Straight lines are obtained when the logarithm of the mole fraction of the fatty acid is plotted against the reciprocal of the absolute freezing temperature for that portion of the binary freezing point diagrams in which the fatty acid is the solid phase. The heats of fusion calculated from the slopes of these lines are 12,600 cal./mole for lauric acid, 15,800 for myristic acid, 18,900 for palmitic acid, and 20,900 for stearic acid. These are all considerably higher than the theoretical values: 8,750,[4] 10,750,[4] 13,100[5] and 16,350[6] cal./mole, respectively. Since the formation of the equimolecular compound would result in low calculated heats of fusion and the association of the acetamide would result in higher values, the association seems to be the predominant factor involved in these deviations.

It is apparent from Fig. 1 that the freezing point depression of either form of acetamide per mole % of added fatty acid is greater the shorter the chain length of the fatty acid. This is consistent with the idea that the degree of dissociation of the equimolecular compound decreases with a decrease in chain length of the fatty acid as was found to be the case in dioxane.

NEW ORLEANS, LOUISIANA

(4) W. E. Garner, F. C. Madden and J. E. Rushbrooke, *J. Chem. Soc.*, 2491 (1926).

(5) T. L. Ward and W. S. Singleton, in press.

(6) W. S. Singleton, T. L. Ward and F. G. Dollear, *J. Am. Oil Chem. Soc.*, **27**, 143 (1950).

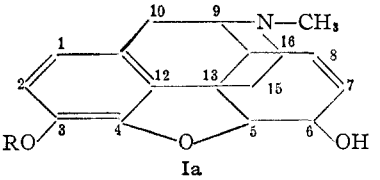
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

Stereochemical Studies in the Morphine Series. The Relative Configuration at Carbons Six and Thirteen[1]

BY HENRY RAPOPORT AND GEORGE B. PAYNE[2]

Dihydrocodeine and dihydroisocodeine were degraded to nitrogen-free products in order to establish the stereochemical relationship between the ethanamine chain at carbon 13 and the hydroxyl at carbon 6. While both compounds gave material in which the hydroxyl group had been methylated, only in the case of dihydroisocodeine was the compound resulting from alkylation of the hydroxyl with the ethane chain formed. On the basis of the formation of this cyclic ether, 6-codiran (VIII), the carbon-13 ethanamine chain and the carbon-6 hydroxyl were assigned the *cis*-configuration in isocodeine and hence the *trans* in codeine. The 13-carboxylic acids corresponding to codeine and isocodeine were also prepared from the respective 13-vinyl compounds, but lactonization could not be effected. Integrated with previous stereochemical evidence for carbons 5 and 6, this leads to the conclusion that the ethanamine chain at carbon 13 and the hydrogens at 5 and 6 are all *cis*.

The stereochemistry of morphine (Ia, R = H), with its five asymmetric centers and fused ring system, presents an interesting and as yet unsolved problem. Until recently, work on this subject had been confined to several deductions based on mechanistic interpretations. These were reviewed in our initial report[3] which advanced new experimental evidence for assignment of the relative configuration at carbons 5 and 6. In this report we wish to present work relating, stereochemically, the hydroxyl group at carbon 6 to the ethanamine chain at carbon 13. The quaternary carbon 13 affords an



Ia

excellent reference point, and it is the ultimate objective of these studies to relate configurations at carbons 9, 14, 5 and 6 to this center.

In seeking a reaction that might be dependent on the spatial relationship between the 6-hydroxyl and the ethanamine chain and hence reflect their relative configuration, a fruitful approach appeared to be the degradation, to nitrogen-free compounds, of codeine (Ia, R = CH_3) and isocodeine, epimeric alcohols differing only in the configuration at carbon 6. Recently[4] the observation was made that dihydrocodeine, when subjected to two successive Hofmann degradations, yielded an appreciable amount of material in which the 6-hydroxyl was converted to its methyl ether. Since the methyl group must have originated from the quaternary ammonium ion, this represents a reaction involving possible interaction between carbon 6 hydroxyl and carbon 13 ethanamine chain. If this were true, the nature and distribution of products might be influenced by the proximity of the reacting groups and the potentiality, in the *cis*-compound, for intramolecular reaction.

Also, on degradation to nitrogen-free material, compounds containing a free hydroxyl at carbon 4[5] or 14[6] have frequently formed cyclic ethers as degradation products. This may be considered as similar to the methyl ether formation cited above, alkylation of the hydroxyl taking place with the ethane chain rather than with the methyl group. In the case of codeine and isocodeine, such cyclic ether formation should occur only in the sterically favorable *cis*-compound to give structure VIII.

Consequently, the degradation products from dihydrocodeine and dihydroisocodeine (II)[7] have been examined in detail. The degradation of dihydrocodeine, following the sequence outlined in the

(1) Presented in part before the Division of Medicinal Chemistry, American Chemical Society, Cleveland, Ohio, April 10, 1951.

(2) U. S. Rubber Company Fellow, 1949–1950.

(3) H. Rapoport and G. B. Payne, *J. Org. Chem.*, **15**, 1093 (1950).

(4) H. Rapoport, *ibid.*, **13**, 714 (1948).

(5) L. Small and G. L. Browning, *ibid.*, **3**, 618 (1939); L. Small, *ibid.*, **7**, 158 (1942).

(6) C. Schöpf, *Ann.*, **452**, 249 (1927).

(7) In formulas II through XVI, the broken and solid lines at carbon 6 are used merely to designate the epimeric compounds. No stereochemical relationship with the rest of the molecule is intended.

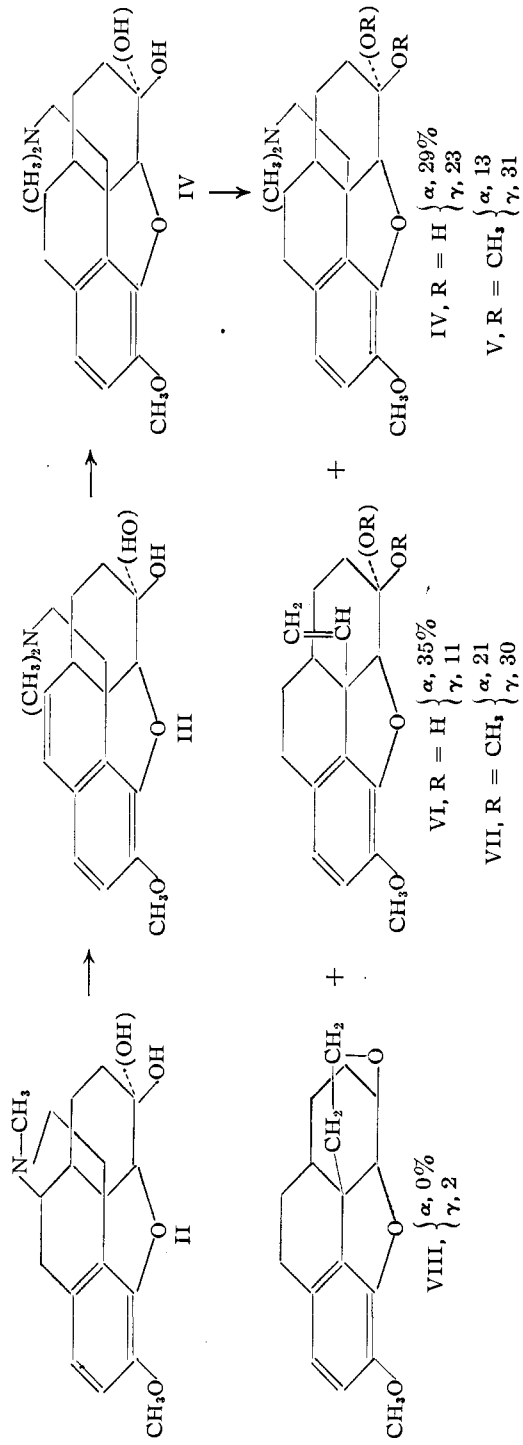
formula diagram, has been previously reported.[4] However, since some of the end products were not fully characterized, the last step, the degradation of tetrahydro-α-methylmorphimethine (IV),[8] was repeated. The reaction product was separated into a basic and a neutral fraction, and each fraction in turn was separated into alcoholic and non-alcoholic portions. These latter separations were accomplished by conversion of the alcoholic material into its *p*-phenylbenzoyl ester followed by sublimation.

The basic fraction consisted of a mixture of methine (IV) and its 6-methoxy analog (V), while the neutral material was composed of 6-α-hydroxy-13-vinyloctahydromethylmorphenol (VI) and the 6-α-methoxy compound (VII). It was the homogeneity of this latter compound, an oil, that was especially scrutinized, since any cyclic ether (VIII) would be expected to occur here as a difficultly separable impurity. Quantitative hydrogenation (and isolation of the crystalline 13-ethyl compound[4]) and methoxyl determinations established the absence of any non-olefinic and non-methoxylated material. Also, the method used successfully for separating non-olefinic material in the γ-series (see below) was applied and showed the product to be entirely olefinic. From this evidence we have concluded that the degradation of dihydrocodeine to nitrogen-free material results in no cyclic ether formation.

The parallel degradation of dihydroisocodeine (II) was then carried out and proceeded through the methiodide, by boiling with aqueous alkali, to Δ^9-dihydro-γ-methylmorphimethine (III) which was hydrogenated to tetrahydro-γ-methylmorphimethine (IV). This was converted to methohydroxide and decomposed by dry distillation. As in the α-series, the distillate was an oil which was separated into basic and neutral fractions, and each fraction in turn was separated into alcoholic and non-alcoholic portions by sublimation after esterifying with *p*-phenylbenzoyl chloride in pyridine.

Methine (IV) and methine methyl ether (V) were isolated from the basic fraction, while saponification of the residual *p*-phenylbenzoate of the neutral fraction gave 6-γ-hydroxy-13-vinyloctahydromethylmorphenol (VI). Crystallization of the non-alcoholic sublimate gave the nicely crystalline 6-γ-methoxy-13-vinyloctahydromethylmorphenol (VII) whose structural assignment is based on analogy with the α-isomer, hydrogenation, methoxyl determination, and lack of alcoholic, phenolic or ketonic properties. Although the mother liquors retained considerable material, no further crystalline γ-methoxy compound (VII) could be isolated. Hydrogenation and methoxyl analyses on the crude residue indicated the presence of appreciable non-olefinic material, lower in methoxyl content, and since the cyclic ether (VIII) would be expected to occur at this point and have the above effect, these residues from the mother liquors were further examined.

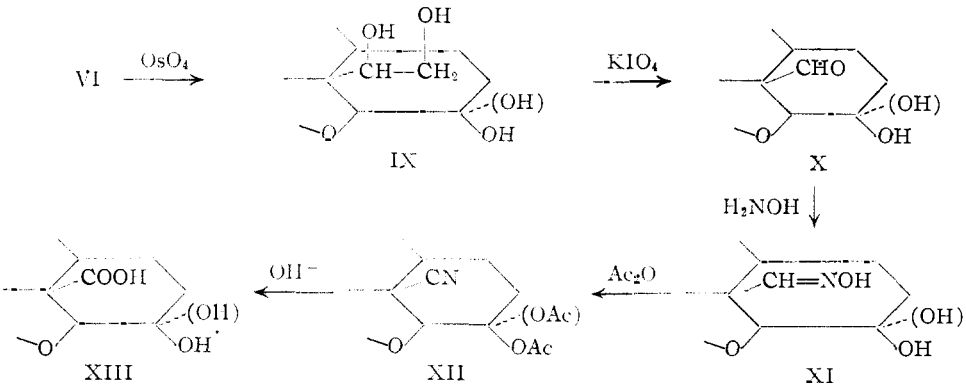
In order to separate any cyclic ether (VIII) from accompanying vinylmethoxy compound (VII), a chemical method was sought which would oxidize



the vinyl group to carboxyl and thus produce an easily removable derivative. Ozonolysis and oxidation with potassium permanganate both caused extensive breakdown at other parts of the molecule as well, so recourse was made to the quite selective osmium tetroxide method for oxidizing olefins.[9] When a benzene solution of the residues from crystallization of the γ-methoxy compound (VII) was treated with osmium tetroxide and pyridine, precipitation occurred and was completed by dilution with hexane. This precipitate was the pyridine

(8) The α or γ prefix refers to the carbon 6 configurational relationship to codeine or isocodeine, respectively.

(9) R. Criegee, B. Marchand and H. Wannowius, *Ann.*, **550**, 99 (1942); J. W. Cook and R. Schoental, *J. Chem. Soc.*, 170 (1948).



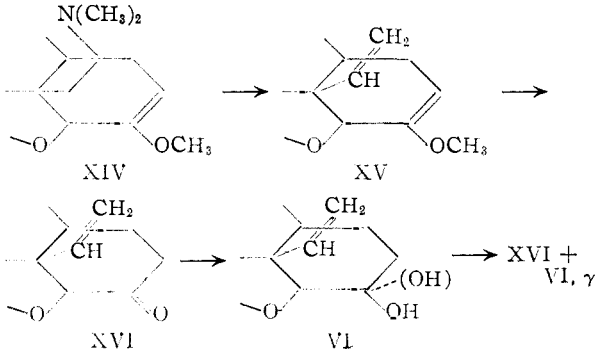
complex of the osmate ester resulting from oxidation of the olefin to a diol, and its insolubility in benzene–hexane served as a convenient means for separating olefinic from non-olefinic material.

From the benzene–hexane solution, by fractional sublimation and crystallization from pentane, was isolated the crystalline cyclic ether, 6-codiran[10] (VIII). Its structural assignment is based on its analysis, including methoxyl determination, and absence of any phenolic, alcoholic, ketonic or olefinic properties. Ring closure conceivably could have taken place at carbon 15 to give a five-membered ring. However, the six-membered ring structure appears much more probable, considering the mechanism of the Hofmann degradation[11] and that 6-codiran must have arisen by intramolecular alkylation during the degradation. Also, this structure is supported by a study of models.

The isolation of 6-codiran (VIII) from the degradation of dihydroisocodeine and the absence of any such internal ether in the dihydrocodeine degradation products establish the configuration of the hydroxyl at carbon 6 and the ethanamine chain at carbon 13 as *trans* in codeine and *cis* in isocodeine, since only in the case of a *cis* relationship would intramolecular ether formation be sterically possible. It was hoped that also the distribution of products would reflect the stereochemical relationships, but although the γ-isomer (isocodeine) did give a greater proportion of methyl ether in each case, it is difficult to draw any significant conclusions from these differences.

Confirmatory evidence for the assigned configurations was then sought in the possible oxidation of the 6-hydroxy-13-vinyl compounds (VI) to the corresponding 13-carboxylic acids, followed by lactonization of the *cis*-(γ)-hydroxy acid. Using the 6-methoxy compounds (VII) as models, a satisfactory method for this conversion was developed and is illustrated in the reaction sequence below. Since direct oxidation with permanganate or ozone could not be used (see above), a more selective and circuitous path was necessary. The triol (IX), readily prepared by the action of osmium tetroxide, was oxidized with potassium periodate to the aldehyde (X), which resisted all efforts (cold permanganate, cold chromic acid, Tollens reagent, silver oxide, peracetic acid, Cannizzaro reaction) toward direct conversion to the acid. However, the oxime formed in good yield and was dehydrated to nitrile (XII) which was then hydrolyzed to the acid (XIII). The over-all yield in this process was 25 and 23% for the α- and γ-isomers, respectively.

In order to prepare a sufficient quantity of γ-acid before proceeding with lactonization attempts, an alternative method was sought for the preparation of the 6-γ-hydroxy-13-vinyl compound (VI), which had been formed in relatively poor yields from dihydroisocodeine. A very satisfactory procedure was achieved starting with Δ^6-tetrahydrothebaine methine (XIV), readily available from thebaine. Dry distillation of the methohydroxide followed by acid hydrolysis of the enol ether (XV) gave 6-keto-13-vinyloctahydromethylmorphenol (XIV), which was hydrogenated to the known 13-ethyl compound.[12]



An overnight reflux of the ketone (XVI) in isopropyl alcohol containing aluminum isopropoxide followed by removal of the acetone formed resulted in a mixture of α- and γ-alcohols (VI) that was 52% γ-. A longer reflux period did not change this proportion. Since it has been observed[13] that dihydrocodeine is oxidized to dihydrocodeinone by benzophenone in the presence of potassium *t*-butoxide whereas dihydroisocodeine is unaffected, the mixture of alcohols was subjected to these oxidizing conditions. The alcoholic fraction remaining in the reaction mixture was separated as hydrogen phthalate, and saponification gave the desired γ-alcohol (VI) together with benzhydrol from which

(10) Codiran has been chosen as a convenient name for cyclic ethers of this type with the oxide ring intact [*cf.* morphirane, a compound in which the oxide ring was open and cyclization took place with the 4-hydroxyl; K. W. Bentley and R. Robinson, *Experientia*, **6**, 353 (1950)]. The number designation may be used to distinguish other potential codirans, *e.g.*, the 8- and 14-.

(11) W. Hanhart and C. K. Ingold, *J. Chem. Soc.*, 997 (1927); C. K. Ingold and C. C. N. Vass, *ibid.*, 3125 (1928).

(12) R. S. Cahn, *ibid.*, 702 (1930).

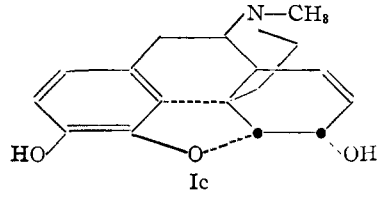
(13) H. Rapoport, R. Naumann, E. R. Bissell and R. M. Bonner, *J. Org. Chem.*, **15**, 1103 (1950).

the latter was removed during oxidation to the γ-triol (IX) with osmium tetroxide.

With an adequate supply of the γ-compound thus assured, lactonization attempts were carried out on both the α- and γ-hydroxy acids (XIII). Although the epimers differed significantly in their reactions, in no case could any lactone be detected from reaction with refluxing acetic anhydride,[14] heating with a mixture of glacial acetic acid and concentrated hydrochloric acid,[15] or heating at 190° in toluene[16]—procedures which have been used successfully in the past for lactone formation. Numerous variations of these procedures as well as several other methods also failed to form any lactone.

The hindered nature of the carboxyl group can be only partly responsible for this failure, since on heating in ethanol at 230° each epimer formed its ethyl ester. The explanation probably lies in the distance between the carboxyl and hydroxyl groups, and the resistance to five-membered lactone formation offered by the rigid, fused ring system. In contrast, the six-membered cyclic ether in 6-codiran (VIII), can be formed without appreciable strain, and this difference is clearly delineated by a study of the models.

The assignment of the stereochemical relationship between the hydroxyl at carbon 6 and the ethanamine chain at carbon 13 as *trans* in codeine thus has been made on the basis of 6-codiran formation in the degradation of isocodeine and its absence in the degradation of codeine. Since it has been established previously that in morphine the hydroxyl at carbon 6 and the oxygen bond at carbon 5 are *cis*,[17] it follows that the ethanamine chain and the hydrogens at carbons 13, 5 and 6 are all *cis*. This leads to the very reasonable conclusion that the five-membered oxide ring is fused in a *cis* configuration.[18] Also, the ring-juncture of the ethanamine chain at carbons 13 and 9 must be *cis*, since a *trans* fusion to form a six-membered ring across these positions would not be possible.[19] Thus the configurations at carbons 5, 6 and 9 have been related to that at carbon 13, and the only asymmetric center in the molecule for which incontrovertible evidence is as yet unavailable is carbon 14. These conclusions have been incorporated in a conventional line representation, Ic.



Ic

Experimental[20]

Degradation of Tetrahydro-α-methylmorphimethine (IV).—The degradation was carried out as previously described[4] by dry distillation of the methohydroxide. The distillate from 23 g. (0.05 mole) of methiodide was dissolved in ether and washed with dilute hydrochloric acid to remove basic material. Evaporation of the ether left 7.64 g., 56% yield,[21] of oily neutral material. Basification of the aqueous acid washings, extraction with ether, and evaporation of the ether gave 6.85 g., 43%, of recovered methines.

A. Separation of Basic Products.—Using the procedure described below for the γ-isomers, the mixture of recovered methines was esterified with *p*-phenylbenzoyl chloride in pyridine and then distilled. From 6.85 g. of recovered methines there was obtained as distillate 2.1 g., 31% of the mixture or 13% based on original methine methiodide degraded, of tetrahydro-γ-dimethylmorphimethine. It formed a methiodide, m.p. 247–249°, which gave no depression in a mixed melting determination with an authentic sample (m.p. 246–248°) and gave the correct methoxyl analysis.

The residual *p*-phenylbenzoyl derivative of the alcoholic fraction was saponified as described for the γ-isomer, and 4.6 g., 67% of the mixture, of tetrahydro-α-methylmorphimethine was obtained. Its methiodide melted at 225–227°, and the melting point was not depressed on mixing with an authentic sample (m.p. 225–227°).

B. Separation of Neutral Products.—This separation has been described.[4] **The 6-α-methoxy-13-vinyloctahydromethylmorphenol** persisted as an oil, $n^{25}D$ 1.5631; $[\alpha]^{25}D$ +2.6° (*c* 1.54, ethanol).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.5; H, 7.7; OCH_3, 21.7. Found: C, 75.7; H, 7.6; OCH_3, 21.6.

6-α-Hydroxy-13-vinyloctahydromethylmorphenol (VI), previously described[4] as an oil, solidified after several months standing and was crystallized from aqueous ethanol (1:1), m.p. 57–59°; $[\alpha]^{25}D$ +19.2° (*c* 1.02°, ethanol).

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 75.0; H, 7.4. Found: C, 75.1; H, 7.2.

6-α-Methoxy-13-(α,β-dihydroxyethyl)-octahydromethylmorphenol.—To a solution of 2.0 g. (7.9 millimoles) of osmium tetroxide in 20 ml. of benzene containing 1.3 ml. of pyridine was added a solution of 2.5 g. (8.7 millimoles) of 6-α-methoxy-13-vinyloctahydromethylmorphenol in 30 ml. of benzene. The solution became dark brown and was allowed to stand for 18 hours, at which time 150 ml. of pure hexane was added to complete precipitation of the osmate ester. Evaporation of the benzene–hexane solution left no residue. To decompose the osmate ester, the precipitate, dissolved in 75 ml. of ethanol, was heated under reflux for two hours with a solution of 11 g. of sodium sulfite in 50 ml. of water[22] and the mixture was then filtered hot, washing the insoluble material with two 25-ml. portions of hot ethanol. The filtrate was evaporated to 25 ml., 50 ml. of water was added, and this solution was concentrated to 15 ml., causing crystallization. Cooling gave 1.7 g. (61%) of the glycol, m.p. 157–158°, after crystallization from ethyl acetate; $[\alpha]^{25}D$ −92.0° (*c* 1.20, ethanol).

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.5; H, 7.5. Found: C, 67.4; H, 7.4.

(14) C. W. Shoppee, *J. Chem. Soc.*, 1032 (1948).

(15) Y. Asahina and M. Ishidate, *Ber.*, **68**, 555 (1935).

(16) M. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **27**, 1631 (1944).

(17) This assignment was made on the basis of the relative rate of oxidation by lead tetraacetate of the epimeric 5,6-diols derived from codeine and isocodeine by opening the aromatic ring (ref. 3). However, in view of the recent observation [E. Boyland and G. Wolf, *Biochem. J.*, **47**, 64 (1950)] of an exception to the rule that the *cis*-glycol is the more rapidly oxidized isomer, the effect of these compounds on the *p*H of a boric acid solution (J. Böeseken, "Advances in Carbohydrate Chemistry," Vol. IV, Academic Press, Inc., New York, N. Y., 1949, p. 189) was also examined. Three successive 5-mg. portions of tetrahydromorphitetrol picrate (*cis*), when added to 4 ml. of 0.1 *M* boric acid, changed the *p*H of the solution from the initial 5.20 to 4.23, 4.09 and 4.01, respectively. With tetrahydro-α-isomorphitetrol picrate (*trans*), the *p*H changed from 5.20 to 5.06, 4.96 and 4.85, thus confirming the original *cis* and *trans* assignments.

(18) C. Schöpf and T. Pfeiffer, *Ann.*, **483**, 162 (1930), reached the same conclusion from a study of models and oxide ring-opening and closing experiments.

(19) M. W. Cronyn, *J. Org. Chem.*, **14**, 1013 (1949), has shown that only the *cis*-lactam is formed from 3-aminocyclohexaneacetic acid. The rigidity of the present molecule would undoubtedly further eliminate any possibility of *trans*-juncture.

(20) All melting points are corrected, and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California.

(21) Yields on all degradations have been calculated on the basis that all the material still contains a free hydroxyl at carbon 6. Since some of the product has been converted to methyl ether, these calculations are probably high by 1 to 3%.

(22) A. Butenandt, J. Schmidt-Thomé and H. Paul, *Ber.*, **72**, 1112 (1939).

Δ^9-Dihydro-γ-methylmorphimethine (III).—Ten grams (0.023 mole) of dihydroisocodeine[23] methiodide was degraded as described[4] for the α-isomer. The solution was cooled and the solid product was crystallized from aqueous ethanol to give 6.4 g. (90%) of methine, m.p. 149–151° (reported[24] m.p. 151°).

Tetrahydro-γ-methylmorphimethine (IV).—To a solution of 10 g. (0.032 mole) of Δ^9-dihydro-γ-methylmorphimethine in 50 ml. of methanol was added 2.0 g. of 5% palladium-on-barium sulfate and the mixture hydrogenated at atmospheric pressure and room temperature. Within 15 minutes, hydrogenation ceased with an uptake of 1.0 mole of hydrogen. After filtering, the methanol solution was evaporated to a viscous oil which solidified on cooling. About 0.5 g. of this solid was used to isolate the free base, while the remaining 9.5 g. was converted to the **methiodide**, 11.7 g. (85%), m.p. 300° with decomposition (reported[25] m.p. 300°).

The half-gram of methine was crystallized from dilute ethanol, m.p. 119–121°; $[\alpha]^{21}D$ −35.0° (*c* 0.97, ethanol). Since the reported[25] melting point is 115°, the sample was analyzed.

Anal. Calcd. for $C_{19}H_{27}O_3N$: C, 71.9; H, 8.6; N, 4.4. Found: C, 71.8; H, 8.5; N, 4.4.

Degradation of Tetrahydro-γ-methylmorphimethine.[26]—The procedure used was that of Rapoport[4] for the α-isomer. From the liquid nitrogen trap, trimethylamine was isolated and identified through its picrate, m.p. 221–224°. The distillate from 22.95 g. (0.05 mole) of tetrahydro-γ-methylmorphimethine methiodide was separated into 8.5 g. (54%)[21] of basic material (mixture of recovered methines) and 6.0 g. (44%) of neutral material.

A. Separation of Basic Products.—A solution of 8.5 g. (0.027 mole, assuming all alcohol) of basic material in 50 ml. of dry pyridine was warmed on the steam-bath for 3 hours with 5.8 g. (0.027 mole) of *p*-phenylbenzoyl chloride and then allowed to stand at room temperature overnight. The pyridine was removed at the water pump and the residual magma heated on the steam-bath with 90 ml. of 0.5 *N* potassium carbonate for 30 minutes, after which 250 ml. of hot benzene was added. From this point on, all solutions were kept warm, in order to minimize emulsion formation. The benzene layer was washed with four 50-ml. portions of 0.5 *N* potassium carbonate and two 50-ml. portions of water, and each wash portion was in turn extracted with two 50-ml. portions of benzene. After drying over potassium carbonate, the combined benzene solutions were evaporated on the steam-bath and the residue distilled at 150° (0.1 mm.) in a modified molecular still to give 4.9 g., 58% of the mixture or 31% based on original methine degraded, as a pale yellow oily distillate. A sample of this material, tetrahydro-γ-dimethylmorphimethine, was redistilled at 125° (0.05 mm.); $[\alpha]^{21}D$ −15.3° (*c* 1.11, ethanol); $n^{25}D$ 1.5453.

Anal. Calcd. for $C_{20}H_{29}O_3N$: C, 72.5; H, 8.8; N, 4.2; OCH_3, 18.7. Found: C, 73.1; H, 8.7; N, 4.5; OCH_3, 18.9.

The **methiodide** was prepared in the usual fashion and was crystallized from ethanol, m.p. 261.5–263°; $[\alpha]^{21}D$ −35.8° (*c* 1.10, water).

Anal. Calcd. for $C_{21}H_{32}O_3NI$: C, 53.3; H, 6.8; OCH_3, 13.1. Found: C, 53.0; H, 6.9; OCH_3, 13.6.

The **methine perchlorate** was prepared by dissolving the base in absolute ethanol and treating this with 1 *N* alcoholic perchloric acid until the solution was acid to congo. The precipitate was crystallized from absolute ethanol, m.p. 229–231° (dec.); $[\alpha]^{21}D$ −19.0° (*c* 0.84, acetone).

Anal. Calcd. for $C_{20}H_{30}O_7NCl$: C, 55.6; H, 7.0; OCH_3, 14.4. Found: C, 55.7; H, 6.9; OCH_3, 14.6.

The residual *p*-phenylbenzoyl derivative of the alcoholic methine was crystallized from dilute ethanol, giving 4.1 g. of **p-phenylbenzoyltetrahydro-γ-methylmorphimethine.** It melted at about 80°, and then resolidified as the temperature was increased, melting finally at 127–128°; $[\alpha]^{20}D$ −132.7° (*c* 0.81, dioxane).

Anal. Calcd. for $C_{32}H_{35}O_4N$: C, 77.2; H, 7.1; N, 2.8. Found: C, 77.4; H, 6.9; N, 2.9.

The methine ester was saponified by dissolving 6.6 g. (0.013 mole) in 150 ml. of ethanol, adding 150 ml. of 5 *N* ethanolic potassium hydroxide, and heating the solution under reflux for 3 hours in a nitrogen atmosphere. After cooling and filtering the precipitated potassium *p*-phenylbenzoate, the filtrate was concentrated under reduced pressure, water was added, and the concentration repeated. The resulting oily solution was extracted with ether, the ether was washed, dried, and evaporated to a residue of 4.1 g., and this was dissolved in 60 ml. of ethanol and warmed with methyl iodide. The resulting **methiodide** weighed 5.2 g. (88% from the ester) and was identical with tetrahydro-γ-methylmorphimethine methiodide.

B. Separation of Neutral Products.—The separation of alcoholic from non-alcoholic material in the neutral fraction proceeded in the same manner as described[4] for the α-isomer. From 5.9 g. there was obtained 4.4 g., 75% of the mixture or 33% based on original methine degraded, of oily solid distillate. The residual *p*-phenylbenzoate was crystallized from ethanol to give **6-γ-hydroxy-13-vinyl-octahydromethylmorphenol *p*-phenylbenzoate**, m.p. 117–119°; $[\alpha]^{20}D$ −171° (*c* 0.88, dioxane).

Anal. Calcd. for $C_{30}H_{23}O_4$: C, 79.6; H, 6.2. Found: C, 79.5; H, 6.5.

The ester was saponified in the manner described for the methine ester, and 1.0 g. of 6-γ-hydroxy-13-vinyloctahydromethylmorphenol (VI) was obtained as an oil from 1.74 g. of *p*-phenylbenzoate.

6-γ-Methoxy-13-vinyloctahydromethylmorphenol (VII) was obtained in a yield of 3 g. by crystallizing 4 g. of the oily solid distillate (from the esterification reaction) from dilute aqueous ethanol, m.p. 73.5–75°; $[\alpha]^{21}D$ +14.1° (*c* 1.06, dioxane).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.5; H, 7.7; OCH_3, 21.7. Found: C, 75.5; H, 7.8; OCH_3, 21.6.

6-Codiran (VIII).—The mother liquors from crystallization of the 6-γ-methoxy-13-vinyloctahydromethylmorphenol were combined and evaporated to give a mixture from which the cyclic ether was separated by oxidation of the methoxy compound with osmium tetroxide. To a solution of 490 mg. (1.9 millimoles) of osmium tetroxide in 5 ml. of benzene was added a solution of 0.32 ml. of pyridine and 680 mg. (2.4 millimoles) of the mixture of methoxy compound and cyclic ether in 5 ml. of benzene. The reaction mixture became dark immediately, and after about 15 minutes oily material appeared on the walls of the tube. After 3 hours, 30 ml. of hexane was added to force out more osmate ester, and the mixture was centrifuged and the supernatant decanted. This process was repeated with a second 30-ml. portion of hexane and the combined benzene–hexane solution was filtered. The filtrate, now containing crude cyclic ether free of olefin, was shaken vigorously for a few minutes with 20 ml. of a 1% potassium hydroxide solution containing 10% mannitol to remove all traces of osmium from the organic solution, which was then washed with 20 ml. of water and dried over magnesium sulfate. Evaporation of the solvent gave 93 mg. of a colorless oil, which was added to about 200 mg. of oil obtained from other smaller runs and was sublimed at 0.03 mm. A small amount of oily material which distilled at room temperature was removed, and the temperature was then raised to 80°, giving a crystalline sublimate. This was crystallized three times from pentane and sublimed again to give 35 mg. of 6-codiran, m.p. 88–90°; $[\alpha]^{25}D$ +17.0° (*c* 0.53, ethanol).

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 75.0; H, 7.4; OCH_3, 11.4. Found: C, 74.8; H, 7.5; OCH_3, 11.5.

6-Codiran was non-phenolic (diazotized sulfanilic acid test), did not react with *p*-phenylbenzoyl chloride in pyridine, failed to form an oxime, and absorbed no hydrogen on catalytic hydrogenation.

6-γ-Methoxy-13-(α,β-dihydroxyethyl)-octahydromethylmorphenol.—The solid osmate ester, removed by centrifugation from the solution of 6-codiran, was dissolved in 25 ml. of ethanol and treated with a solution of 2.3 g. of sodium sulfite in 15 ml. of water. The solution was boiled under reflux for 1.5 hours, then filtered hot, and the precipitate was washed with two 25-ml. portions of hot ethanol. Evapo-

(23) Prepared from bromocodide (ref. 3). However, the recent method of M. M. Bazier, A. Loter, K. S. Ellner and D. R. Satriana, *J. Org. Chem.*, **16**, 543 (1951), appears to be superior.

(24) E. Speyer and W. Krauss, *Ann.*, **432**, 233 (1923).

(25) E. Speyer and K. Koulen, *ibid.*, **438**, 34 (1924).

(26) The degradation of this material by boiling with aqueous alkali has been previously reported (ref. 25); however, only 0.1 g. of oil was obtained from 5 g. of methiodide.

ration of the filtrate on the steam-bath gave a residue which was dissolved in 50 ml. of chloroform. The chloroform solution was washed with water, concentrated to 10 ml., and cooled to give 300 mg. of 6-γ-methoxy-13-(α,β-dihydroxyethyl)-octahydromethylmorphenol, m.p. 155–157° after crystallization from water; $[\alpha]^{21}D$ −53.5° (*c* 1.11, dioxane).

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.5; H, 7.6. Found: 67.2; H, 7.3.

6-γ-Methoxy-13-ethyloctahydromethylmorphenol.—To a solution of 200 mg. (0.70 millimole) of 6-γ-methoxy-13-vinyloctahydromethylmorphenol in 5 ml. of methanol was added 5 mg. of platinum oxide and the solution was hydrogenated at room temperature and atmospheric pressure. After 10 minutes, hydrogenation ceased with an absorption of 1.0 mole of hydrogen. Removal of catalyst and solvent gave 200 mg. of an oil which distilled at 60–70° (0.1 mm.).

Anal. Calcd. for $C_{18}H_{24}O_3$: OCH_3, 21.5. Found: OCH_3, 22.0.

6-γ-Methoxy-13-aldehydooctahydromethylmorphenol.—To a solution of 660 mg. (2.06 millimoles) of 6-γ-methoxy-13-(α,β-dihydroxyethyl)-octahydromethylmorphenol in 5 ml. of ethanol was added 150 ml. of 0.02 *M* potassium periodate and 30 ml. of saturated sodium bicarbonate solution. On standing at room temperature for two hours there was precipitated 480 mg. (81%) of aldehyde, melting at 104–107°. Crystallization from 60% ethanol–water gave material of m.p. 105–107°; $[\alpha]^{26}D$ −9.9° (*c* 0.81, ethanol).

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.8; H, 7.0. Found: C, 70.9; H, 7.3.

The semicarbazone was prepared by adding 330 mg. of semicarbazide hydrochloride and 0.33 ml. of pyridine to a solution of 330 mg. of aldehyde in 5 ml. of ethanol. After a two-hour reflux, the solvent was evaporated and the solid residue was washed with two 25-ml. portions of warm water. The 280 mg. (70%) of semicarbazone thus prepared, after recrystallization from *n*-propanol, melted at 193–195°; $[\alpha]^{26}D$ +28.6° (*c* 0.84, ethanol).

Anal. Calcd. for $C_{18}H_{23}O_4N_3$: C, 62.6; H, 6.7. Found: C, 62.5; H, 7.0.

The oxime was prepared by treating a solution of 100 mg. of the aldehyde in 1 ml. of ethanol with 100 mg. of hydroxylamine hydrochloride and 0.1 ml. of pyridine and heating the solution under reflux overnight. The ethanol was then evaporated, ether was added, and the ether solution was washed with dilute hydrochloric acid and with water. Removal of the ether and crystallization of the residue from ethanol gave oxime of m.p. 148–149°; $[\alpha]^{25}D$ +25.4°, (*c* 1.12, ethanol).

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.3; H, 7.0; N, 4.6. Found: C, 67.4; H, 6.9; N, 4.8.

6-α-Methoxy-13-aldehydooctahydromethylmorphenol.—To a solution of 1.5 g. (4.7 millimoles) of 6-α-methoxy-13-(α,β-dihydroxyethyl)-octahydromethylmorphenol in 100 ml. of ethanol was added a solution of 1.6 g. (7.0 millimoles) of of potassium periodate in 250 ml. of water and 50 ml. of saturated sodium bicarbonate. The reaction mixture was allowed to stand at room temperature for three hours and was then extracted with five 100-ml. portions of ether. The ether was washed, dried, and evaporated to an oily residue of 1.1 g. which was converted to *oxime* in the manner described for the γ-isomer. Crystallization from benzene–pentane gave 600 mg.of oxime melting at 118–120°; $[\alpha]^{25}$ +8.7° (*c* 0.92, ethanol).

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.3; H, 7.0; N, 4.6. Found: C, 67.4; H, 6.9; N, 5.0.

6-α-Methoxy-13-cyanooctahydromethylmorphenol.—After heating a solution of 360 mg. (1.2 millimoles) of the α-methoxy oxime in 4 ml. of acetic anhydride under reflux for an hour, 20 ml. of saturated sodium bicarbonate solution was added and the mixture heated another half-hour. After cooling, the reaction mixture was extracted with ether and the ether was washed with water, dried, and evaporated to a solid residue of 330 mg. Crystallization from benzene–pentane gave 200 mg. (59%) of the nitrile, m.p. 115–117°.

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.6; H, 6.7; N, 4.9. Found: C, 71.5; H, 6.6; N, 5.1.

6-α-Methoxy-13-carboxyoctahydromethylmorphenol.—A solution of 160 mg. (0.56 millimole) of the α-methoxy nitrile in 25 ml. of 2 *N* potassium hydroxide in ethylene glycol was heated at 120° for four days by which time 77% of the theoretical amount of ammonia had been evolved. The reaction mixture was poured into 100 ml. of water, the *p*H was brought to 9 by careful addition of hydrochloric acid, and the solution was extracted with two 50-ml. portions of ether. The aqueous solution was then made strongly acid with concentrated hydrochloric acid and extracted with five 50-ml. portions of ether, which were combined, washed with water, dried, and evaporated to an oily residue. Two crystallizations from benzene–hexane gave 100 mg. (59%) of acid melting at 129–131°; $[\alpha]^{25}D$ +107° (*c* 1.00, benzene).

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.1; H, 6.6; equiv. wt., 304. Found: C, 67.4; H, 7.0; equiv. wt., 315.

6-α-Hydroxy-13-(α,β-dihydroxyethyl)-octahydromethylmorphenol (IX).—To a solution of 1.5 g. (5.9 millimoles) of osmium tetroxide in 15 ml. of benzene containing 1.0 ml. of pyridine was added a solution of 1.62 g. (5.9 millimoles) of 6-α-hydroxy-13-vinyloctahydromethylmorphenol in 15 ml. of benzene, and the reaction mixture was allowed to stand at room temperature for two hours. Addition of 100 ml. of hexane completed the formation of a precipitate which was filtered, washed with hexane, and dissolved in 75 ml. of ethanol. To this solution was added a solution of 6.6 g. of sodium sulfite in 50 ml. of water, the reaction mixture was heated under reflux for two hours, and the hot solution was filtered through a mat of filter-aid, using two 25-ml. portions of hot ethanol as wash. The filtrate was evaporated to dryness on the steam-bath, the residue was digested with 25 ml. of absolute ethanol, and the filtered digest was concentrated to 5 ml. and cooled to give 1.27 g. (70%) of the glycol melting at 212–214°. Recrystallization from ethanol gave material melting at 214–216°; $[\alpha]^{25}D$ −70.2° (*c* 0.96, dioxane).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.6; H, 7.3. Found: C, 66.5; H, 7.5.

6-α-Hydroxy-13-aldehydooctahydromethylmorphenol (X).—The oxidation of 6-α-hydroxy-13-(α,β-dihydroxyethyl)-octahydromethylmorphenol, and formation of the oxime from the resulting aldehyde were carried as described for the preparation of the α-methoxyaldehyde oxime. From 1.5 g. of the glycol there was obtained after crystallization from benzene–pentane, 930 mg. (66%) of oxime (XI) melting at 128–130°. Another crystallization gave material melting at 131–132°; $[\alpha]^{26}D$ +13.9° (*c* 0.75, ethanol).

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.4; H, 6.6. Found: C, 66.4; H, 6.6.

6-α-Acetoxy-13-cyanooctahydromethylmorphenol (XII).—The dehydration of the α-hydroxy oxime was carried out exactly as described for the preparation of 6-α-methoxy-13-cyanooctahydromethylmorphenol. From 360 mg. of oxime there was obtained 310 mg. (80%) of α-acetoxy nitrile, crystallized from aqueous ethanol and melting at 130.5–132°. Sublimation at 115° (0.04 mm.) gave material of m.p. 131–1331; $[\alpha]^{26}D$ +49.6° (*c* 0.95, ethanol).

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 69.0; H, 6.1; N, 4.5. Found: C, 68.7; H, 6.1; N, 4.4.

6-α-Hydroxy-13-carboxyoctahydromethylmorphenol (XIII).—A solution of 860 mg. (2.74 millimoles) of α-acetoxy nitrile in 10 ml. of *n*-propanol was added to 50 ml. of 2 *N* potassium hydroxide in ethylene glycol and the reaction mixture was heated at 105°. At the end of 90 hours, after 70% of the theoretical amount of ammonia had been evolved, the reaction mixture was poured into 150 ml. of water, it was brought to a *p*H of 9 with hydrochloric acid, and the solution was extracted with two 75-ml. portions of ether. The aqueous phase was then made strongly acid with concentrated hydrochloric acid and extracted with three 100-ml. portions of chloroform which were washed with water and then concentrated on the steam-bath to a solid residue of 540 mg. (68%), m.p. 192–194°. Crystallization from water gave material which sublimed unchanged at 175° (0.05 mm.), m.p. 194–195°; $[\alpha]^{26}D$ +33.6° (*c* 1.10, ethanol).

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.2; H, 6.3; equiv. wt., 290. Found: C, 66.0; H, 6.3; equiv. wt., 294.

6-γ-Hydroxy-13-(α,β-dihydroxyethyl)-octahydromethylmorphenol (IX).—This was prepared exactly as described for the α-isomer. From 650 mg. (2.4 millimoles) of the α-vinyl compound there was obtained 590 mg. (81%) of the glycol which melted at 80–90° and then resolidified and melted at 149–152°. Recrystallization from chloroform followed by sublimation at 140° (0.05 mm.) gave material

which showed the same melting point behavior, the final m.p. being 151–153°; $[\alpha]^{19}D$ −63.0 (*c* 0.44, ethanol).

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.6; H, 7.2. Found: C, 66.5; H, 7.4.

6-γ-Hydroxy-13-aldehydoöctahydromethylmorphenol (X).—The oxidation of the glycol and oxime formation from the resulting aldehyde was carried out as described in the preparation of 6-α-methoxy-13-aldehydoöctahydromethylmorphenol oxime. From 500 mg. (1.63 millimoles) of the glycol there was obtained, after crystallization from benzene, 360 mg. (76%) of oxime (XI), m.p. 152–153°; $[\alpha]^{25}D$ −2.6° (*c* 0.95, ethanol).

Anal. Calcd. for $C_{16}H_{19}O_4N$: C, 66.4; H, 6.6. Found: C, 66.5; H, 6.6.

6-γ-Acetoxy-13-cyanoöctahydromethylmorphenol (XII).—The dehydration of the γ-hydroxy oxime was carried out as described for the preparation of 6-α-methoxy-13-cyanooctahydromethylmorphenol. From 300 mg. (1.04 millimoles) of γ-hydroxy oxime (m.p. 147–151°) there was obtained 220 mg. (68%) of γ-acetoxy nitrile, after two crystallizations from aqueous ethanol, m.p. 120–122°; $[\alpha]^{26}D$ +37.5° (*c* 0.61, ethanol).

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 69.0; H, 6.1; N, 4.5. Found: C, 69.0; H, 6.0; N, 4.5.

6-γ-Hydroxy-13-carboxyoctahydromethylmorphenol (XIII).—Hydrolysis of the γ-acetoxy nitrile was carried out as described for the corresponding α-isomer, and the γ-hydroxy acid was isolated in the same manner. From 200 mg. of γ-acetoxy nitrile, 100 mg. (54%) of acid, m.p. 194–196°, was obtained after crystallization from benzene–ethanol (9:1); $[\alpha]^{25}D$ +33.6° (*c* 1.00, ethanol). It sublimed unchanged at 160° (0.04 mm.) and on mixing with the α-hydroxy acid its melting point was depressed to 172–180°.[27]

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.2; H, 6.3; equiv. wt., 290. Found: C, 66.1; H, 6.2; equiv. wt., 293.

6-Keto-13-vinyloctahydromethylmorphenol Δ^6-Methyl Enol Ether (XV).—A solution of 23.6 g. (0.05 mole) of tetrahydrothebaine methine methiodide[28] (m.p. 223–225°, reported[29] m.p. 217–222°) in 400 ml. of 50% methanol–water solution was degraded as described[4] for the degradation of tetrahydro-α-methylmorphimethine methiodide, except that the mixture of methiodide and silver oxide was shaken for 15 minutes rather than overnight. The solid distillate was washed from the receiver with chloroform and the chloroform washings were extracted with 50-ml. portions of 1 *N* hydrochloric acid, half-saturated sodium bicarbonate solution, and water. Evaporation of the chloroform gave 12.1 g. (85%) of 6-keto-13-vinyloctahydromethylmorphenol Δ^6-methyl enol ether, m.p. 117.5–119° after crystallization from ethanol (reported[29] m.p. 119°).

6-Keto-13-vinyloctahydromethylmorphenol (XVI).—A solution of 12.1 g. of the crude enol ether in 125 ml. of ethanol was treated with 12 ml. of concentrated hydrochloric acid, and the solution was warmed on the steam-bath for a half-hour. Careful addition of hot water to the hot reaction mixture caused precipitation, and the solution was cooled and filtered to yield 11.1 g. (96%) of crystalline ketone melting at 125–127°; $[\alpha]^{25}D$ −23.8° (*c* 1.22, ethanol).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.5; H, 6.7; OCH_3, 11.5. Found: C, 75.5; H, 6.8; OCH_3, 11.5.

6-Keto-13-ethyloctahydromethylmorphenol.—A solution of 200 mg. (0.74 millimole) of 6-keto-13-vinyl compound in 10 ml. of ethanol containing 40 mg. of 5% palladium-on-charcoal was hydrogenated at room temperature and atmospheric pressure. After 15 minutes, hydrogen uptake ceased at 1.0 mole. The catalyst was removed and the solvent concentrated to a small volume. Dilution with hot water caused precipitation of the 13-ethyl compound, m.p. 111–113° (reported[12] m.p. 113°).

(27) This mixed melting point was determined in view of the surprising coincidence of m.p. and rotation (confirmed with several samples of each) displayed by the epimeric acids.

(28) We are grateful to Dr. A. H. Homeyer of the Mallinckrodt Chemical Works, St. Louis, Missouri, for a generous gift of thebaine.

(29) H. Wieland and M. Kotake, *Ann.*, **444**, 69 (1925).

Reduction of 6-Keto-13-vinyloctahydromethylmorphenol.—To a solution of 11.8 g. (0.044 mole) of ketone in 50 ml. of isopropyl alcohol was added 100 ml. of a 0.6 *M* solution of aluminum isopropoxide in isopropyl alcohol and the reaction mixture was heated under reflux in a nitrogen atmosphere for 20 hours. Water was then removed from the condenser and solvent was distilled slowly until the distillate gave a negative test for acetone with 2,4-dinitrophenylhydrazine. The bulk of the solvent was then removed under reduced pressure and the residue was cooled and treated with a solution of 30 ml. of concentrated hydrochloric acid in 150 ml. of water. The mixture was extracted with one 100-ml. portion and two 50-ml. portions of ether and the combined ether solutions were washed with half-saturated sodium bicarbonate solution and water, and dried over magnesium sulfate. Evaporation of the ethereal solution gave 11.8 g. of a mixture of epimeric alcohols whose composition was established as being about 1:1 by rotational analysis. The $[\alpha]^{25}D$ of the mixture was −2.4°; of the α-alcohol, +19.2°; and of the γ-alcohol, −22.6°. Therefore, the amount of γ-alcohol present in the mixture was roughly 52%.

Oxidation of the Mixture of 6α- and 6γ-Hydroxy-13-vinyloctahydromethylmorphenol (VI).—The procedure was that used in the oxidation of dihydrocodeine.[13] To a mixture of 37 ml. of *t*-butyl alcohol and 200 ml. of benzene was added 3.0 g. (0.077 mole) of potassium metal in small pieces. After the potassium had dissolved, the excess *t*-butyl alcohol was distilled as the benzene azeotrope. Benzene was added when necessary to keep the base in solution. When the temperature rose to 79° and remained constant for about 25 ml. of distillate, the solution was cooled slightly and a solution of 11.8 g. (0.043 mole) of the mixture of α- and γ-alcohols in 200 ml. of benzene containing 23 g. (0.126 mole) of benzophenone was added. The reaction mixture was allowed to reflux with stirring for 2.5 hours and was then cooled and 50 ml. of 3 *N* hydrochloric acid was added slowly. The mixture was extracted with two 50-ml. portions of ether, and the combined benzene–ether solution was washed with half-saturated sodium bicarbonate solution and water and then dried over magnesium sulfate. Evaporation of the solvent gave 33 g. of a mixture of γ-alcohol, 6-keto compound, benzophenone and benzhydrol.

A solution of this mixture in 40 ml. of pyridine and 25 g. of phthalic anhydride was heated under reflux for 8 hours, and the bulk of the pyridine was then removed at the water-pump. The residual material was dissolved in 150 ml. of benzene, the benzene solution was washed twice with 50-ml. portions of 3.6 *N* sulfuric acid solution and the combined acidic extracts were washed with a 50-ml. portion of benzene which was added to the other benzene extracts. The benzene solution was then extracted with four 125-ml. portions of cold (0–10°) 0.5 *N* potassium hydroxide solution, and the combined alkaline extracts were washed with ether. After adding 72 g. of potassium hydroxide, the aqueous solution was heated under reflux for an hour, and then extracted with three 100-ml. portions of ether. Evaporation of the combined, dried ether extracts gave 6.0 g. of a mixture of γ-alcohol and benzhydrol. The original benzene solution contained a mixture of benzophenone and 6-keto compound.

Preparation of 6-γ-Hydroxy-13-(α,β-dihydroxyethyl)-octahydromethylmorphenol (IX) from the Mixture of γ-Alcohol and Benzhydrol.—To a solution of 4.5 g. (0.018 mole) of osmium tetroxide in 25 ml. of benzene and 3.0 ml. of pyridine was added a solution of the 6.0 g. mixture of γ-alcohol and benzhydrol in 40 ml. of dry benzene. After 5 hours at room temperature, 200 ml. of hexane was added to complete precipitation of osmate ester which was filtered and washed with hexane. The moist solid was dissolved in 150 ml. of ethanol, to this was added a solution of 22 g. of sodium sulfite in 175 ml. of water, and the reaction mixture was boiled under reflux for 2 hours. After filtering the hot mixture through a layer of filter-aid and washing the precipitate with warm ethanol, the total filtrate was evaporated and the residue dissolved in 50 ml. of chloroform. The chloroform solution was washed with water, concentrated to 10 ml., and then cooled thoroughly. There was thus obtained 3.0 g. (22% yield from the original ketone) of 6-γ-13-(α,β-dihydroxyethyl)-octahydromethylmorphenol, identical with the material prepared by degradation of dihydroisocodeine.

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