[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Addition of Organomagnesium Halides to Pseudocodeine Types. II. Preparation of Nuclear Alkylated Morphine Derivatives[1]

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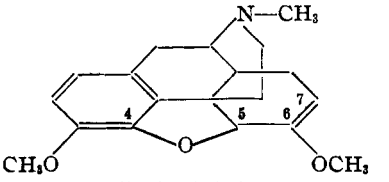
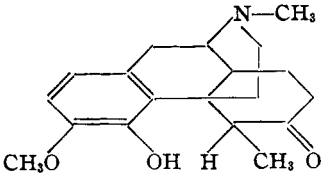
Derivatives of the morphine alkaloids having an alicyclic unsaturated linkage in the β,γ-position to the 4,5-ether linked oxygen atom (*i. e.*, allyl ether types) show a general tendency to undergo reduction or addition reactions in which both the ether oxygen and the double bond are involved.[3] In previous papers we have demonstrated that organomagnesium halides react with pseudocodeinone and desoxycodeine-C to yield phenolic bases containing the organic radical of the Grignard compound used,[4] probably at the 5- or 7-position in the nucleus. The present communication deals with the application of this reaction to dihydrothebaine and with the transformation of the product into a series of nuclear alkylated dihydromorphine derivatives.

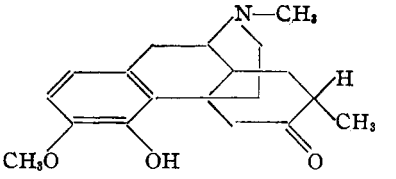
The structure of dihydrothebaine (I), at least as far as the position of the alicyclic unsaturation is concerned, is amply demonstrated by the facile hydrolysis to dihydrocodeinone,[5] and by the behavior toward ozone.[6] The double bond is located as in pseudocodeine and desoxycodeine-C; nevertheless, under the ordinary conditions imposed for reaction with Grignard's reagent, dihydrothebaine is not appreciably affected, a fact which may be attributed in part to its low solubility in ether, and perhaps in part to the presence of the enol ether group. When dihydrothebaine is extracted from a Soxhlet apparatus into boiling ethereal methylmagnesium iodide an addition compound slowly separates, and at the end of five days no more dihydrothebaine can be detected. The product consists principally of a phenolic ketone, methyldihydrothebainone (tentative formula II or III) and in small amount (10% yield), of an isomeric substance, isomethyldihydrothebainone. The enol ether group present in the starting material has been hydrolyzed, either during the reaction or more probably during the isolation of the reaction products, which is necessarily accomplished with the use of acidic reagents. In this respect the dihydrothebaine reaction presents a striking contrast to that of thebaine, where the products (phenyldihydrothebaine or the methyldihydrothebaines) are extremely resistant to hydrolysis. An enol ether of instability com-



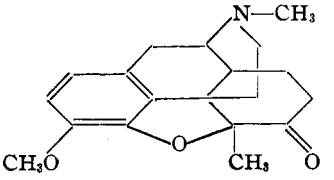
I. Dihydrothebaine



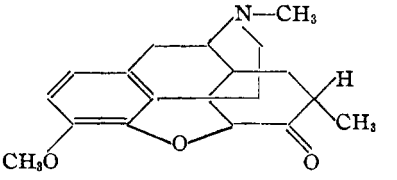
II. 5-Methyldihydrothebainone



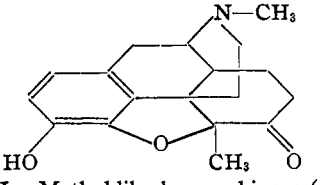
III. 7-Methyldihydrothebainone



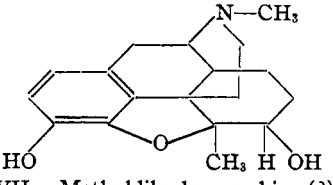
IV. 5-Methyldihydrocodeinone



V. 7-Methyldihydrocodeinone



VI. Methyldihydromorphinone (?)



VII. Methyldihydromorphine (?)

(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia and the University of Michigan.

(2) Squibb Fellow in Alkaloid Chemistry.

(3) (a) Schöpf and Winterhalder, *Ann.*, **452**, 237 (1927); (b) Small and Cohen, THIS JOURNAL, **53**, 2214 (1931); (c) Lutz and Small, *ibid.*, **54**, 4715 (1932); (d) Morris and Small, *ibid.*, **56**, 2159 (1934).

(4) (a) Lutz and Small, *ibid.*, **57**, 2651 (1935); (b) Small and Yuen, *ibid.*, **58**, 192 (1936).

(5) Freund, Speyer and Guttmann, *Ber.*, **53**, 2250 (1920).

(6) Wieland and Small, *Ann.*, **467**, 17 (1928).

parable to that of the hypothetical intermediate methyldihydrothebainone methyl enolate has, however, been isolated in this Laboratory during the reduction of thebaine by the Wieland and Kotake procedure.[7]

The presence of the ketone group at C–6 in methyldihydrothebainone implies an active methylene group at C–5 (III) or at C–7 (II), depending upon whether methylmagnesium iodide has added to dihydrothebaine in the 1,4- or 1,2-manner. Schöpf has demonstrated for dihydrothebainone and for dihydrometathebainone the feasibility of reforming the 4,5-oxide bridge characteristic of the naturally-occurring bases of the morphine series.[8] The compound of formula III (and possibly II) should undergo ether ring closure under similar conditions. Methyldihydrothebainone reacts with two moles of bromine to form a dibromo derivative (not isolated), which on treatment with cold dilute sodium hydroxide is converted to the non-phenolic 1(?)-bromomethyldihydrocodeinone. Elimination of bromine (catalytic hydrogen) yields IV or V, methyldihydrocodeinone. By this series of reactions we arrive at the first known nuclear alkylated derivative of the morphine group.

It has been found by repeated experiments in this Laboratory[9] that dihydrocodeinone can be reduced at the carbonyl group by the catalytic method to give dihydrocodeine, with no detectable amount of the epimer, dihydroisocodeine. Methyldihydrocodeinone, under the same conditions, takes up one mole of hydrogen with formation of methyldihydrocodeine, in which the codeine configuration for the alcoholic hydroxyl group is assumed on the basis of the above cited evidence.

Like most saturated derivatives of the morphine series, the compounds of the group described in this communication are relatively stable toward rearrangement or decomposition in the presence of concentrated halogen acids, and methyldihydrocodeinone can be demethylated smoothly with 48% hydrobromic acid. The product is methyldihydromorphinone (VI), a homolog of the well known drug dihydromorphinone ("Dilaudid"). Methyldihydromorphinone can be reduced at the ketone group, with formation of methyldihydromorphine (VII).[10] The relationship of the latter to the above-mentioned methyldihydrocodeine was established by methylation with diazomethane.

Isomethyldihydrothebainone can be separated from the main reaction product through differences in solubility of the respective hydrochlorides and ultimately through its properties as a cryptophenol. The presence of the phenolic hydroxyl is shown by the formation of an acetyl derivative and by the solubility in alkali, from which, however, in contrast to methyldihydrothebainone, the base can be extracted with ether. On treatment with two moles of bromine, and subsequently with dilute alkali, isomethyldihydrothebainone yields a non-phenolic product, bromoisomethyldihydrocodeinone (not crystalline), which can be debrominated to isomethyldihydrocodeinone (Formula IV or V ?). The demethylation and reduction reactions which will lead to the isomethyldihydromorphinone and isomethyldihydromorphine types have been postponed until more material is available.

Determination of the position of the new methyl group in methyldihydrocodeinone presents serious difficulty, and definite proof will probably be obtained only by degradation. This is at present not practicable because of lack of material. It is certain that in the bromination of methyldihydrothebainone and its isomer one bromine atom enters at C–5, else the ether ring closure would not be possible. This fact may indicate that the methyl group occupies C–7, for it has been shown that in the bromination of 1-methylcyclohexanone, bromine substitutes at the methylene group adjacent to the carbonyl in preference to the methenyl group.[11] Furthermore, the presence of a methyl group on C–5 might well be expected to offer some hindrance to closure of the ether ring. If this reasoning were valid, then isomethyldihydrothebainone would be easily accounted for as a diastereomer, the methyl group having added at C–7 in both possible configurations. The last hypothesis is susceptible of direct proof. If methyldihydrocodeinone and isomethyldihydrocodeinone differ only in the configuration at C–7, their enol acetates must be identical[12] (V, V-a $\longrightarrow$ VIII).

Both methyldihydrocodeinone and isomethyldihydrocodeinone can be acetylated under the conditions which are imposed to transform dihydrocodeinone to its enol acetate ("Acedicon").

(7) Small, Morris and Browning, unpublished results.

(8) Schöpf and Pfeifer, *Ann.*, **483**, 157 (1930); Schöpf and Perrey, *ibid.*, **483**, 169 (1930).

(9) David E. Morris, unpublished results.

(10) Formulas VI and VII are offered with reservation concerning the position of the methyl group.

(11) Kötz and Steinhorst, *Ann.*, **379**, 10, 15 (1911).

(12) This reasoning does not take into account the possibility of an enolization in which the hydrogen atom located on C-5 might participate.

The "methylacedicons" which are obtained from the isomeric ketones can scarcely be other than enol acetates, as is indicated by the ease with which they can be hydrolyzed back to the starting ketones, but they are not identical, a fact which we regard as weighing in favor of the 5-position for the new methyl group.

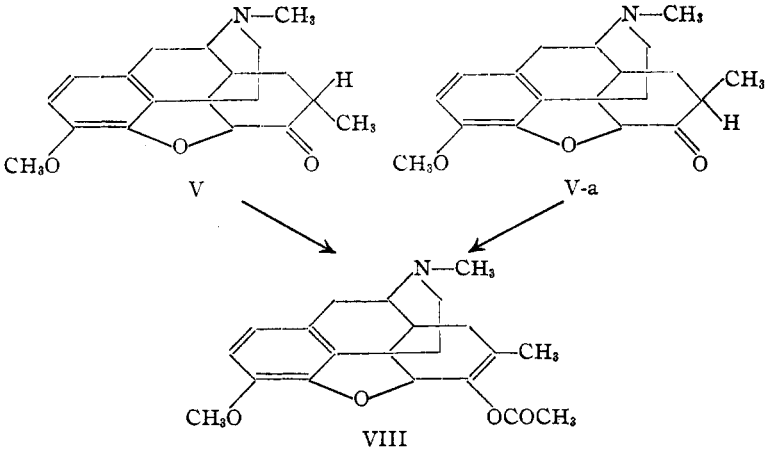
We have not neglected the possibility that methyldihydrothebainone and isomethyldihydrothebainone might have been formed by competing 1,2- and 1,4-additions of methylmagnesium iodide to the ether oxygen, double bond system of dihydrothebaine. The products in this case would owe their isomerism to the position of the methyl group at C–5 and C–7 (Formulas II and III), and, of the isomeric methyldihydrocodeinones, the 5-methyldihydrocodeinone (IV) should contain an active methylene group, in contrast to 7-methyldihydrocodeinone (V). An answer to this question was sought in the condensation reaction with ethyl oxalate according to Claisen,[13] a reaction which proceeds with methylene, but not with methenyl, groups adjacent to a carbonyl. Both of the methyldihydrocodeinones reacted with ethyl oxalate in the presence of absolute alcoholic sodium ethylate (although they were not affected by sodium ethylate alone), which again points to a location of the methyl group in two configurations at C–5. Against any final conclusion to be drawn from the evidence here presented we wish to cite the rather convincing stereochemical speculations of Schöpf,[14] which make it seem doubtful whether a 4,5-ring closure in more than one configuration would be possible.

The fact that one of the methyldihydrothebainones behaves as a cryptophenol while the other is normal in its phenolic nature suggests to us a greater structural difference than diastereoisomerism at C–5. Furthermore, when methyldihydrocodeinone is converted to its enol acetate, the specific rotation is changed only from −147 to −143°, while in the case of isomethyldihydrocodeinone the change is from −179 to −250°, indicating that in the latter an asymmetric center (C–7) may have been disturbed.

(13) Claisen and Stylos, *Ber.*, **20**, 2188 (1887); *ibid.*, **24**, 111 (1891); Willstätter, *ibid.*, **30**, 2684 (1897).

(14) Schöpf and Pfeifer, *Ann.*, **483**, 162–164 (1930).

Incidentally, if it can be proved that the methyl group in one of our methyldihydrothebainones is located at C–5, the Knorr–Wieland formula for morphine (which we do not regard as yet disproved) will be put out of all question, for a linkage of the ethanamine chain at C–5 would exclude bromination and subsequent ring closure at this point.



The pharmacological action of the dihydromorphine and dihydrocodeine homologs described in this communication will be reported from the University of Michigan by N. B. Eddy and coworkers. The chemical studies in the series will be extended to embrace further conversion products of these bases (especially the desoxylated derivatives) and to include the introduction of groups other than methyl.

It is a pleasure to acknowledge our indebtedness to Merck and Co., Rahway, N. J., for the gift of the large amount of thebaine used in this research, and to E. R. Squibb and Sons for the fellowship grant under which most of the work was carried out.

Experimental Part

Dihydrothebaine.—The conditions influencing the hydrogenation of thebaine in acid solution have been so thoroughly studied by Schöpf and Winterhalder[3a] that we shall confine our description of the reduction to the convenient large scale preparation of dihydrothebaine without regard to the by-products formed. To a solution of 75 g. of thebaine (Merck and Co., Rahway, N. J.) in 150 cc. of 3 *N* acetic acid was added 4 cc. of concd. hydrochloric acid, 4 cc. of 1% palladous chloride solution and 0.1 g. of gum arabic. The solution was hydrogenated on the Adams machine at an initial pressure of 46 lb. (3.1 atm.); the pressure dropped 32 lb. (2.1 atm.) in twelve to twenty-four hours, corresponding to absorption of about 1.7 moles of hydrogen. Reduction was found to proceed much faster and more smoothly if the process was made continuous, the next 75 g. batch being put immediately

into the pressure bottle without removal of the residue of used catalyst.

Most of the colloidal palladium was removed by filtration through Norit, and the solution was treated slowly with an excess of dilute sodium hydroxide in the presence of a few cc. of ether. Dihydrothebaine separated crystalline, yield 30 to 40 g. (40–54%). It was recrystallized from alcohol, filtering to remove traces of palladium; 25 g. (33%) of pure white dihydrothebaine, m. p. 161–163°, was obtained, and from the mother liquors, 3 g. more of the same purity. Three kilos of thebaine yielded 1099 g. (36.4%) of dihydrothebaine. The alkaline mother liquors of a 75-g. run gave 15–20 g. of dihydrothebainone on treatment with ammonium chloride. The accumulated oily residues will be examined for the presence of Schöpf's epidihydrothebainone or other isomers.

The Grignard Reaction.—Forty grams of dihydrothebaine in a Soxhlet extractor, on a three-necked flask equipped with a mercury-sealed stirrer, was extracted into 600 cc. (500% of the calculated amount) of molar methylmagnesium iodide in thirty-six hours. Heating and stirring was continued for seventy-two hours longer, during which time the white precipitate increased notably. Attempts to shorten the reaction time by using isopropyl ether were unsatisfactory. The amorphous magnesium complex was decomposed with and dissolved in 800 cc. of 3 *N* hydrochloric acid, and the solution was extracted with 1.5 liters of ether, which removed a little oily material. The aqueous layer, made alkaline with ammonia, was extracted with eight liters of ether, with occasional addition of a little sodium hydrosulfite to prevent oxidation (evidenced by red coloration). Although further extraction with ether or chloroform removed no appreciable amount of material at this point, the aqueous layer gave a strong test with Mayer's reagent, and addition of picric acid precipitated 26 g. (37%) of an amorphous picrate. From this picrate only 1.6 g. of methyldihydrothebainone could be recovered, and the nature of the remaining (resinous) substance could not be ascertained. The ether extracts yielded 18 to 23 g. (45–58%) of oily crystals, which were recrystallized twice from absolute alcohol; yield of pure methyldihydrothebainone, 6 to 7 g. (15–17.5%). The alcohol mother liquors were concentrated and treated with alcoholic hydrogen chloride, giving 6 to 7 g. of hydrochloride, from which 4 to 6 g. of less pure methyldihydrothebainone could be recovered.

The alcohol filtrate from precipitation of the hydrochloride was freed of alcohol, dissolved in water, and treated with excess of sodium hydroxide. The clear alkaline solution was extracted with ether, from which 3.5 to 4.5 g. (9–11%) of crude isomethyldihydrothebainone was obtained. This was purified from acetone; yield 2 to 2.5 g.

Methyldihydrothebainone.—The base is very soluble in organic solvents, soluble in sodium hydroxide and precipitated from the alkaline solution by carbon dioxide. It can be purified from acetone or alcohol. It crystallizes in short rods from absolute alcohol, in plates from 95% alcohol, and the two forms are interconvertible. It sublimes in an oil-pump vacuum at 130°. In alcohol, $[\alpha]^{25}D$ −20.5° (c = 1.026) was found; the m. p. is 192–193°.

Anal. Calcd. for $C_{19}H_{25}O_3N$: C, 72.33; H, 7.99; OCH_3, 9.83. Found: C, 72.11; H, 7.96; OCH_3, 10.13.

The hydrochloride was prepared in absolute alcohol and purified from this medium. It also crystallizes well from water, m. p. 283–285° (evac. tube) with decomp.; $[\alpha]^{25}D$ −6.8° (water, c = 1.025).

Anal. Calcd. for $C_{19}H_{26}O_3NCl$: Cl, 10.08. Found: Cl, 10.18.

The methiodide was prepared by warming the base in methyl iodide, and was purified from acetone; m. p. 212–216° (evac. tube); $[\alpha]^{26}D$ +3.9° (water, c = 1.030).

Anal. Calcd. for $C_{20}H_{28}O_3NI$: I, 27.88. Found: I, 27.63.

The oxime hydrochloride separates crystalline when an aqueous suspension of methyldihydrothebainone is warmed with the calculated amount of hydroxylamine hydrochloride. After two crystallizations from water the hydrochloride had the m. p. 244° (evac. tube, gas evolution) and $[\alpha]^{24}D$ +38.9° (water, c = 0.514). Addition of sodium carbonate to an aqueous solution of the oxime hydrochloride caused precipitation of the oxime, which crystallized from dilute alcohol in rosets of white needles; m. p. 244° (evac. tube, gas evolution), and $[\alpha]^{24}D$ +69.4° (alcohol, c = 0.504).

Anal. Calcd. for $C_{19}H_{26}O_3N_2$: N, 8.48. Found: N, 8.51.

Acetylmethyldihydrothebainone.—One gram of methyldihydrothebainone in 15 cc. of acetic anhydride with 1.0 g. of dry sodium acetate was heated under reflux for one hour. After removal of excess acetic anhydride under diminished pressure at 60°, the oily residue was treated with ice and dilute ammonia, and extracted with ether. The product was recrystallized twice from ethyl acetate and sublimed at 0.01 mm., yield 0.4 g., of m. p. 179–179.5°. Prolonged heating with acetic anhydride yielded no diacetyl derivative. The monoacetyl compound has $[\alpha]^{26}D$ +13.1° (alcohol, c = 0.992).

Anal. Calcd. for $C_{21}H_{27}O_4N$: C, 70.55; H, 7.62. Found: C, 70.87; H, 7.81.

Bromomethyldihydrocodeinone.—A solution of 20 g. of methyldihydrothebainone in 200 cc. of glacial acetic acid, mechanically stirred, was treated dropwise with 193 cc. (2 moles) of a solution of bromine in glacial acetic acid (32 g. of bromine in 300 cc. of solution). The addition took about three hours, the bromine color being destroyed rapidly and hydrogen bromide evolved. The clear yellow solution was concentrated to a viscous mass at 70° under a water-pump vacuum, the oil was dissolved in water, treated with excess of 10 *N* sodium hydroxide, and the precipitated base extracted into ether. The ether was washed with four 100-cc. portions of normal sodium hydroxide and yielded 18.2 g. (73%) of slightly oily crystals of bromomethyldihydrocodeinone. The base is very soluble in organic media, but could be purified from ethyl acetate; white crystals of m. p. 143.5–145°; $[\alpha]^{24}D$ −109.4° (alcohol, c = 1.024). It sublimed in a high vacuum with slight decomposition.

Anal. Calcd. for $C_{19}H_{22}O_3NBr$: Br, 20.33. Found: Br, 20.08.

Bromomethyldihydrothebainone.—The alkaline mother liquor and washings from the preparation of bromomethyldihydrocodeinone were treated with an excess of

ammonium chloride and extracted with ether until the Mayer's test was negative. The product was 4.1 g. of yellow powder which was obtained white by crystallization from acetone or ethyl acetate; it sublimes with slight decomposition in a high vacuum. The m. p. is 207–208° (evac. tube) with dec., $[\alpha]^{24}D$ −33.2° (alcohol, c = 0.995). Its nature as bromomethyldihydrothebainone was shown not only by analysis, but by catalytic debromination to methyldihydrothebainone. It appears to result from incomplete bromination of methyldihydrothebainone, but the use of correspondingly larger quantities of bromine did not increase the yield of the desired bromomethyldihydrocodeinone.

Anal. Calcd. for $C_{19}H_{24}O_3NBr$: Br, 20.23. Found: Br, 20.14.

Methyldihydrocodeinone.—A solution of 18.2 g. of crude bromodihydrocodeinone in 200 cc. of 2 *N* acetic acid with 5 g. of potassium acetate, a little gum arabic and 10 cc. of 1% palladous chloride solution took up 1142 cc. (corr.) of hydrogen (calcd. for one mole, 1062 cc.). The solution was made alkaline with sodium hydroxide after removal of the catalyst, and extracted with 2 liters of ether. The ether, after thorough washing with dilute alkali, yielded 12.0 g. (83%) of white crystalline methyldihydrocodeinone of m. p. 138–140°. The alkaline extracts gave 1.5 g. of a wax-like unidentified solid. Methyldihydrocodeinone is very soluble in organic media, but can be purified from ethyl acetate, acetone, or ether; long needles of m. p. 144–144.5°, $[\alpha]^{23}D$ −146.9° (alcohol, c = 0.994). It sublimes at 130° in a high vacuum.

Anal. Calcd. for $C_{19}H_{23}O_3N$: C, 72.80; H, 7.40. Found: C, 72.71; H, 7.41.

The methiodide was prepared by warming the base with methyl iodide, and crystallizing from alcohol. It melts at 246–248° (evac. tube) and has $[\alpha]^{24}D$ −74.2° (water, c = 1.024).

Anal. Calcd. for $C_{20}H_{26}O_3NI$: I, 27.88. Found: I, 27.67.

The oxalate, sulfate and hydrochloride are also crystalline.

Ethyl Oxalate Condensation.—Before attempting to demonstrate the presence of an active methylene group in methyldihydrocodeinone through Claisen's ethyl oxalate condensation, it was necessary to show that this condensation reaction proceeds with morphine bases which are known to contain an active methylene group, and does not take place with a typical base lacking such a group.[15] Two grams of dihydrocodeinone and 1.5 g. of ethyl oxalate were dissolved in 10 cc. of absolute alcohol containing 0.31 g. of sodium. After two days the solution was fluorescent red; removal of the alcohol left an amorphous mass, 90% of which was soluble in water and could not be extracted into ether. It probably consisted of dihydrocodeinone-7-glyoxalic acid, or its internal salt. Treatment of 2.0 g. of dihydrocodeine with ethyl oxalate in exactly the same manner resulted in recovery of 1.9 g. of unchanged dihydrocodeine.

(15) An erroneous structural concept of pseudocodeinone was for many years based on the ability of this compound to condense with benzaldehyde [Knorr and Hörlein, *Ber.*, **40**, 3341 (1907)]; it has only recently been shown that a benzaldehyde condensation takes place with dihydrocodeine, and therefore is inacceptable as evidence for the $COCH_2$ group in the morphine series (ref. 4a).

Two grams of methyldihydrocodeinone, treated with ethyl oxalate as described above, gave a red fluorescent solution in two days. Alcohol was removed under diminished pressure, and the residue extracted with 500 cc. of ether, and 200 cc. of benzene; total extracted oily material, 0.3 g. The undissolved product was taken up in a little water (readily soluble), and extracted with ether (0.2 g. of unreacted methyldihydrocodeinone), then with much benzene and chloroform, which removed a little red oil. The aqueous layer, made just acid, was treated with excess of picric acid; yield 0.7 g. of picrate. The picrate was suspended in dilute hydrochloric acid, and extracted with isoamyl alcohol until all picric acid was removed. Evaporation of the aqueous layer gave the crystalline hydrochloride of methyldihydrocodeinone glyoxalic acid, which could be purified by recrystallizing from 3 *N* hydrochloric acid.

Anal. Calcd. for $C_{21}H_{24}O_6NCl$: C, 59.76; H, 5.73; Cl, 8.41. Found: C, 59.58; H, 5.81; Cl, 8.75.

Methyldihydrocodeinone in sodium ethylate solution without the ethyl oxalate was recovered unchanged.

Methyldihydrocodeinone Enol Acetate (Methyl Acedicon).—A solution of 1 g. of methyldihydrocodeinone in 15 cc. of acetic anhydride with 1 g. of anhydrous sodium acetate was heated under reflux for six hours. Acetic anhydride was removed under diminished pressure, and the oily residue was treated with ice and ammonia and extracted with ether. The crystals obtained from the ether (0.5 g.) were purified from ethyl acetate and sublimed in a high vacuum at 150°. The pure product melted at 191.5–194.5° and had in alcohol $[\alpha]^{23}D$ −142.9° (c = 0.980).

Anal. Calcd. for $C_{21}H_{25}O_4N$: C, 70.95; H, 7.10. Found: C, 70.87; H, 7.17.

On boiling the enol acetate for three minutes with 3 *N* hydrochloric acid, methyldihydrocodeinone was obtained.

Methyldihydrocodeine.—A solution of 1.9 g. of methyldihydrocodeinone in 30 cc. of alcohol with 0.1 g. of platinum oxide absorbed 183 cc. of hydrogen slowly (0.1 g. catalyst added during the reduction); calculated for one mole, 180 cc. The oil resulting from concentration of the solution crystallized when rubbed with ethyl acetate, yield 1.1 g. Methyldihydrocodeine crystallizes as the monohydrate in 8-sided crystals from acetone, ethyl acetate, ether or 50% alcohol; m. p. 98–102°, $[\alpha]^{24}D$ −84.8° (alcohol, c = 0.990).

Anal. Calcd. for $C_{19}H_{25}O_3N + H_2O$: C, 68.42; H, 8.17; H_2O, 5.41. Found: C, 68.39; H, 8.05; H_2O, 5.64.

By sublimation in a high vacuum, a crystalline anhydrous form of m. p. 85–88° is obtained.

The hydrochloride, which may be used advantageously to purify methyldihydrocodeine, was prepared in and purified from absolute alcohol. It melts at 286–287° (evac. tube) and has $[\alpha]^{23}D$ −64.5° (water, c = 0.992).

Anal. Calcd. for $C_{19}H_{26}O_3NCl$: Cl, 10.08. Found: Cl, 10.28.

The methiodide, prepared in the usual way, was purified from alcohol. It melts at 269–271° (evac. tube) and has $[\alpha]^{24}D$ −47.9° (water, c = 1.024).

Anal. Calcd. for $C_{20}H_{28}O_3NI$: I, 27.76. Found: I, 27.76.

Methyldihydromorphinone.—A solution of 2 g. of methyldihydrocodeinone in 10 cc. of 48% hydrobromic acid was boiled for twenty-five minutes (complete alkali solubility). The solution was diluted, made strongly alkaline, and extracted with ether (0.1 g. of unchanged material). Addition of ammonium chloride caused precipitation of the phenolic product, 1.7 g. of brown powder; yield after sublimation in a high vacuum at 180°, 1.4 g. of white crystals. Methyldihydromorphinone is only sparingly soluble in organic media. It crystallizes from alcohol in long needles of m. p. 243–245° (evac. tube, sintering at 235°); $[\alpha]^{24}D$ −140.7° (alcohol, c = 1.009).

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.18; H, 7.05. Found: C, 72.46; H, 7.10.

The hydrochloride was prepared in absolute alcohol and was recrystallized from alcohol. It melts with decomp. at 315–318° (evac. tube) and has $[\alpha]^{24}D$ −104.8° (water, c = 1.002).

Anal. Calcd. for $C_{18}H_{22}O_3NCl$: Cl, 10.57. Found: Cl, 10.67.

Methyldihydromorphine.—Preparation of methyldihydromorphine by demethylation of methyldihydrocodeine was unsuccessful because of extensive decomposition. A suspension of 1.4 g. of methyldihydromorphinone in 30 cc. of alcohol with 0.1 g. of platinum oxide absorbed one mole of hydrogen slowly (0.1 g. of catalyst added during the reduction). The product was isolated as in the case of methyldihydrocodeine, and was purified by crystallization from ethyl acetate and sublimation in a high vacuum at 180°; yield 1.2 g. The compound melts at 206–207° and has $[\alpha]^{24}D$ −92.9° (alcohol, c = 1.017).

Anal. Calcd. for $C_{18}H_{23}O_3N$: C, 71.71; H, 7.70. Found: C, 71.74; H, 7.72.

By methylation of methyldihydromorphine with diazomethane, the above-described methyldihydrocodeine was obtained.

Methyldihydromorphine hydrochloride was prepared in absolute alcohol and purified from alcohol. It melts at 316–317° with dec. (evac. tube) and has $[\alpha]^{23}D$ −65.7° (water, c = 1.004).

Anal. Calcd. for $C_{18}H_{24}O_3NCl$: Cl, 10.50. Found: Cl, 10.40.

The hydriodide was prepared in the usual way and purified from absolute alcohol. It melts at 289–291° (evac. tube) and has $[\alpha]^{23}D$ −50.5° (water, c = 0.991).

Anal. Calcd. for $C_{18}H_{24}O_3NI$: I, 29.58. Found: I, 29.42.

Isomethyldihydrothebainone.—This compound, isolated as described above, crystallizes from acetone in white needles of m. p. 168–168.5°. It is soluble in dilute sodium hydroxide, and is precipitated from the alkaline solution by carbon dioxide. It can be sublimed in an oil-pump vacuum at 140°. In alcohol, $[\alpha]^{24}D$ −57.0° (c = 1.023).

Anal. Calcd. for $C_{19}H_{25}O_3N$: C, 72.33; H, 7.99; OCH_3, 9.83. Found: C, 72.66; H, 8.03; OCH_3, 9.85.

The oxime was prepared by boiling an aqueous suspension of the base for several minutes with 2 moles of hydroxylamine hydrochloride. The oxime hydrochloride did not crystallize in this case, and the oxime was precipitated with sodium carbonate and recrystallized from alcohol, long silky needles of m. p. 191–192° (evac. tube, gas evolution at 210°); in alcohol, $[\alpha]^{24}D$ −82.4° (c = 0.498).

Anal. Calcd. for $C_{19}H_{26}O_3N_2$: N, 8.48. Found: N, 8.37.

Acetylisomethyldihydrothebainone.—The acetyl derivative was prepared exactly as described under methyldihydrothebainone, and was purified by crystallization from acetone and sublimation at 135° (0.01 mm.). It forms white crystals of m. p. 157–158°, $[\alpha]^{24}D$ −9.9° (alcohol, c = 0.452).

Anal. Calcd. for $C_{21}H_{27}O_4N$: C, 70.55; H, 7.62. Found: C, 70.43; H, 7.63.

Isomethyldihydrocodeinone.—A solution of 10.2 g. of isomethyldihydrothebainone in 100 cc. of glacial acetic acid was treated with 2 moles of bromine as described for methyldihydrothebainone. Acetic acid was removed at 60°, the oily product dissolved in water, treated with excess sodium hydroxide, and extracted with 3 liters of ether. The oil obtained from the ether was dissolved in hydrochloric acid, and precipitated as an amorphous powder with sodium hydroxide; yield of crude bromoisomethyldihydrocodeinone, 9.5 g. (75%). It could not be induced to crystallize. The crude product was hydrogenated as described under methyldihydrocodeinone (absorption, 1 mole) and yielded from ether 6.9 g. of crude isomethyldihydrocodeinone. It was dissolved in hydrochloric acid, and precipitated crystalline with excess of sodium hydroxide (yield 5.0 g.). Pure white crystals were obtained after two crystallizations from ethyl acetate. The compound sublimes in a high vacuum at 130°; the melting point is 144–145°. A depression of 25° is observed in the mixed melting point with methyldihydrocodeinone. In alcohol, isomethyldihydrocodeinone has $[\alpha]^{24}D$ −179.4° (c = 0.995).

Anal. Calcd. for $C_{19}H_{23}O_3N$: C, 72.80; H, 7.40. Found: C, 72.57; H, 7.32.

Condensation of isomethyldihydrocodeinone with ethyl oxalate under the conditions described above gave a water-insoluble oil from which no crystalline derivatives could be obtained. None of the ketone could be recovered unchanged from the reaction. While no analytical product could be isolated, it appears as though condensation with the ethyl oxalate must have taken place, for isomethyldihydrocodeinone was found to be largely unaffected by sodium ethylate in the absence of ethyl oxalate.

Isomethyldihydrocodeinone Enol Acetate.—Acetylation of 1 g. of isomethyldihydrocodeinone under the conditions described for methyldihydrocodeinone gave 1.1 g. of oily crystals which were purified from ethyl acetate and 50% alcohol, 0.6 g., m. p. 123–124°. It sublimes in a high vacuum at 110°; $[\alpha]^{24}D$ −250.3° (alcohol, c = 1.00).

Anal. Calcd. for $C_{21}H_{25}O_4N$: C, 70.95; H, 7.10. Found: C, 70.90; H, 7.30.

Hydrolysis of the enol acetate with 3 *N* hydrochloric acid gave isomethyldihydrocodeinone in poor yield.

Summary

1. Dihydrothebaine reacts with methylmagnesium iodide to yield two isomeric phenolic ketones, methyldihydrothebainone and isomethyldi-

hydrothebainone. In these the ether ring present in dihydrothebaine has been opened, the enol ether group at position-6 has been hydrolyzed, and a methyl group has been added to the nucleus.

2. Nuclear methylated analogs of dihydrocodeinone, namely, methyldihydrocodeinone and isomethyldihydrocodeinone, can be prepared by closure of the 4,5-ether bridge.

3. By demethylation and reduction, methyldihydrocodeinone can be converted to nuclear methylated analogs of dihydromorphinone, dihydromorphine and dihydrocodeine.

4. The nuclear position of the new methyl group is not certain, but the fact that the isomeric methyldihydrocodeinones yield isomeric enol acetates suggests that in one isomer the methyl group may be at C–5, and in the other at C–7.

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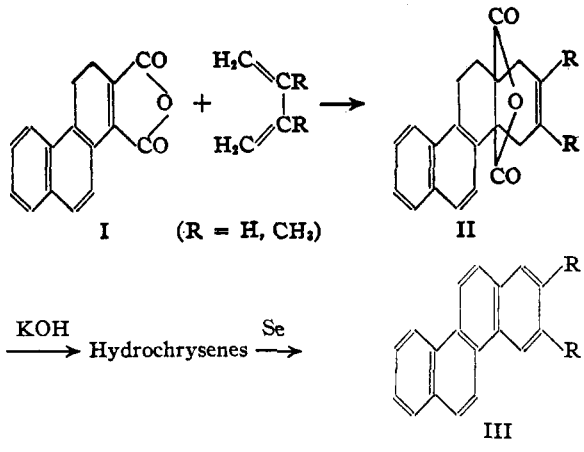
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Synthesis of Phenanthrene and Hydrophenanthrene Derivatives. III. Hydrocarbons of the Chrysene, Acechrysene, and 3,4-Benzphenanthrene Series; 1,2-Benzpyrene Derivatives

BY L. F. FIESER, M. FIESER AND E. B. HERSHBERG

On investigating further applications of the hydrocarbon synthesis of Fieser and Hershberg[1] it has been found that chrysene and 2,3-dimethylchrysene can be obtained conveniently from 3,4-dihydrophenanthrene-1,2-dicarboxylic anhydride[2] (I) by the reactions indicated. The yields were very satisfactory throughout and the two aromatic



hydrocarbons were easily obtained in a highly pure condition. The synthetic chrysene agreed well in melting point (254.5–255°, corr.) with other synthetic preparations[3] and it was indistinguishable from the purified material from coal tar employed in Baxter and Hale's[4] atomic weight work. Incidentally the synthetic phenanthrene previously described[1] was found to be incompletely dehydrogenated, and after suitable treatment the material melted at 100.7–101°, corr., a temperature appreciably higher than most values reported for highly purified samples from coal tar.[5]

The distillates obtained after fusing the diene addition products of the type II with alkali solidified easily but, as in the cases previously studied, they appeared to consist of mixtures of hydrocarbons in different stages of hydrogenation. The material from the butadiene product (R = H) seems to undergo disproportionation in solution, for after repeated crystallization some chrysene was obtained. The crude distillate gave with picric acid a stable compound having the composition of a dihydrochrysene picrate, and the regenerated hydrocarbon exhibited the same mutation in solution as the crude material.

In further extensions of the synthetic method little difficulty was experienced in obtaining the unsaturated anhydrides[2] required for the Diels–Alder reaction or in effecting the diene addition with these substances. 3,4-Dihydronaphthalene-1,2-dicarboxylic anhydride adds cyclopentadiene and cyclohexadiene about as readily as it does the open-chain dienes. The alkali fusion and the final step of dehydrogenation, however, are not always satisfactory. Although compounds of the type IV were obtained in good yield (80%) from 1,2-dihydrophenanthrene-3,4-dicarboxylic anhydride[2] and butadiene or 2,3-dimethylbutadiene, difficulties were encountered in attempting to con-

(1) Fieser and Hershberg, THIS JOURNAL, **57**, 2192 (1935).

(2) Fieser and Hershberg, *ibid.*, **57**, 1851 (1935).

(3) Ruzicka and Hösli [*Helv. Chim. Acta*, **17**, 470 (1934)] record the value 255°, corr.

(4) Baxter and Hale, THIS JOURNAL, **58**, 510 (1936).

(5) Unfortunately a typographical error was made in reporting Dr. R. D. Haworth's melting point for 2,3-dimethylphenanthrene styphnate; this should read 147–148°.