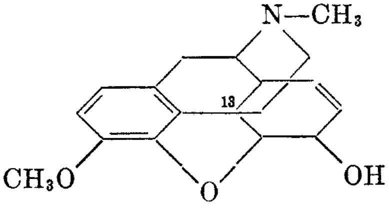
[Contribution from the Chemical Laboratory of the University of California]

STRUCTURE STUDIES IN MORPHINE. THE DEGRADATION OF DIHYDROCODEINE TO NITROGEN-FREE COMPOUNDS

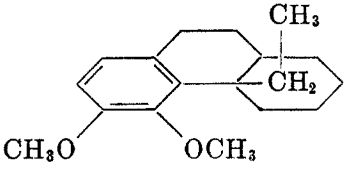
HENRY RAPOPORT

Received May 13, 1948

The formula for morphine and its methyl ether, codeine (I), accepted at present[1] as best explaining the many and complicated facts of morphine chemistry (3) is that of Gulland and Robinson (4). However, an important point still without direct experimental proof is the juncture of the ethanamine chain at carbon 13.[2] It is the objective of this work ultimately to provide evidence on this question by degrading codeine to 13-ethyloctahydrodimethylmorphol (II)[3] by a series of reactions which would cause no rearrangements in the fundamental skeleton of the molecule. This degradation product, containing only two asymmetric carbon atoms, might be amenable to an unambiguous synthesis and thus supply an absolute proof of structure. At present, we are reporting some preliminary degradative results.



I



II

Degradation of codeine itself has invariably led to ejection or migration of the ethanamine chain and completely aromatic phenanthrene derivatives (3, 5). However, in derivatives where aromatization has been blocked by prior hydrogenation of the alicyclic double bond, degradation has proceeded to nitrogen-free compounds without loss of the two-carbon chain (6), but as yet compound II has not been realized.

Because of the above considerations, dihydrocodeine (IV), which has the hydrogenated structure necessary for retention of the ethanamine chain, was selected as starting material for the degradation. Previous attempts to obtain a nitrogen-free compound from dihydrocodeine have usually resulted in unidentified oils (7, 8). In only one case (9) was a crystalline substance isolated (in very

---

[1] Some of the recent data on the phenyldihydrothebaines (1) that seem inexplicable on the basis of the present formula have been interpreted by Robinson in a preliminary note (2) by assuming a fundamental rearrangement in the morphine skeleton.

[2] The most direct experimental evidence supporting juncture at carbon 13 has been presented by Schöpf, *Ann.*, **452**, 211 (1927); however, this work still does not supply the unqualified proof desired.

[3] For consistency with previous work, the nomenclature of morphine chemistry is retained throughout.

low yield), and we shall show subsequently that the structure assigned to this product is probably incorrect. It is difficult to perceive why the degradation of dihydrocodeine should give such indeterminate results if the assigned structure (IV) is correct; therefore, these reactions and products were re-examined in detail.

Dihydrocodeine was converted to dihydro-α-methylmorphimethine (Δ-9,10) (V) in almost quantitative yield, and the methine degraded by refluxing its methohydroxide with alkali according to Speyer and Krauss (9). In contrast to their results, the only product was a small amount of an intractable red solid. However, when the methohydroxide, prepared from the methiodide and silver oxide, was dry distilled in vacuum, considerable oily distillate was obtained that could be separated into a basic fraction, 34% of the original calculated as recovered methine, and a neutral fraction corresponding to 59% of the original. After all attempts to crystallize this neutral fraction failed, recourse was made to the possible preparation of crystalline derivatives.

By esterifying the neutral fraction with *p*-phenylbenzoyl chloride in pyridine, it could be separated by vacuum distillation into a relatively volatile non-alcoholic fraction (40 to 50%) and the residual *p*-phenylbenzoate of the alcoholic portion. Analysis of the purified, oily non-alcoholic fraction showed it had the composition $C_{18}H_{20}O_3$, which was a carbon and two hydrogens more than expected. It was non-phenolic, contained two methoxyl groups (Zeisel), absorbed two moles of hydrogen, and was recovered unchanged from attempts to prepare ketone derivatives. On the basis of these reactions, it was assigned the structure 6-methoxy-13-vinylhexahydromethylmorphenol (Δ-9,10) (VIII). This assigned structure was confirmed by the identity of its crystalline hydrogenation product with the 6-methoxy-13-ethyloctahydromethylmorphenol (XII) prepared by degradation of codeine methyl ether (XIII).

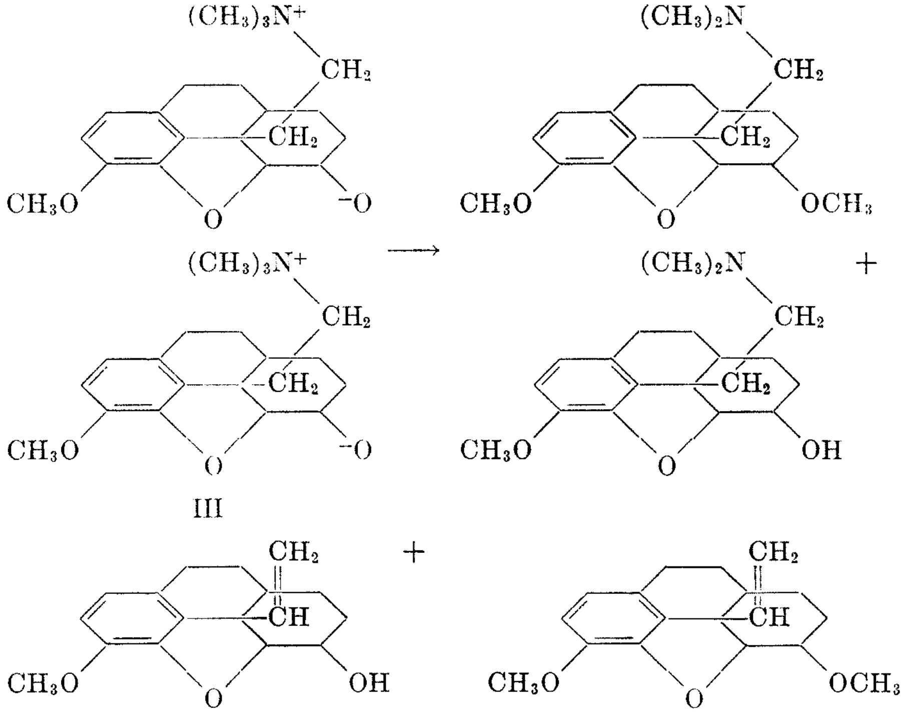
The surprising discovery in the neutral fraction of material with the 6-hydroxyl group methylated indicated that the recovered methine might also be partially etherified. Therefore, the basic fraction was converted to methiodide, which after repeated crystallization melted over a wide range and appreciably lower than the methiodide of the original methine, possibly due to the presence of both 6-hydroxy and 6-methoxy methines in the recovered material.

The alcoholic fraction of the neutral, degraded material was isolated in 81% yield as the crystalline *p*-phenylbenzoate and saponification gave the free alcohol, m.p. 102–103°, which was non-phenolic and absorbed 2 moles of hydrogen. This alcohol, to which the structure 6-hydroxy-13-vinylhexahydromethylmorphenol (Δ-9,10) (VII) is assigned, has been previously reported (9) as melting at 115°. However, the above evidence and the fact that the earlier workers obtained their compound crystalline only after several months standing in aqueous ethanol and in extremely low yield makes structure VII very improbable for the higher-melting material.

In order to establish the structure of these degradation products as securely as possible, tetrahydro-α-methylmorphimethine (VI) was subjected to a similar degradation and found to give identical results. Also, to eliminate any possible cyclization reactions involving the hydroxyl group and the double bonds, the crude degraded material was purified both before and after hydrogenating. In every case, 6-hydroxy-13-ethyloctahydromethylmorphenol (XI) and the 6-methoxy analog (XII) were obtained as the end products and in good yield. Both the dihydromethine (V) and the tetrahydro methine (VI) gave recovered basic material whose methiodides melted over a wide range, possibly due to the presence of both 6-hydroxy and 6-methoxy methines. The composition of these fractions is being examined further and will be reported at a later date.

The presence among the degradation products of morphine alkaloids of compounds in which the alcoholic hydroxyl has been methylated during the degradative procedure has heretofore been unreported, and it is interesting to consider how such compounds might have originated. Any explanation must take into account the fact that the hydroxyl group in the parent substance, dihydrocodeine (IV), is indifferent to methylation by the Rodionov procedure (10). It must also explain why degradation of tetrahydro-α-methylmorphimethine (VI) gives 40 to 50% of recovered methine whereas from the 6-methoxy analog (XV) only 2 to 3% of undegraded material is obtained.

The above observations might indicate the existence of an intermediate in the degradation of the 6-hydroxy compound which makes the hydroxyl group more susceptible to etherification and influences the course of the degradation to give a higher proportion of undegraded material. A possible intermediate that fulfills these requirements is the inter-molecular salt (III), which on dry distillation could theoretically give all four products, shown below.



III

Work is continuing on the mechanism of the degradation with compounds containing the 6-hydroxyl group, and also on the conversion of 6-hydroxy-13-ethyloctahydromethylmorphenol (XI) to 13-ethyloctahydrodimethylmorphol (II).

We are indebted to Mallinckrodt Chemical Works, St. Louis, Mo., for the generous gift of codeine used in this research.

EXPERIMENTAL

All melting points are corrected, and all above 200° were taken in evacuated tubes; rotations are in 95% ethanol unless otherwise stated. Microanalyses were performed by C. W. Koch and V. H. Tashinian.

Dihydrocodeine (IV). Dihydrocodeine was prepared by a modification of the method of Wieland and Koralek (8). A solution of 50 g. (0.158 mole) of codeine ($\cdot H_2O$) in 175 ml. of methanol containing 2.5 g. of 10% palladium on barium sulfate was hydrogenated at room temperature and thirty pounds pressure. After two hours, hydrogenation ceased with the absorption of 1.04 moles of hydrogen. Filter-aid was added, the solution filtered, and the filtrate concentrated on the steam-bath to a syrupy residue which gave 50 g. (94%) of dihydrocodeine ($\cdot 2H_2O$), m.p. 53–55° (11), on addition of 100 ml. of water and cooling. This dihydrate, when heated at 75° and 0.1 mm. pressure gave a crystalline sublimate of the anhydrous form, m.p. 112°, $[\alpha]_D^{20}$ −145° (ethanol, $c = 1.38$).

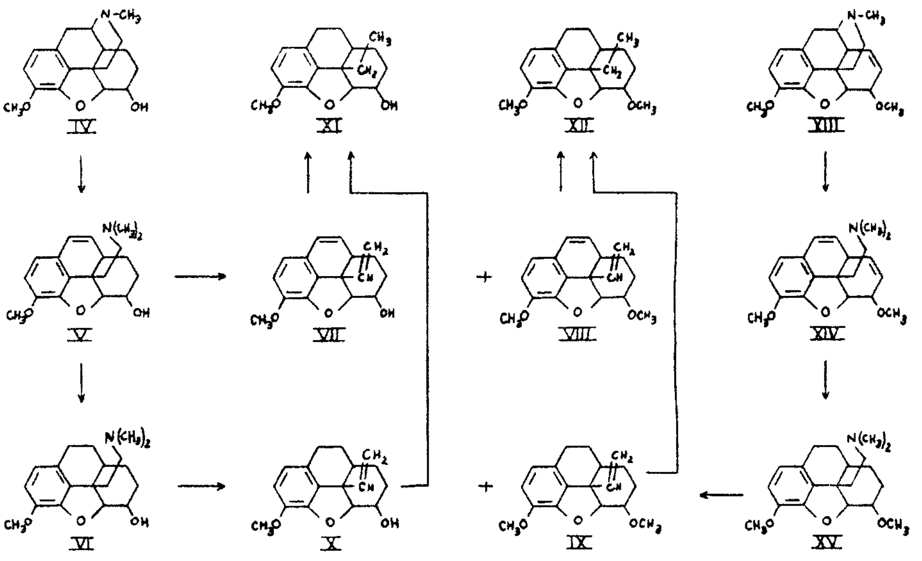
The *methiodide* was prepared in quantitative yield directly from the dihydrate in 95% ethanol and, after drying in a vacuum at 125° overnight, melted at 258–260° (8).

Dihydro-α-methylmorphimethine (Δ-9,10) (V). To a solution of 65 g. (0.147 mole) of dihydrocodeine methiodide in 200 ml. of water was added 200 ml. of a 30% potassium hydroxide solution and the mixture refluxed for 30 minutes. After cooling, the oily layer was removed by extraction with one 250-ml. portion and three 125-ml. portions of ether, the combined ether extracts were dried over potassium carbonate, filtered, and the ether evaporated on the steam-bath. The residual oily methine was converted directly to the *methiodide* by dissolving in 200 ml. of ethanol and warming on the steam-bath with methyl iodide. One recrystallization from ethanol gave 63.2 g., 91%, of the monohydrate, m.p. 154–156° with loss of solvent. Drying in a vacuum at 125° overnight gave the anhydrous form, m.p. 224–226° (12).

Tetrahydro-α-methylmorphimethine (VI). The dihydro-α-methylmorphimethine obtained from the degradation of 59.4 g. (0.134 mole) of dihydrocodeine methiodide was hydrogenated in the manner described previously for the reduction of codeine. After three hours, hydrogenation ceased with a total absorption of 1.02 moles of hydrogen. The residue after evaporation of the methanol was converted to the *methiodide* by warming in 150 ml. of ethanol with methyl iodide. One recrystallization from ethanol and drying in a vacuum at 125° overnight gave 57.2 g., 93% based on dihydrocodeine methiodide, of the anhydrous methiodide, m.p. 225–227° (7).

Degradation of dihydro-α-methylmorphimethine (Δ-9,10) (V). A. By the method of Speyer and Krauss (9). Degradation of dihydro-α-methylmorphimethine (Δ-9,10) methodide as directed by Speyer and Krauss (9) gave only a dark brown solid which failed to crystallize from aqueous ethanol even after months of standing. None of the material they reported melting at 115° could be obtained.

B. By dry distillation of the methohydroxide. Silver oxide was freshly prepared by adding 125 ml. of 3 *N* sodium hydroxide to a solution of 34.0 g. (0.20 mole) of silver nitrate in 125 ml. of water. The precipitate was washed with water until the washings were neutral and then with a portion of water previously boiled to remove carbon dioxide. From this point on, precaution was taken to exclude carbon dioxide from the reaction mixture. Using 150 ml. of water to effect the transfer, the silver oxide thus prepared was added to a warm solution of 22.85 g. (0.050 mole) of dihydro-α-methylmorphimethine methiodide in 350 ml. of water and the mixture was shaken at room temperature for 8 hours. Filter-aid was then added, the mixture filtered using two 75-ml. portions of hot water as wash, and the filtrate concentrated to about 75 ml. at reduced pressure (water-pump) and a bath temperature not above 50°. The evaporation was continued by adding the pale brown concentrate dropwise to the 125 ml. bulb of a two-bulb distilling flask maintained at 25° and about 5 mm. pressure. After drying in a vacuum overnight, the residue was decomposed by cautious heating under reduced pressure. Decomposition began at 90° (bath temperature) and was substantially complete by 140°, after which the temperature was increased rapidly and a colorless oil distilled from 170–190°/0.4 mm. From the liquid-nitrogen trap, trimethylamine was isolated and identified through its picrate, m.p. 222–224°. The distillate was washed from the receiver bulb with ether and the combined ether washings, 100 ml., were extracted with 35-ml. portions of 1 *N* HCl, water, half-saturated $NaHCO_3$, and water. From the acid and first water wash, on basifying, extracting into ether, evaporating the ether, and converting the residue into methiodide, there was obtained 7.66 g., 34%,[4] of recovered methine methiodide. Repeated crystallization of this methiodide from ethanol did not raise its m.p. above 210° which indicates, together with the other evidence, that it is probably a mixture of the methiodides of dihydro-α-methylmorphimethine and dihydro-α-dimethylmorphimethine.



DEGRADATION OF DIHYDROCODEINE AND CODEINE METHYL ETHER

The neutral material remaining in the original ether solution was obtained as an oil on evaporation of the ether; 7.95 g., 59% yield based on total methiodide used or 89% allowing for recovered undegraded methine. It was separated into alcoholic and nonalcoholic fractions both directly and after hydrogenation.

1. *Direct separation of neutral material into alcoholic and non-alcoholic fractions.* A solution of 7.95 g. (0.029 mole, assuming all alcohol, VII) of neutral degraded material in 50 ml. of dry pyridine was warmed on the steam-bath for 3 hours with 5.04 g. (0.023 mole)[5] of

---

[4] Yields in this and subsequent degradations are calculated on the basis that all the material still contains a free hydroxyl on carbon 6. Since it has been shown that a portion of the material was converted to methyl ether, these yields are probably too high by 1 to 3%.

[5] Preliminary experiments indicated this neutral material was from 35 to 50% non-alcoholic; hence, only 80% of the molar equivalent of acid chloride was used.

p-phenylbenzoyl chloride and then allowed to stand at room temperature overnight. The pyridine was removed by distillation at the water-pump and the residual magma was heated on the steam-bath with 80 ml. of 0.5 *N* K_2CO_3 for 20 minutes, after which 125 ml. of benzene was added. Using warm solutions to prevent emulsion formation, the benzene layer was washed with four 40-ml. portions of 0.5 *N* K_2CO_3 and two 40-ml. portions of water, and each wash portion was in turn extracted with two 40-ml. portions of benzene. After drying over K_2CO_3, the combined benzene solutions were evaporated on the steam-bath and the residue distilled for 15 hours at 135°/0.1 mm. in a modified molecular distillation apparatus to give 3.96 g., 50% of the original, as a colorless, oily distillate. A sample of this material, *6-methoxy-13-vinylhexahydromethylmorphenol* (Δ-*9,10*) (*VIII*), was redistilled at 100°/0.05 mm. It is a fairly mobile oil with $[\alpha]_D^{20}$ +61.0° (ethanol, $c = 1.532$); n_D^{27} 1.5861.

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.02; H, 7.09.
Found: C, 75.92; H, 7.05.

A sample of this compound, hydrogenated in methanol with a platinum oxide catalyst, absorbed 1.9 moles of hydrogen in 15 minutes, after which hydrogenation ceased. Evaporation of the solvent gave the crystalline tetrahydro derivative (XII) described below.

The residue from the 15-hour distillation was taken up in 150 ml. of ethanol and, after decolorizing with carbon, gave 4.66 g. of crystalline material on cooling. Concentration of the mother liquor to about 30 ml. gave an additional 0.73 g.; total 5.39 g., m.p. 165–170°, 81% yield of *6-hydroxy-13-vinylhexahydromethylmorphenol* (Δ-*9,10*) *p-phenylbenzoate*, based on the nonrecovered fraction. Several crystallizations from ethanol gave material melting at 173–174° which very slowly sublimed at 160°/0.05 mm., $[\alpha]_D^{20}$ +73.4° (dioxane, $c = 0.92$).

Anal. Calc'd for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82.
Found: C, 79.70; H, 5.73.

The ester was saponified by adding 200 ml. of 5 *N* ethanolic KOH to a solution of 8.9 g. (0.02 mole) of ester in 200 ml. of ethanol and refluxing in a nitrogen atmosphere for 3 hours. After cooling, the solution was filtered from the precipitated potassium *p*-phenylbenzoate and the filtrate concentrated at reduced pressure. Water was added, the concentration repeated, and 100 ml. of water added to the residue followed by extraction with one 100-ml. portion and two 50-ml. portions of ether. After washing with water and drying over Na_2SO_4, the combined ether extracts were evaporated on the steam-bath to give a slightly yellow residue which crystallized on cooling; yield 5.12 g., 96%, of material melting at 97–101°. Several crystallizations from hexane and a sublimation at 80°/0.05 mm. gave a sample of *6-hydroxy-13-vinylhexahydromethylmorphenol* (Δ-*9,10*) (*VII*) that had m.p. 102–103° and $[\alpha]_D^{20}$ +77.1° (ethanol, $c = 1.012$).

Anal. Calc'd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71.
Found: C, 75.43; H, 6.58.

Hydrogenation of this compound in methanol with a platinum oxide catalyst ceased after the absorption of 2 moles of hydrogen in 30 minutes and gave the tetrahydro derivative (XI) described below.

2. *Separation of neutral material into alcoholic and non-alcoholic fractions after hydrogenation.* Crude neutral degraded material, 7.5 g. (0.028 mole, assuming all alcohol, VII), was dissolved in 40 ml. of methanol and hydrogenated using 0.75 g. of 10% palladium on barium sulfate as catalyst. After the absorption of 1.7 moles of hydrogen in 3 hours, hydrogenation ceased, and evaporation of the methanol left 7.42 g. of hydrogenated material. This was esterified with *p*-phenylbenzoyl chloride exactly as described above and sublimation of the esterification reaction product at 125°/0.3 mm. for 15 hours gave 2.2 g., 30%, of a waxy, crystalline sublimate, m.p. 45–49°. In preliminary experiments to determine the structure of this compound, it was recovered quantitatively and unchanged from attempted oxime and semicarbazone formation. Its structure was established as *6-methoxy-13-ethyloctahydromethylmorphenol* (*XII*) by its identity with the compound prepared from codeine methyl ether as described below. Purification with considerable loss was effected by several crystallizations from pentane in which it is quite soluble even cold, and a final sublimation at 40°/0.05 mm. gave material of m.p. 51–52°, $[\alpha]_D^{20}$ −44.0° (ethanol, $c = 1.376$).

Anal. Calc'd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; OCH_3, 21.5.
Found: C, 74.90; H, 8.35; OCH_3, 21.1.

The residue from the sublimation of the esterified mixture was dissolved in 200 ml. of ethanol and filtered after treating with carbon. Concentration of the filtrate to 75 ml. and cooling gave 4.9 g. of crystalline material; further concentration of the mother liquor to 20 ml. gave 0.7 g. more; total, 5.6 g., m.p. 167–171°, 65% yield based on unrecovered material. Several crystallizations from ethanol gave pure *6-hydroxy-13-ethyloctahydromethylmorphenol p-phenylbenzoate*, m.p. 170–172°, $[\alpha]^{20}_{D}$ −3.42° (dioxane, c = 1.022).

Anal. Calc'd for $C_{30}H_{30}O_4$: C, 79.27; H, 6.65.
Found: C, 79.14; H, 6.65.

6-Hydroxy-13-ethyloctahydromethylmorphenol (XI) was obtained in 85% yield by saponification of the pure *p*-phenylbenzoate ester (above) with alcoholic KOH as described previously for the ester of the hexahydro derivative (VIII). It is a viscous, colorless oil that distills rapidly at 100°/0.05 mm. and shows no tendency to crystallize.

Degradation of tetrahydro-α-methylmorphimethine (VI). The degradation of tetrahydro-α-methylmorphimethine by dry distillation of its methohydroxide was carried out exactly as described above for the dihydro compound. From 23 g. (0.05 mole) of methiodide there resulted 6.85 g. of basic material, equivalent to a 43% recovery of methine. Conversion to the methiodide and repeated crystallization of the latter from ethanol gave material melting from 229–233°, indicating it was probably a mixture of tetrahydro-α-methylmorphimethine methiodide, m.p. 225–227°, and tetrahydro-α-dimethylmorphimethine methiodide, m.p. 247° (13).

The neutral fraction consisted of a viscous oil, 7.64 g., 56% yield based on total methiodide or 98% allowing for recovered methine. It was separated into alcoholic and non-alcoholic fractions both directly and after hydrogenation, exactly as described above for the degraded material from the dihydro compound (V), and the following products were obtained:

6-Methoxy-13-vinyloctahydromethylmorphenol (IX). Esterification of the neutral degraded material with *p*-phenylbenzoyl chloride and distillation of the reaction mixture under reduced pressure gave the oily 6-methoxy-13-vinyloctahydromethylmorphenol in 36% yield. Hydrogenation in methanol with a 10% palladium on barium sulfate catalyst ceased after the absorption of 1.0 mole of hydrogen in one hour. Evaporation of the methanol and sublimation of the residue resulted in a 96% yield of 6-methoxy-13-ethyloctahydromethylmorphenol as a crystalline sublimate, m.p. 47–49°; after one crystallization from pentane, m.p. 50–52°.

6-Hydroxy-13-vinyloctahydromethylmorphenol (X). The residue from the vacuum distillation of the esterification reaction mixture, on crystallization from ethanol, gave a 76% yield of *6-hydroxy-13-vinyloctahydromethylmorphenol p-phenylbenzoate*, m.p. 168–170° after several crystallizations from ethanol; $[\alpha]^{20}_{D}$ +53.9° (dioxane, c = 0.946).

Anal. Calc'd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24.
Found: C, 79.48; H, 6.49.

Saponification of this ester with ethanolic KOH in the manner described above gave a 91% yield of 6-hydroxy-13-vinyloctahydromethylmorphenol as a viscous oil that absorbed 1.02 moles of hydrogen on reduction in methanol with a 10% palladium-barium sulfate catalyst.

Hydrogenation of the crude neutral degraded material (1.0 mole of hydrogen absorbed) and esterification of the reduced mixture with *p*-phenylbenzoyl chloride gave, on separation in the manner described above, a 34% yield of 6-methoxy-13-ethyloctahydromethylmorphenol (XII), m.p. 48–50°, and a 69% yield of 6-hydroxy-13-ethyloctahydromethylmorphenol (XI) as the *p*-phenylbenzoate, m.p. 170–172°.

Preparation of 6-methoxy-13-ethyloctahydromethylmorphenol (XII) from codeine methyl ether (XIII). Codeine methyl ether (XIII). Codeine methyl ether was prepared directly as the methiodide from morphine by the method of Pschorr and Dickhauser (14); m.p. 252–254° (lit. m.p. 257°).

α-Dimethylmorphimethine (XIV). Degradation of codeine methyl ether methiodide by refluxing with aqueous sodium hydroxide resulted in a 72% yield of α-dimethylmorphimethine, m.p. 92–94° (14).

Tetrahydro-α-dimethylmorphimethine (XV). Hydrogenation of α-dimethylmorphimethine was carried out by the method of Faltis and Suppan (13). The tetrahydro reduction product was converted directly to the *methiodide* in ethanol, 81% yield, m.p. 246–248° (13).

6-Methoxy-13-vinyloctahydromethylmorphenol (IX). Tetrahydro-α-dimethylmorphimethine was degraded by dry distillation of the methohydroxide exactly as described above. From 15 g. (0.032 mole) of methiodide there was recovered 0.27 g., 2.6%, of methine (methiodide, m.p. 246–248°) and 7.90 g. of oily 6-methoxy-13-vinyloctahydromethylmorphenol, 87% yield based on total methiodide, or 90% allowing for recovered methine.

6-Methoxy-13-ethyloctahydromethylmorphenol (XII). Hydrogenation of 7.90 g. (0.028 mole) of 6-methoxy-13-vinyloctahydromethylmorphenol in 50 ml. of methanol with 0.79 g. of 10% palladium-barium sulfate ceased after 2 hours at room temperature and atmospheric pressure with the absorption of 1.05 moles of hydrogen. The catalyst was removed and the filtrate evaporated to dryness on the steam-bath to give a crystalline residue that was sublimed at 50°/0.1 mm. There was thus obtained 7.52 g., 94%, of 6-methoxy-13-ethyloctahydromethylmorphenol as a crystalline sublimate, m.p. 47–49°. Crystallization from pentane gave material whose m.p. of 51–52° was not depressed on admixture with the neutral, completely hydrogenated, non-alcoholic fraction resulting from the various degradations above, thus establishing the identity of the compounds.

SUMMARY

6-Hydroxy-13-ethyloctahydromethylmorphenol and 6-methoxy-13-ethyloctahydromethylmorphenol have been obtained from the degradation of dihydrocodeine.

The structure of 6-methoxy-13-ethyloctahydromethylmorphenol from dihycodeine has been established by its identity with the degradation product from codeine methyl ether.

Degradation of dihydro- and tetrahydro-α-methylmorphimethine has been shown to proceed with partial methylation of the hydroxyl group on carbon six.

BERKELEY, CALIFORNIA

REFERENCES

(1) SMALL, SARGENT, AND BRALLEY, *J. Org. Chem.*, **12**, 839 (1947).
(2) ROBINSON, *Nature*, **160**, 815 (1947).
(3) SMALL AND LUTZ, "Chemistry of the Opium Alkaloids", Suppl. 103, Public Health Reports.
(4) GULLAND AND ROBINSON, *Mem. Proc. Manchester Lit. Phil. Soc.*, **69**, 79 (1925).
(5) SMALL, *J. Org. Chem.*, **7**, 158 (1942).
(6) WIELAND AND KOTAKE, *Ann.*, **444**, 69 (1925); FREUND, SPEYER, AND GUTTMANN, *Ber.*, **53**, 2250 (1920); CAHN, *J. Chem. Soc.*, 702 (1930); SMALL AND BROWNING, *J. Org. Chem.*, **3**, 618 (1939); SMALL AND RAPOPORT, *J. Org. Chem.*, **12**, 284 (1947).
(7) FREUND, MELBER, AND SCHLESINGER, *J. prakt. Chem.*, **101**, 1 (1920).
(8) WIELAND AND KORALEK, *Ann.*, **433**, 267 (1923).
(9) SPEYER AND KRAUSS, *Ann.*, **432**, 233 (1923).
(10) RODIONOV, *Bull. soc. chim.*, [4] **39**, 305 (1926); SCHÖPF AND WINTERHALDER, *Ann.*, **452**, 232 (1927).
(11) DIETERLE AND DICKENS, *Arch. Pharm.*, **264**, 257 (1926).
(12) VON BRAUN AND CAHN, *Ann.*, **451**, 55 (1927).
(13) FALTIS AND SUPPAN, *Pharm. Monatsh.*, **4**, 189 (1923).
(14) PSCHORR AND DICKHÄUSER, *Ber.*, **44**, 2633 (1911).