N_4O_{11}$: C, 51.1; H, 6.0.
Found: C, 50.8; H, 5.8.

Tetrahydro-α-isomorphitetrol tetraacetate methiodide. A solution of 200 mg. (0.65 millimole) of α-isotetrol in a mixture of 1 ml. of pyridine and 1 ml. (10.6 millimoles) of acetic anhydride was warmed overnight on the steam-bath and the tetraacetate isolated and converted to methiodide in the same manner as was the normal tetrol tetraacetate (above). Two recrystallizations from absolute ethanol gave a methiodide which melted with decomposition at 203°, $[\alpha]_D^{18}$ −8.5° (water, *c*, 1.015).

Anal. Calc'd for $C_{26}H_{40}INO_8$: C, 50.2; H, 6.5; I, 20.4.
Found: C, 50.1; H, 6.4; I, 20.5.

Lead tetraacetate oxidations. The procedure is based on that of Hockett, Dienes, and Ramsden (20). The lead tetraacetate was prepared according to McClenahan and Hockett (21) and a solution in specially dried acetic acid was made up as 0.0986 *N* and dispensed from an all-glass automatic buret protected from moisture by magnesium perchlorate. The weight of dry sample corresponding to 0.25 millimole was dissolved in 46.0 ml. of specially dried acetic acid in a 100-ml. volumetric flask. To this was added (noting the time of first contact) 52.0 ml. (2.56 millimoles) of 0.0986 *N* lead tetraacetate solution. The reaction solution was then made up to 100 ml. with specially dried acetic acid and placed in the thermostat. Samples were removed at intervals with a 10-ml. pipet and added to 25-ml. volumes of a solution containing about one-half gram of sodium iodide and 5 g. of potassium acetate; the pipet was washed down with acetic acid in order to standardize the drainage. Liberated iodine was titrated with 0.0200 *N* sodium thiosulfate, and the results were plotted as the moles of oxidant consumed per mole of substance taken against time in minutes.

1-Bromobromocodide. A. By the action of thionyl bromide on 1-bromocodeine. To a solution of 2.2 g. (5.8 millimoles) of dry bromocodeine, prepared by the method of Speyer and

Rosenfeld (22), in 10 ml. of dry chloroform was added 1.23 g. (0.46 ml., 5.8 millimoles) of thionyl bromide. The reaction mixture was heated on the steam-bath for an hour and the product was isolated as in the preparation of bromocodide. Crystallization of the crude solid from absolute ethanol gave 1.2 g. (47%) of the yellow crystalline 1-bromobromocodide, m.p. 171–173°, $[\alpha]_D^{22}$ +39.0° (dioxane, *c*, 1.065).

Anal. Calc'd for $C_{18}H_{19}Br_2O_2$: C, 49.1; H, 4.1; Br, 36.3.
Found: C, 49.5; H, 4.5; Br, 36.6.

B. By the action of thionyl bromide on codeine. In an apparatus with stirrer, condenser, and protection from moisture, a solution of 14.8 g. (0.071 mole, 6.0 ml.) of thionyl bromide was added over a ten-minute period to a solution of 10 g. (0.035 mole) of dry codeine in 20 ml. of chloroform, cooled with an ice-salt bath and stirred vigorously during the addition. After completion of the addition, the reaction mixture was heated under reflux for two hours and the alkaloidal material isolated as in the preparation of bromocodide. Crystallization of the crude solid from 200 ml. of absolute ethanol gave 7.9 g. of yellow-brown material melting from 162 to 169°. Four more recrystallizations from the same solvent gave 3.4 g. (23%) of 1-bromobromocodide, m.p. 171–173°, no depression in melting point when mixed with the material prepared above.

SUMMARY

An improved preparation of bromocodide and dihydroisocodeine is described. It is shown by the rate of lead tetraacetate oxidation of suitable derivatives that the carbon-oxygen bonds at carbons 5 and 6 are *cis* in morphine and *trans* in α-isomorphine.

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