

[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH]

The Preparation and Properties of Codeinone¹

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The present investigation was undertaken because of the reputed difficulty of preparing pure codeinone, II, by means of the chromic acid oxidation of codeine.² This difficulty seems to be due both to the sensitiveness of codeinone to the conditions necessary for its formation and to its troublesome separation from degradation products. There is recorded, to be sure, a German patent according to which this ketone is obtained in 40% yield by the addition of aqueous chromium trioxide to a solution of codeine in dilute acetic acid,³ but it seems that no ordinary ability can equal the results claimed for this method. Although codeinone has also been prepared by other impractical means,^{4,5,6} it was decided that some variation of a chromic acid oxidation would most likely afford convenient access to this ketone.

An observation made during the course of several unsuccessful efforts to duplicate the claims of the patent procedure suggested that codeinone resulted from the oxidation of a crystalline polychromate of codeine. Accordingly the action of chromium trioxide in aqueous acetic acid on the simplest chromate of codeine, prepared by metathesis from potassium chromate and codeine sulfate, was investigated. It was found that this process furnished a 14% yield of essentially pure codeinone together with a similar quantity of less

pure base and gave reproducible results over a wide variation in the scale of operations. In one experiment a small amount of hydroxycodeinone,⁷ C₁₈H₁₉NO₄, was isolated.

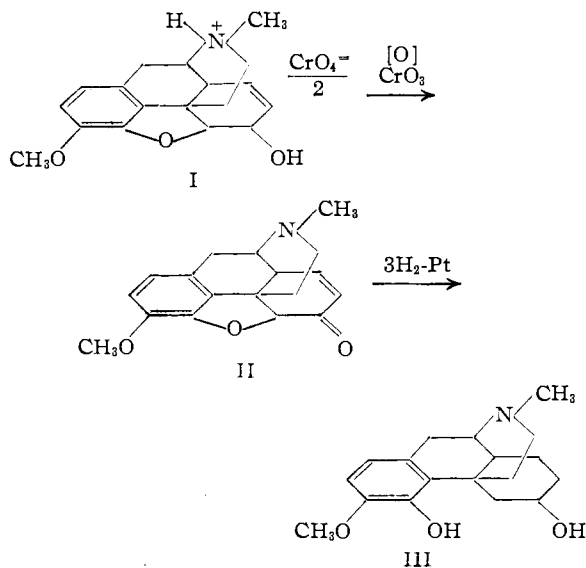
This method is not generally applicable to the conversion of alkaloid alcohols to the corresponding ketones. The simple chromates of dihydrocodeine and neopine were too soluble to permit oxidation in a heterogeneous system. Quinine chromate, though possessing the requisite insolubility, is caused to agglomerate by chromic acid in dilute acetic acid.

In preliminary experiments a number of familiar dehydrogenation processes were unsuccessfully applied to the conversion of codeine to codeinone. Codeine slowly converts benzophenone to benzopinacol in the sunlight,⁸ but no codeinone could be isolated. The alternative use of cyclohexanone as hydrogen acceptor, with Raney nickel as catalyst,⁹ resulted not in dehydrogenation but in isomerization of codeine to dihydrocodeinone in moderately good yield.

Except for the lower melting point of codeinone methiodide, the physical properties of our preparation and its derivatives are in close agreement with those found by Ach and Knorr.² Exposed to light, codeinone turns rose red, but it is apparently completely stable in the dark. Its reported irritating action on the skin was not observed by us.

It has been found that, when palladium is replaced by Adams catalyst, codeinone consumes three moles of hydrogen instead of one,¹⁰ to give a mixture from which the higher-melting form of the diastereoisomeric dihydrothebanols, III,¹¹ can be isolated in moderate yield.

Ach and Knorr referred to the conversion of codeinone to codeine but did not describe the manner of it. Later it was recorded by Hill that codeinone is reduced quantitatively to codeine by boiling aqueous sodium hydrosulfite.^{12,13} Because of the remarkable stereospecificity of such a process and also the evident lack of an authentic prototype, the reaction described was tried. Only complex transformation products of codeinone were obtained. Similar results attended the endeavor to reproduce its reported conversion to codeine with hydrazine hydrate.¹² Inasmuch as the solubility in alcohol of Hill's starting ma-



(1) This investigation was aided by award of a United States Public Health Service Postdoctorate Fellowship to S. P. F.

(2) Ach and Knorr, *Ber.*, **36**, 3067 (1903).

(3) E. Merck, German Patent 408,770; *Frdl.*, **14**, 1303 (1921-1925).

(4) Knorr and Hörlein, *Ber.*, **40**, 4890 (1907).

(5) Knorr, *ibid.*, **39**, 1409 (1906).

(6) Freund, *ibid.*, **39**, 844 (1906).

(7) Freund and Speyer, *J. prakt. Chem.*, **94**, 135 (1910).

(8) Cf. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Company, New York, N. Y., 1941, p. 202.

(9) Kleiderer and Kornfeld, *J. Org. Chem.*, **13**, 455 (1948).

(10) Mannich and Löwenheim, *Arch. Pharm.*, **258**, 295 (1920).

(11) Skita, Nord, Reichert and Stukart, *Ber.*, **54**, 1560 (1921).

(12) K. A. T. Hill, Dissertation, Frankfurt a/M, 1925.

(13) Cf. Small and Lutz, "Chemistry of the Opium Alkaloids," United States Government Printing Office, Washington, 1932, p. 247.

terial was considerably greater than ours, the conjecture is that he mistakenly began with codeine which is much more soluble than codeinone in this solvent.

On long standing in dilute hydrochloric acid codeinone, $C_{18}H_{19}NO_3$, is transformed to a phenolic, higher-melting substance, $C_{18}H_{21}NO_4$, by addition of the elements of water. The new base reacts with hydroxylamine to give what is apparently an oxime. Also, it readily consumes one mole of hydrogen in the presence of Adams catalyst to furnish a phenolic dihydro base. An investigation of this compound is in progress.

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Experimental¹⁴

Preliminary Oxidation Experiments.—A mixture of codeine (10 g.), redistilled cyclohexanone (100 ml.), dry toluene (300 ml.), and Raney nickel (20 g.) was refluxed for twenty-four hours.⁹ The catalyst was removed and the base shaken into *N* hydrochloric acid. After making ammoniacal the aqueous phase was extracted several times with ether and the base removed. Three crystallizations from ethyl acetate furnished 3 g. (30%) of dihydrocodeinone, m. p. 193.5–195.5°; no depression of melting point after mixture with an authentic sample of dihydrocodeinone. Its oxime had m. p. 259–264° dec., (reported, 264°) and it had $[\alpha]^{20}_D -174^\circ$ (*c*, 0.9, 98% alcohol).

On long standing in sunlight a mixture of codeine, benzophenone, and tertiary butanol deposited benzopinacol, but no codeinone could be isolated.⁸

Observations on the Patent Procedure.—According to this method by adding chromium trioxide to a solution of codeine in aqueous acetic acid and rubbing, a chromate salt of codeinone is formed which on appropriate treatment gives 40% of pure codeinone. Several experiments, in each of which 20 g. of codeine was used, demonstrated that, on this scale of operations at least, this process is unreliable. Even in the most successful experiments the crude product aggregated less than 40% of the theoretical yield and contained phenolic impurities which were difficult to remove.

Codeinone. (a) **Preparation of Codeine Chromate.**—Codeine sulfate pentahydrate (115 g.) dissolved in 1 l. of hot water was cooled to 40° and the supersaturated solution mixed with 31 g. of potassium chromate in 200 ml. of water. Shiny yellow plates of the chromate precipitated at once. Like such compounds as ammonium dichromate and ammonium hexabromohypoantimonate, the ionic components of which do not fit well together, codeine chromate has a low thermal stability, decomposition beginning about 45°.

Anal. Calcd. for $(C_{18}H_{22}NO_3)_2CrO_4 \cdot 5H_2O$: C, 53.6; H, 6.8; N, 3.5; Cr_2O_3 , 9.4. Found: C, 55.3; H, 6.7; N, 3.2; Cr_2O_3 , 9.0.

(b) **Oxidation of Codeine Chromate.**—To a suspension of 20 g. of finely divided codeine chromate in 80 ml. of water at 38° was added dropwise with stirring a solution of 3.64 g. (10% excess) of chromium trioxide in 25 ml. of water and 18.2 ml. of 6.0 *N* acetic acid over a period of ten minutes. The mixture was stirred three and one-half hours during which interval the chromate salt, under the influence of the added chromic acid, changed in color from yellow to orange to brick red and ultimately to light greenish yellow. The salt was filtered off, washed, and immediately added to and shaken with 300 ml. of 1.5 *N* ammonia and 2 l. of ether. The ether phase was washed with water, several times with 100 ml. volumes of molar sodium hydroxide to remove phenolic by-products, and again

with water. The chilled ether solution was extracted with 70 ml. and 30 ml. portions of 1 *N* sulfuric acid. The combined acid extracts were neutralized at once with molar sodium hydroxide and the dried, white precipitate (6.5 g.) crystallized twice from ethyl acetate: 2.0 g. (14%), m. p. 182–182.5°, $[\alpha]^{20}_D -202.5 \pm 0.5^\circ$ (*c*, 0.81, 99% alcohol). About the same quantity of crude material can be recovered from the mother liquors. The above method is superior to older procedures in reproducibility and in furnishing better yields by minimizing the formation of phenolic by-products. Knorr considered these impurities to be codeine and eliminated them by laborious fractional crystallization.² Likewise it has been found in this investigation that the picrate and sulfate prepared from crude codeinone are not readily purified by fractional crystallization.

Hydroxycodeinone.—The filtrate from the chromate salt contains phenolic by-products and some codeinone which mixture can be recovered by adding alkali and extracting with ether. In a large scale operation this material was found to contain a small amount of insoluble, high-melting base which was separated from the accompanying impurities by its insolubility in ethyl acetate. From ethyl acetate it furnished a *methiodide*, m. p. 249.5°, and crystallized from benzene in brown rosettes, m. p. 268–269.5° (reported 275°).

Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 69.1; H, 6.12; N, 4.47. Found: C, 69.1; H, 6.11; N, 4.38.

Properties of Codeinone.—Codeinone, recrystallized to constant rotation from ethyl acetate, consists of colorless prisms: m. p. 181.5–182.5° (reported, 185°) and $[\alpha]^{20}_D -205^\circ$ (*c*, 0.8, 99% alcohol) (reported, -205^{02}) and -218° (*c* 1.1 chloroform). It sublimes about 140° (0.3 mm.). At 20°, 10 ml. of pure ether dissolves 0.017 g. of the ketone.

Codeinone methiodide, prepared in ethyl acetate, was crystallized three times from water: m. p. 175° (reported, 180°).²

Codeinone hydrochloride was prepared in and crystallized from water; m. p. 180–181°.

Anal. Calcd. for $C_{18}H_{19}NO_3 \cdot HCl + H_2O$: C, 61.4; H, 6.31. Found: C, 61.4; H, 6.40.

Codeinone sulfate was prepared in and purified from water, m. p. 176–177°.

Anal. Calcd. for $(C_{18}H_{19}NO_3)_2 \cdot H_2SO_4 + H_2O$: C, 60.8; H, 5.95. Found: C, 61.2; H, 5.95.

Codeinone picrate was purified from 70% alcohol, shiny, yellow prisms, m. p. 208.5° (dec., reported, 205°). From equivalent amounts of hydroxylamine hydrochloride and the ketone in hot absolute alcohol codeinone oxime hydrochloride precipitated. It was crystallized twice from absolute alcohol: tiny prisms, m. p. 258°, (dec. reported 260°). Codeinone oxime, crystallized from absolute alcohol as white needles; m. p. 209–210° (dec., reported, 212°). Heating the oxime at 125° (2 mm.) for six hours effected little or no loss of the alcohol of solvation.

Anal. Calcd. for $C_{18}H_{20}N_2O_3 + C_2H_5OH$: C, 67.1; H, 7.32; $CH_3O + C_2H_5O$, 21.2. Found: C, 67.4; H, 7.18; $CH_3O + C_2H_5O$, 20.3.

Codeinone 2,4-dinitrophenylhydrazone was purified from hot chloroform by adding alcohol; orange tablets, m. p. 261° (*in vacuo*).

Anal. Calcd. for $C_{24}H_{23}N_3O_6$: C, 60.4; H, 4.87. Found: C, 60.4; H, 4.88.

Dihydrothebainol.—Two grams (0.0067 mole) of codeinone in 100 ml. of alcohol consumed about 0.020 mole of hydrogen in the presence of Adams catalyst. The catalyst-free solution was concentrated *in vacuo* when about 0.6 g. of granular product separated. This was crystallized several times from ethyl acetate: small prisms, m. p. 168–169° (no m. p. depression on admixture with an authentic sample of dihydrothebainol), $[\alpha]^{20}_D -28^\circ$ (*c*, 0.72, alcohol; reported, -36.5^{11}). Its methiodide melted at 273.5–274° and at 276° *in vacuo* (reported, 273°¹⁰) and its picrate at 202–203°.

(14) All melting points are corrected.

Reduction Experiments.—A mixture of 10 ml. of water, 1.0 g. of sodium hydrosulfite, and 0.5 g. of codeinone was refluxed ten minutes, cooled, made alkaline with ammonia, and extracted with ether. From the dried solvent 0.1–0.2 g. of white residue was recovered. Though not all of the alkaloid was removed from the aqueous phase, an acidified portion gave a negative Mayer test. Perhaps the alkaloid is converted by this treatment in part to compounds similar to the codine oxide sulfonic acids. The ether-soluble residue was only partially soluble in ethyl acetate. Furthermore, the soluble material gradually underwent a change as indicated by its increasing insolubility in this solvent. Its melting point was 140–165°. Although it has been reported that under such conditions codeinone is reduced quantitatively to codeine^{12,13} none of the latter was found to result from the above treatment.

A mixture of 0.50 g. of codeinone, 1.43 g. of 42% aqueous hydrazine and 10 ml. of absolute alcohol was heated at 70°. The mixture soon became yellow. After fifteen minutes, it was diluted with water and cooled. The yellow amorphous product which separated furnished no crystalline material from aqueous alcohol and was insoluble in ether.

Acid Transformation Product.—A solution of 7.5 g. of codeinone in 750 ml. of *N* hydrochloric acid was set aside for thirty days, made neutral with solid potassium carbonate, and extracted twice with 150-ml. volumes of chloroform to remove unreacted codeinone. The aqueous phase was made strongly alkaline with carbonate and extracted several times more with chloroform. Recovered from the chloroform, the base (about 3 g.) was crystallized three times from ethyl acetate: irregular plates, *m. p.* 200° [α]_D²⁰ –135° (*c.* 0.92, alcohol). The base is soluble in alcohols and water as well as in chloroform and hot ethyl acetate; insoluble in ligroin. Inasmuch as it gives a red color with diazosulfanilic acid, it is presumably phenolic.

Anal. Calcd. for C₁₈H₂₁NO₄: C, 68.7; H, 6.73; N, 4.44. Found: C, 68.7, 68.6; H, 6.72, 6.84, N, 4.50.

With hydroxylamine hydrochloride it gave a salt, *m. p.* 262° (*in vacuo*), which on basification furnished what is presumed to be the free oxime, *m. p.* 274°. The analytical data for this derivative appear anomalous and are, therefore, reserved.

The dihydro derivative is obtained in good yield by hydrogenation of the new product in alcohol using Adams catalyst. Three crystallizations from ethyl acetate afforded pure material: stout hexagons and prisms, *m. p.* 207°; [α]_D²⁰ –115° (*c.* 0.8, alcohol). With diazosulfanilic acid it furnished a red dye, presumably a phenol.

Anal. Calcd. for C₁₈H₂₃NO₄: C, 68.2; H, 7.32. Found: C, 68.3; H, 7.32.

Chromate of Neopine.—When a warm solution containing stoichiometric quantities of neopine hydrobromide and potassium chromate was cooled, neopine hydrobromide precipitated. The chromate obtained from a concentrated solution of the hydrochloride and potassium chromate was obtained in relatively small amount and was contaminated by darker products from the spontaneous degradation of this salt.

Chromate of Dihydrocodeine.—Dilute (1 *N*) hydrobromic acid was added to the base until the solution was only slightly basic to methyl red. Then a slight excess of solid potassium chromate was dissolved in this solution; yellow, transparent rhombohedra of the chromate separated on standing. These effloresce in air to opaque, chrome yellow prisms.

Anal. Calcd. for (C₁₈H₂₄O₃N)₂CrO₄: C, 60.1; H, 6.72; N, 3.89; Cr₂O₃, 10.5. Found: C, 59.0; H, 6.45; N, 3.76; Cr₂O₃, 10.42.

Chromate of Quinine.—This salt was prepared by mixing a dilute solution of quinine hydrochloride with aqueous potassium chromate.

Anal. Calcd. for (C₂₀H₂₅N₃O₂)₂CrO₄·2H₂O: C, 59.8; H, 6.78; N, 6.98; Cr₂O₃, 9.92. Found: C, 60.0; H, 6.99; N, 6.71; Cr₂O₃, 9.03.

Addition of chromic acid in dilute acetic acid to the chromate suspended in water caused it gradually to collect in an orange sticky mass which impeded stirring. The reaction was not studied further.

Summary

1. It has been found that a suspension of codeine chromate is oxidized by chromium trioxide to codeinone, and from this observation a reliable method for preparing this ketone has been developed. Unfortunately this process for obtaining a ketone from a basic alcohol is not generally applicable.

2. Attempts to convert codeine to codeinone by dehydrogenation were unsuccessful.

3. Certain of the physical and chemical properties of codeine are described.

4. It was discovered that in hydrochloric acid solution codeinone is transformed into a new base, C₁₈H₂₁NO₄.

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The Preparation and Degradation of 6-Methylcodeine¹

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In continuance of the search for compounds having improved analgesic characteristics, the preparation and properties of 6-methylcodeine have been investigated. Although ketones derived from the morphine alkaloids (*e. g.*, codeinone² and dihydrocodeinone³) do not react readily with Grignard reagents in the customary manner, Small and Rapoport demonstrated

recently that dihydrocodeinone and dihydro-morphinone do react with organolithium reagents to furnish the anticipated tertiary alcohols.⁴ However, from codeinone (A) and methylolithium they were unsuccessful in isolating pure 6-methylcodeine (B), a failure which was ascribed to the quality of the ketone.

The method for preparing codeinone having been improved,⁵ it has been found that methylolithium acts upon codeinone to furnish the ex-

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(2) Small and Lutz, "Chemistry of the Opium Alkaloids," United States Government Printing Office, Washington, D. C., 1932, p. 248.

(3) Lutz and Small, *THIS JOURNAL*, **57**, 2651 (1935).

(4) Small and Rapoport, *J. Org. Chem.*, **12**, 284 (1947).

(5) Findlay and Small, *THIS JOURNAL*, **72**, 3247 (1950).