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

THE PREPARATION OF SOME DIHYDRO KETONES IN THE MORPHINE SERIES BY OPPENAUER OXIDATION

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Among the more important morphine derivatives are the ketones dihydromorphinone (V) and dihydrocodeinone (VI). They have been used directly as analgesics themselves and also are key intermediates in the syntheses of metopon (1) and 6-methyldihydromorphine (2), two of the more promising morphine derivatives (3).

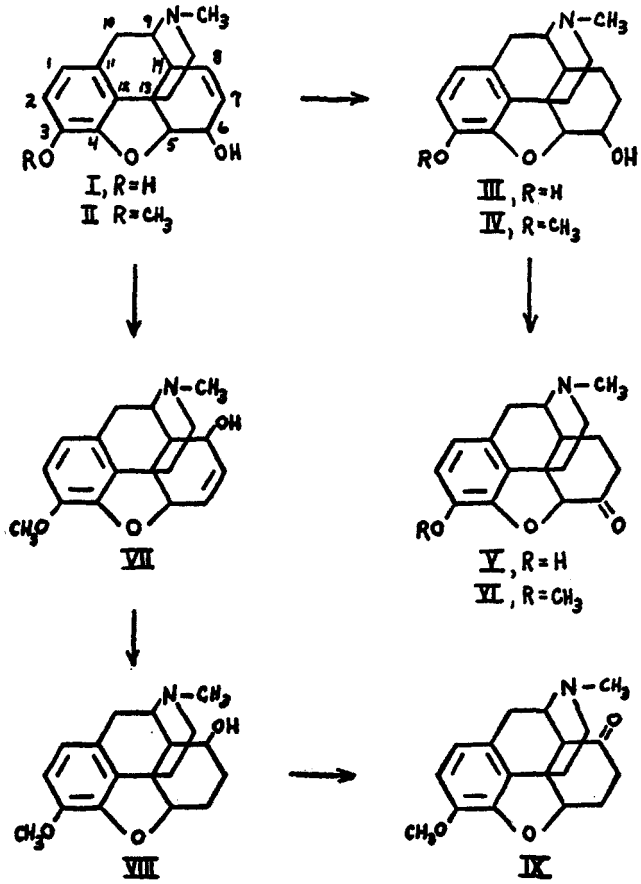
An attractive method for preparing these ketones easily and in yields approaching theoretical has been claimed, in the patent literature (4), to be the rearrangement of the parent morphine or codeine to the corresponding ketone under the catalytic influence of finely divided palladium or platinum, with or without the presence of hydrogen. However, after thorough investigation (5), we were unable to obtain yields higher than 50% by this method. Dihydrocodeinone is available by an alternative path from thebaine through dihydrothebaine (6), but the yield is only 36% and the starting material is relatively rare.

For these reasons, we have sought a better method for preparing the ketones, and have examined the Oppenauer oxidation of the dihydro alcohols. Codeine and morphine were reduced to dihydrocodeine (IV) and dihydromorphine, respectively, in practically quantitative yield, and the latter were subjected to oxidation. The best conditions found were the use of potassium *tert*-butoxide as catalyst and benzophenone as oxidant (7) in refluxing benzene. A benzene solution of potassium *tert*-butoxide free of *tert*-butyl alcohol was conveniently prepared by removing the excess alcohol, after dissolution of the potassium, by azeotropic distillation with benzene. The dihydro alcohol and benzophenone were then added and the solution heated under reflux for $2\frac{1}{2}$ hours, resulting in an 83% yield of dihydrocodeinone and a 71% yield of dihydromorphinone.

To test the generality of this reaction in the morphine series, it was applied to the codeine isomers. Dihydroisocodeine (IV), differing from codeine only in the configuration of the hydroxyl group at carbon 6, was recovered unchanged with no evidence of ketonic material when subjected to the same conditions that had resulted in an 83% yield of ketone from dihydrocodeine. At higher temperatures (refluxing toluene), a small amount of dihydrocodeinone (about 3%) was formed and isolated as the oxime.

With the isomers at carbon 8, dihydropseudocodeine and dihydroallopseudocodeine (VIII), the same striking difference was observed in the reactivity of the epimers. The conditions under which dihydrocodeine was oxidized gave only recovered starting material when applied to dihydropseudocodeine. More drastic conditions resulted in lower recoveries, and no ketonic material could be obtained. Dihydroallopseudocodeine, on the other hand, was easily oxidized to

dihydropseudocodeinone (IX) in 40% yield. This conversion could probably be improved, but there was insufficient dihydroallopseudocodeine on hand to examine the reaction more thoroughly.



Thus we find a marked distinction, on the basis of susceptibility to Oppenauer oxidation, between the pair dihydrocodeine and dihydroallopseudocodeine, which are easily oxidized, and the pair dihydroisocodeine and dihydropseudocodeine, which are resistant to oxidation. Eddy (8) has observed the same parallel in the physiological activity of codeine and allopseudocodeine as contrasted to that of isocodeine and pseudocodeine.

A possible explanation of these pairings might be provided by stereochemical considerations. It has been recently shown (9) that on Meerwein-Ponndorf reduction of a large variety of α-substituted cyclic ketones, the principal reduction products were alcohols with the *cis*-configuration. This is in agreement with other strong evidence for the pseudo-six membered ring intermediate in oxidation-reduction reactions involving carbonyl-carbinol systems and catalyzed by various metal alkoxides (10). Since the more stable (less hindered) configuration of this intermediate would be that one with the pseudo-ring *trans* to the α-sub-

stituent, the chief reduction product of a ketone should be the *cis*-alcohol, and the *cis*-alcohol should be more easily oxidized than the *trans*.

On the basis of this mechanism and the Oppenauer oxidation data presented above, it would follow that the hydroxyl group in codeine is *cis* to the carbon-oxygen bond at carbon 5, while in isocodeine the hydroxyl is *trans* to this bond. For the carbon-8 epimers, the hydroxyl of pseudocodeine would be *trans* to the 9,14 carbon-carbon bond and that of allopseudocodeine would be *cis*. These deductions for the codeine-isocodeine pair are confirmed by recent independent findings on their stereochemistry (11).

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.

Dihydrocodeine (IV). Codeine was hydrogenated (11) in dilute acetic acid using a palladium on barium sulfate catalyst to give a 93% yield of dihydrocodeine, m.p. 109–111°.

Dihydrocodeinone (VI). *tert*-Butyl alcohol (50 ml.), previously distilled from sodium, was redistilled from a small amount of sodium directly into a thoroughly-dried three-necked flask equipped with a mercury-sealed stirrer and a reflux condenser. To the alcohol was added 150 ml. of dry benzene followed by 4 g. (0.1 mole) of potassium in small portions. After the potassium had dissolved, the reflux condenser was replaced with a two-foot Vigreux column, and, with stirring, the excess *tert*-butyl alcohol was distilled as the benzene azeotrope (12), adding more benzene, when necessary, to keep the potassium *tert*-butoxide in solution. When the boiling point reached 80° and remained constant for 25 ml. of distillate, the column was replaced with a reflux condenser, the system was flushed with nitrogen, and a solution of 10 g. (0.033 mole) of dihydrocodeine and 60.1 g. (0.33 mole) of benzophenone in 50 ml. of dry benzene was added. In a nitrogen atmosphere, the reaction mixture was then heated under reflux for 2½ hours after which it was thoroughly cooled and 50 ml. of 3 *N* hydrochloric acid was added. The benzene layer was separated, extracted with three more 50-ml. portions of 3 *N* hydrochloric acid, and the combined aqueous extract washed with two 50-ml. portions of ether. After basifying the aqueous solution with concentrated sodium hydroxide, it was extracted with three 100-ml. portions of ethyl acetate, and these were combined, dried over magnesium sulfate, and evaporated on the steam-bath to about 25 ml. at which point appreciable crystalline material had separated from the hot solution. Cooling gave 8.3 g., 83%, of *dihydrocodeinone*, m.p. 194–195° [reported (13) m.p. 197–198°]; *oxime*, m.p. 264–265° [reported (14) m.p. 266°]; *methiodide*, m.p. 253–255° [reported (13) m.p. 250–255°].

Dihydromorphine (III). Morphine was hydrogenated in the same manner as described above for codeine to give a 97% yield of dihydromorphine, m.p. 153–155°. After crystallization from ethanol it melted at 155–157° [reported (13) m.p. 155–157°].

Dihydromorphinone (V). The oxidation of dihydromorphine to the ketone was carried out by the same procedure as described above for oxidizing dihydrocodeine except for the following modifications: the molar ratio of potassium to alkaloid was increased from 3:1 to 4.5:1, and the benzophenone and dihydromorphine were added as solids rather than as a benzene solution due to the insolubility of the latter in benzene. The combined acid extract of the reaction mixture was basified with concentrated aqueous ammonia, extracted exhaustively with ethyl acetate, and the ethyl acetate solutions were dried and concentrated on the steam-bath until solid material began to precipitate. Cooling at this point followed by filtration gave the first crop of ketone and an additional portion was isolated by further concentration of the filtrate. From 9.7 g. (0.034 mole) of dihydromorphine there was obtained 6.9 g., 71% yield, of dihydromorphinone (5.5 g., m.p. 266–267°, and 1.4 g., m.p. 260–263°). Repeated crystallization from ethanol did not raise the melting point above 266–267° [reported (4) m.p. 262–263°]; $[\alpha]_D^{25}$ −194° (dioxane, *c*, 0.98).

The *oxime* was prepared by warming a suspension of 0.5 g. of dihydromorphinone in 50 ml. of water containing 0.15 g. of hydroxylamine hydrochloride until solution was complete. After heating an additional hour, the solution was basified with aqueous ammonia to precipitate the oxime, m.p. 234–235° [reported (15) m.p. 231–232°].

Oxidation of dihydroisocodeine (IV). After substituting toluene for benzene and increasing the reflux period from 2½ to three hours, the general oxidative procedure described above for dihydrocodeine was applied to 3.0 g. (0.01 mole) of dihydroisocodeine (11). Evaporation of the ethyl acetate extracts of the reaction mixture left 1.5 g. of an oily residue from which the non-alcoholic portion was obtained by sublimation at 125–150°/0.01 mm. after esterifying with 1.5 g. of *p*-phenylbenzoyl chloride in 10 ml. of pyridine (16). The sublimate (about 200 mg.) was heated on the steam-bath for two hours with 0.5 g. of hydroxylamine hydrochloride in 10 ml. of water, after which the mixture was filtered and the filtrate basified with sodium carbonate. Crystallization of the precipitate from aqueous ethanol gave 50 mg. of pure dihydrocodeinone oxime, m.p. 264° (14).

Attempted oxidation of dihydropseudocodeine (VIII). Using the general oxidative procedure described above, twelve attempts were made to oxidize dihydropseudocodeine (17) to dihydropseudocodeinone, varying the time of reflux, the temperature (refluxing benzene, toluene, and xylene), and the oxidant (benzophenone and fluorenone). In no case was any ketone obtained, and the amount of dihydropseudocodeine recovered decreased as the conditions became more drastic. Esterification with *p*-phenylbenzoyl chloride in pyridine was employed to separate alcoholic from non-alcoholic material (16), but the only product isolated was the *p-phenylbenzoate of dihydropseudocodeine*, m.p. 191–192° after several crystallizations from absolute ethanol; $[\alpha]_D^{25}$ +44.7° (dioxane, *c*, 1.04).

Anal. Calc'd for $C_{31}H_{31}NO_4$: C, 77.3; H, 6.5.

Found: C, 77.1; H, 6.6.

Dihydropseudocodeinone (IX). Exactly the same procedure used for oxidizing dihydrocodeine (above) was applied to the free base from 2.0 g. (0.0044 mole) of dihydroallopseudocodeine acid tartrate (18). The oily reaction product was separated into alcoholic and non-alcoholic fractions by sublimation after esterifying with *p*-phenylbenzoyl chloride in pyridine (16), and 0.55 g., 40% yield, of dihydropseudocodeinone, m.p. 93–110°, was obtained. Crystallization from ether gave ketone melting at 113–114°, $[\alpha]_D^{25}$ +38° (ethanol, *c*, 0.92) [reported (19) m.p. 114°, $[\alpha]_D^{25}$ +37° (ethanol, *c*, 0.62)].

The *oxime* was prepared as directed (19) and melted at 245–247° [reported (19) m.p. 244–245°]; $[\alpha]_D^{25}$ −24.6° (dioxane, *c*, 1.017).

SUMMARY

Dihydromorphinone, dihydrocodeinone, and dihydropseudocodeinone have been prepared in 71, 83, and 40% yield, respectively, from dihydromorphine, dihydrocodeine, and dihydroallopseudocodeine by Oppenauer oxidation.

Dihydroisocodeine and dihydropseudocodeine have been found to be relatively inert to Oppenauer oxidation.

Stereochemical considerations, based on the mechanism of the Oppenauer oxidation, indicate that the hydroxyl and α-substituent in codeine and allopseudocodeine are *cis*, whereas they are *trans* in isocodeine and pseudocodeine.

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