[CONTRIBUTION FROM THE DIVISION OF PHYSIOLOGY, NATIONAL INSTITUTE OF HEALTH]

NUCLEAR SUBSTITUTED MORPHINE DERIVATIVES

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The introduction of organic radicals into ring III of the morphine nucleus has heretofore been accomplished through reaction of the Grignard reagent with derivatives having a double bond in conjugation with the cyclic ether oxygen, as in dihydrothebaine or dihydrocodeinone enol acetate (1). In these reactions the ether ring is invariably opened. The carbonyl group of the morphine ketones is inexplicably inert toward RMgX compounds. Codeinone does not react with methylmagnesium iodide up to 170° (2); dihydrocodeinone is recovered nearly quantitatively under ordinary conditions (3), but if the reaction is forced, behaves like the 6,7-unsaturated types, to give, for example methyldihydrothebainone (4), in which the carbonyl group is still present.[2] Pseudocodeinone likewise suffers rupture of the ring, with retention of the carbonyl, and dihydropseudocodeinone is completely indifferent (3).

In view of the greater activity of organolithium compounds (5), it was of interest to investigate their action upon some of these recalcitrant ketones. The mode of addition proved to be radically different from that of Grignard reagents, and resulted, in most instances, in excellent yields of tertiary carbinols in which the new organic group can scarcely be other than at the 6 position. The reaction thus makes available entirely new types of nuclear substituted morphine derivatives for chemical and pharmacological studies.

With dihydrocodeinone (I) and methyllithium in ether, reaction took place instantaneously at 0°, giving an almost quantitative yield of 6-methyldihydrocodeine (II). Although a new asymmetric center was created at C-6, only the one diastereomer was formed, as was true in the other reactions studied. Whereas 6-methyldihydrocodeine was easily crystallized, and formed a series of well-crystallized salts, as the organolithium reagent was changed from methyl to phenyl, ethyl, *n*-amyl, the properties of the products became progressively less favorable. 6-Phenyldihydrocodeine could not be crystallized, but formed good salts, the resinous ethyl compound gave only a methiodide and picrate, and no crystalline derivative of the *n*-amyl compound could be obtained.

The reaction of methyllithium with 1-chloro- and 1-bromo-dihydrocodeinones proceeded smoothly without elimination of the halogen atom, and the resulting 1-halo-6-methyldihydrocodeines were obtained in good yield. Although halogen-metal interconversion has been observed with the halogenated anisoles (6),

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[2] In a private communication received after this manuscript had been accepted for publication, we are informed by A. H. Homeyer and J. A. Caughlan of the Mallinckrodt Chemical Works that methylmagnesium chloride can be caused to act on dihydrocodeinone to form 6-methyldihydrocodeine. We have identified their product by mixed melting point and rotation. Footnote added Nov. 14, 1946.

the halogen in the halodihydrocodeinones is apparently not reactive enough to be affected under the conditions used.

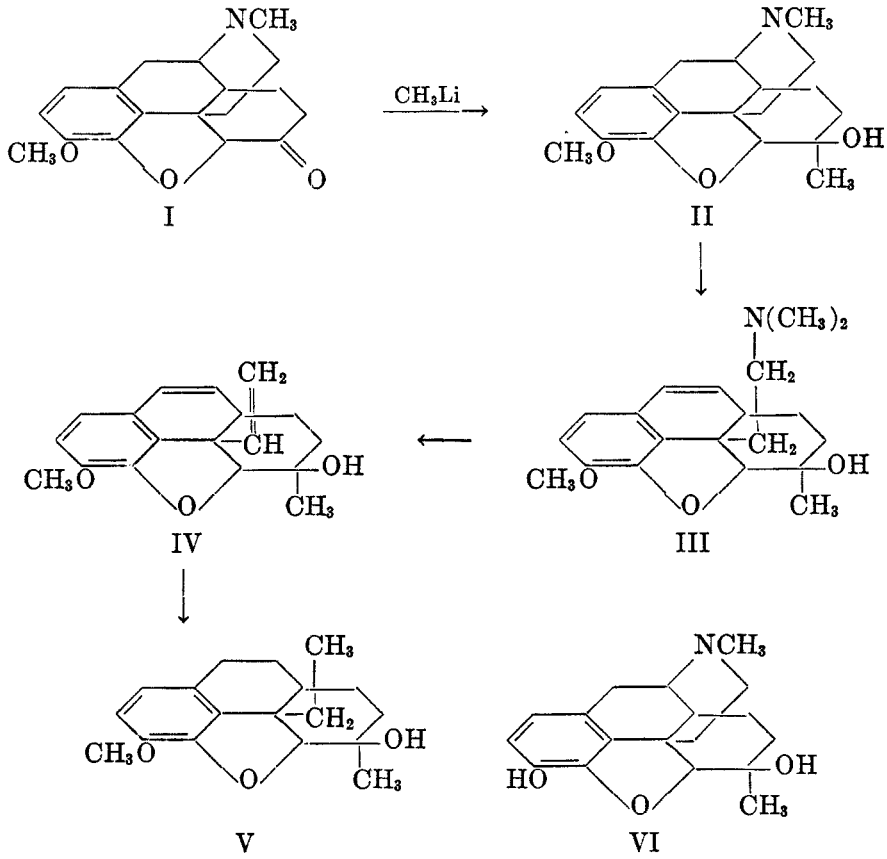
Cleavage of the methoxyl group of 6-methyldihydrocodeine, to arrive at the morphine analog, was unsuccessful; with the usual acidic and alkaline demethylating agents, only resinous products were formed. In attempting to proceed through dihydromorphinone-3-methoxymethyl ether, it was observed that the sodium salt of dihydromorphinone is quite soluble in ether. The methyllithium reaction was therefore applied to dihydromorphinone itself, using sufficient reagent to compensate for that consumed by the phenolic hydroxyl. The lithium salt was freely soluble in ether, permitting reaction of the carbonyl, to give the desired 6-methyldihydromorphine (VI). Etherification of the phenolic group with diazomethane gave 6-methyldihydrocodeine, identical with that from the dihydrocodeinone reaction.

The tertiary alcoholic group of 6-methyldihydrocodeine, as expected, was difficult to acetylate. Acetyl chloride in pyridine, and acetyl chloride and magnesium in ether (7) left it unaffected. A modification of the method of Houben (8), using methyllithium and treating the lithium salt with acetic anhydride, gave the ester, 6-methyl-6-acetyldihydrocodeine, demonstrating the presence of the alcoholic hydroxyl.

The Hofmann degradation of 6-methyldihydrocodeine methiodide with 30% KOH gave in the first step 6-methyldihydromethylmorphimethine (III). The methiodide of this resisted wet degradation, and it was necessary to resort to dry-distillation (under a vacuum) of the methohydroxide to obtain the nitrogen-free product (IV), 6-methyl-6-hydroxy-13-vinylhexahydromethylmorphenol; for consistency with previous work we retain the nomenclature of morphine chemistry. Catalytic reduction of IV (2 moles of hydrogen) gave the corresponding 13-ethyloctahydromethylmorphenol derivative (V).

Replacement of the alcoholic hydroxyl of 6-methyldihydrocodeine by chlorine was attempted with the intention of proceeding through 6-methylchlorodihydrocodide by dehydrohalogenation to the pharmacologically interesting desoxycodeine types. Heating with conc'd HCl in a sealed tube after the method of Knorr and Hörlein (9) gave unchanged material. When, however, the carbinol was refluxed in chloroform with thionyl chloride, a new product which contained no chlorine was isolated in 65% yield. It was non-phenolic, and decolorized potassium permanganate in acetone slowly. Analysis established it to be a 6-methyldesoxycodeine, resulting from loss of a molecule of water from 6-methyldihydrocodeine, or of hydrogen chloride from an intermediate 6-methylchlorodihydrocodide. Such a facile transformation is surprising, in view of the failure of dihydrocodeine or dihydroisocodeine to undergo a parallel change, and the drastic treatment required to remove hydrogen chloride from chlorodihydrocodide (10). The compound was assigned the structure of 6-methyldesoxycodeine-C (VII) on the basis of these observations: Alkali-insolubility and negative diazosulfanilic acid test showed that the oxygen bridge was not ruptured. On ozonolysis it gave no formaldehyde, but treatment of the ozonolysate with iodine and alkali yielded iodoform, indicating that the unsaturation is endocyclic,

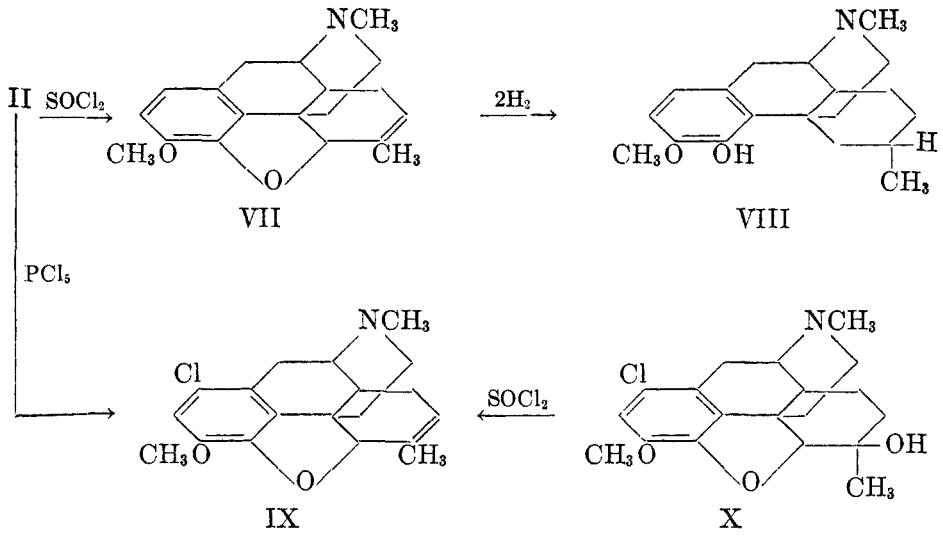
Formula Scheme A



and in position 5,6 or 6,7 (*i.e.*, ozonolysis resulted in a methyl ketone). If it were at 5,6, the compound would be a vinyl ether type and should be easily hydrolyzed by dilute acids, whereas it was found to be stable. Definite evidence for the 6,7-position was furnished by catalytic hydrogenation, which proceeded with absorption of two moles, and reductive scission of the ether bridge (VII → VIII), in the manner typical of pseudocodeine types (11). Dehydration of 6-methyldihydrocodeine with phosphorus pentoxide in toluene according to Prelog and Moor (12) gave only a small yield of the desoxy compound; most of the product was insoluble in organic media, and probably consisted of phosphoric esters.

The reaction of 6-methyldihydrocodeine with PCl_5 in chloroform (13) gave a product which contained one chlorine atom, but which had also lost the elements of water. From the known reactivity of the 1-position in the morphine series it is apparent that this must be 1-chloro-6-methyldesoxycodeine-C (IX). This assumption was verified by subjecting 1-chloro-6-methyldihydrocodeine (X) to the thionyl chloride reaction, which resulted in the same product.

Formula Scheme B



The hydrogenation of 6-methyldesoxycodeine-C with platinum oxide invariably took place in the "abnormal" manner, even under conditions that had been found to give normal reduction of the alicyclic unsaturation alone in other pseudocodeine types (11). The resulting 6-methyltetrahydrodesoxycodeine (VIII) gave a positive test for phenolic hydroxyl with diazosulfanilic acid, but like its unmethylated analog, tetrahydrodesoxycodeine (14), was practically insoluble in dilute alkali.

With palladous chloride and gum arabic buffered with sodium acetate, hydrogenation stopped at 1.3 moles, but the product was entirely phenolic, and the only isolable pure compound was the tetrahydro derivative. Continued reduction of the mixture with platinum oxide gave absorption of an additional 0.6 mole to yield pure tetrahydro derivative. It seems probable that the palladium reduction resulted in one or more dihydrodesoxycodeine types, in which the oxide ring was opened before the double bond was reduced.

In preliminary experiments, codeinone was found to react readily with methyllithium to give principally a crystalline, non-phenolic product, 6-methylcodeine, together with a small amount of phenolic material. The investigation of this series is being deferred until a reliable preparative method for codeinone is developed.

6-Methyldihydrocodeine and 6-methyldihydromorphine were tested for analgesic action by the Woolfe-Macdonald method (15). The intensity of action was not greater, but the duration of analgesia was about twice that of their unmethylated analogs. The toxicity of the methylated and unmethylated compounds was similar, but the former did not produce a Straub reaction, and apparently had much less effect on the spinal cord. Further details will be published elsewhere (N. B. Eddy).

We are indebted to C. A. Kinser and Betty Mount of this Laboratory for the microanalyses.

EXPERIMENTAL

All melting points are corrected, and all above 200° were taken in evacuated tubes; rotations are in 95% alcohol unless otherwise specified.

Organolithium reagents. All organolithium reagents were prepared by the method of Perrine and Rapoport (16), titrated in the usual way, and stored at 0°.

6-Methyldihydrocodeine (II). In an apparatus with stirrer, condenser, and protection from moisture, 25 g. (0.084 mole) of dihydrocodeinone was added during 10 minutes to 140 ml. of 0.9 *M* methyllithium (0.126 mole) at 0°. It was stirred at room temperature for 30 minutes; Michler's ketone test showed excess methyllithium present. The solution was poured into 850 ml. of cold 2% acetic acid (this volume is necessary to prevent precipitation of alkaloid hydriodide derived from lithium iodide in the reagent), separated, and the aqueous phase washed with 100 ml. of peroxide-free ether. On slow addition of 6 *N* ammonia, the base precipitated crystalline, yield 20 g. It is appreciably soluble in water, and chloroform extraction gave an additional 5 g., total 95%. It is extremely soluble in organic media, and was purified from ether or 40% alcohol; sublimed for analysis at 130°/0.1 mm. it melted at 116°, $(\alpha)_D^{20}$ −139° (alcohol, c = 1.02).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.4; H, 7.99.
Found: C, 72.5: H, 8.05.

The *hydrochloride* was prepared with alcoholic hydrogen chloride and ether, and recrystallized from abs. alcohol-ether (1:2); m.p. 268–273°, $(\alpha)_D^{20}$ −112° (alcohol, c = 0.96)

Anal. Calc'd for $C_{19}H_{26}ClNO_3$: C, 64.8; H, 7.45.
Found: C, 64.8; H, 7.31.

The *methiodide* was prepared in and purified from methanol, m.p. 251–252°, $(\alpha)_D^{20}$ −86.3° (alcohol, c = 1.09).

Anal. Calc'd for $C_{20}H_{28}INO_3$: C, 52.5; H, 6.17.
Found: C, 52.7; H, 6.18.

The *acid oxalate*, prepared with abs. alcoholic oxalic acid and crystallized from 95% alcohol, appeared to be a hemihydrate; m.p. 240–241°, $(\alpha)_D^{20}$ −99.5° (alcohol, c = 0.97).

Anal. Calc'd for $C_{21}H_{27}NO_7 + 0.5H_2O$: C, 60.9; H, 6.81.
Found: C, 60.9; H, 6.44.

6-Methyl-6-acetyldihydrocodeine. A solution of 2 g. of 6-methyldihydrocodeine (0.006 mole) in 40 ml. of abs. ether was added slowly to 25 ml. of 0.9 *M* methyllithium (0.023 mole) (strong gas evolution). After 10 min. 2.5 ml. (0.025 mole) of acetic anhydride was added with good cooling. The resulting magma was heated to boiling, and allowed to stand 12 hours. It was decomposed with 100 ml. of 2% acetic acid, and the aqueous layer was basified with 2 *N* sodium carbonate, giving 1.5 g. (66%) of the crystalline acetyl derivative. After purification from petroleum ether (30–60°), it melted at 119–121°; sublimed at 130°/0.1 mm., m.p. 124.5–125.5°, $(\alpha)_D^{20}$ −85.1° (alcohol, c = 0.96).

Anal. Calc'd for $C_{21}H_{27}NO_4$: C, 70.5; H, 7.61.
Found: C, 70.7; H, 7.55.

Degradation. 6-Methyldihydromethylmorphimethine (III). A suspension of 15 g. of 6-methyldihydrocodeine methiodide in 100 ml. of 30% KOH was refluxed for 15 min. The alkali and resin were extracted with five 50-ml. portions of ether, from which 9 g. (83%) of pale yellow oily methine was obtained. It was extremely soluble, and could not be crystallized.

The *hydrochloride* was prepared with alcoholic hydrogen chloride and precipitated with abs. ether; it was recrystallized from abs. alcohol-ether (1:1), m.p. 241–243°, $(\alpha)_D^{20}$ −6.7° (alcohol, c = 0.41).

Anal. Calc'd for $C_{20}H_{28}ClNO_3$: C, 65.6; H, 7.71.
Found: C, 65.4; H, 7.78.

The *salicylate* was prepared in abs. alcohol; m.p. 198–200°, $(\alpha)_D^{20}$ −2.3° (alcohol, c = 0.99).

Anal. Calc'd for $C_{27}H_{33}NO_6$: C, 69.4; H, 7.11.
Found: C, 69.7; H, 7.11.

The *methiodide* was prepared in and purified from methanol; drying at 155° in a vacuum was necessary to obtain solvent-free material; m.p. 269–271°, $(\alpha)_D^{20}$ +8.1° (alcohol, c = 0.98).

Anal. Calc'd for $C_{21}H_{30}INO_3$: C, 53.5; H, 6.42.
Found: C, 53.4; H, 6.38.

6-Methyl-6-hydroxy-13-vinylhexahydromethylmorphenol (IV). Freshly precipitated and thoroughly washed silver oxide (from 7.7 g., 0.045 mole, of silver nitrate) and 7 g. (0.015 mole) of 6-methyldihydromethylmorphimethine methiodide in 175 ml. of water were heated on the steam-bath for several minutes, and shaken for 2 hours at room temperature. It was filtered hot, and evaporated to dryness under reduced pressure at 40°. The residue was distilled in a high vacuum onto a cold-finger; decomposition began at 90°, and was continued at 100–110° for 20 hours. The condensate was removed with 100 ml. of ether, which was washed with N HCl, N Na_2CO_3, and water. It yielded 2.6 g. (62%) of crystals, purified from petroleum ether (30–60°) and by sublimation at 100°/0.1 mm.; $(\alpha)_D^{20}$ +24.4° (alcohol, c = 0.93).

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.0; H, 7.09.
Found: C, 76.0; H, 6.99.

The acid washings yielded 300 mg. of the methine hydrochloride. The dry-ice trap in the decomposition apparatus yielded a small amount of trimethylamine; picrate m.p. 216–218° (lit. 216°).

6-Methyl-6-hydroxy-13-ethyl-5,6,7,8,9,10,13,14-octahydromethylmorphenol (V). Hydrogenation of 100 mg. of the N-free product (IV) in 10 ml. of methanol with 10 mg. of platinum oxide stopped at 2 moles. The product was sublimed at 100°/0.1 mm., m.p. 98–100°, $(\alpha)_D^{20}$ −29.9° (alcohol, c = 1.07).

Anal. Calc'd for $C_{18}H_{24}O_3$: C, 75.0; H, 8.39.
Found: C, 75.2; H, 8.09.

6-Methyldesoxycodeine-C (VII). To a solution of 45 g. (0.143 mole) of 6-methyldihydrocodeine in 270 ml. of absolute chloroform, at 0° with good stirring, was added during 30 min. 20.4 g. (0.172 mole) of thionyl chloride in 90 ml. of chloroform. The solution was refluxed for two hours and poured into 900 ml. of cold water. It was basified with ammonia, and extracted well with chloroform. The residue from the chloroform was dissolved in 250 ml. of alcohol and decolorized; dilution with 250 ml. of hot water gave 23.5 g. of product, and 4 g. more on further dilution (65% yield). It was purified from alcohol, m.p. 172–174°, sublimed at 120°/0.2 mm., m.p. 173–174°, $(\alpha)_D^{20}$ −242° (alcohol, c = 1.07); diazosulfanilic acid test negative, $KMnO_4$ in acetone slowly decolorized.

Anal. Calc'd for $C_{19}H_{23}NO_2$: C, 76.7; H, 7.80.
Found: C, 76.9; H, 7.71.

The *hydrochloride*, from abs. ethanol-ether, melted at 262–263°, $(\alpha)_D^{20}$ −192° (alcohol, c = 1.02).

Anal. Calc'd for $C_{19}H_{24}ClNO_2$: C, 68.3; H, 7.25.
Found: C, 67.9; H, 7.37.

The *methiodide* crystallized from methanol, m.p. 280–281°, $(\alpha)_D^{20}$ −149° (alcohol, c = 1.00).

Anal. Calc'd for $C_{20}H_{26}INO_2$: C, 54.7; H, 5.97.
Found: C, 54.8; H, 6.04.

The desoxy compound was also obtained by the action of phosphorus pentoxide in toluene, but the yield was only 10%. 6-Methyldesoxycodeine-C was recovered unchanged from normal HCl after 15 min. at 100°.

Ozonolysis. Oxygen containing 2.7% ozone was passed through a solution of 1.7 millimoles of 6-methyldesoxycodeine-C in normal HCl at the rate of 12 l. per hour. In 30 min. 1.9 millimoles was absorbed. The methone test for formaldehyde was negative, but with iodine and alkali a precipitate of iodoform, m.p. 119–120° was obtained.

6-Methyltetrahydrodesoxycodeine (VIII). A solution of 3 g. of 6-methyldesoxycodeine-C

in 150 ml. of 5% sulfuric acid with 150 mg. of platinum oxide absorbed 2.0 moles of hydrogen in 1.5 hours. The product was precipitated with solid potassium carbonate and recrystallized from acetone, yield 66%; sublimed at 125°/0.2 mm. it melted at 157.5–158.5°, $(\alpha)_D^{20}$ −4.5° (alcohol, c = 0.61).

Anal. Calc'd for $C_{19}H_{27}NO_2$: C, 75.7; H, 9.03.
Found: C, 75.8; H, 9.08.

The *hydrochloride* crystallized from abs. alcohol-ether, m.p. 254–255°, $(\alpha)_D^{20}$ +8.0° (alcohol, c = 0.81).

Anal. Calc'd for $C_{19}H_{28}ClNO_2$: C, 67.5; H, 8.35.
Found: C, 67.8; H, 8.54.

The *acid oxalate*, from alcohol-ether, had the m.p. 171–172°, $(\alpha)_D^{20}$ +4.8° (alcohol c = 0.68).

Anal. Calc'd for $C_{21}H_{29}NO_6$: C, 64.4; H, 7.47.
Found: C, 64.5; H, 7.57.

The *methiodide*, from methanol-ether, melted at 265–266°; $(\alpha)_D^{20}$ +6.4° (alcohol, c = 0.47).

Anal. Calc'd for $C_{20}H_{30}INO_2$: C, 54.2; H, 6.82.
Found: C, 54.3; H, 6.78.

Hydrogenation of 4.4 g. of 6-methyldesoxycodeine-C in 120 ml. of methanol with 2.2 g. of sodium acetate, 40 mg. of gum arabic, and 4.5 ml. of 1% palladous chloride stopped completely at 1.3 moles of hydrogen. Fractionation gave the tetrahydro compound as the only pure product; the phenolic residues absorbed 0.6 mole of hydrogen with platinum oxide to yield an additional quantity.

1-Chloro-6-methyldesoxycodeine-C (*IX*). To a solution of 6.5 g. (0.031 mole) of phosphorus pentachloride in 25 ml. of abs. chloroform at 0° was added 5.0 g. (0.016 mole) of 6-methyldihydrocodeine in small portions over 10 min. The solution was refluxed for 4 hours, 500 ml. of water was added, and the chloroform removed at reduced pressure. After filtration from a little insoluble material, the solution was basified and extracted with ether, which yielded 4.4 g. of syrupy residue. Digestion with abs. ether gave 1.5 g. of crystals, purified from abs. alcohol and sublimed at 150°/0.1 mm.; m.p. 171–172°, $(\alpha)_D^{20}$ −226° (alcohol, c = 1.12). It decolorized $KMnO_4$ in acetone at 20°.

Anal. Calc'd for $C_{19}H_{22}ClNO_2$: C, 68.8; H, 6.68; Cl, 10.7.
Found: C, 68.9, 68.6; H, 6.63, 6.45; Cl, 10.4.

The same compound was obtained when the base from 2.0 g. of 1-chloro-6-methyldihydrocodeine perchlorate in 15 ml. of abs. chloroform with 0.63 g. of thionyl chloride was refluxed for two hours. The product, purified as above, 0.5 g., melted at 171–172°, no depression in mixture, and had $(\alpha)_D^{20}$ −227° (alcohol, c = 1.14).

1-Chloro-6-methyldihydrocodeine (*X*). This was prepared essentially like the unchlorinated analog, but was obtained from ether extraction as an oil. It was dissolved in abs. ethanol and converted to the *perchlorate* with normal alcoholic $HClO_4$, yield 76%. The salt was purified from abs. ethanol, m.p. 238–239°, $(\alpha)_D^{20}$ −81.4° (alcohol, c = 0.96).

Anal. Calc'd for $C_{19}H_{25}Cl_2NO_7 + 0.5\ H_2O$: C, 49.7; H, 5.71.
Found: C, 49.4; H, 5.61.

The *hydriodide* was prepared with 15% alcoholic hydriodic acid, and purified from abs. alcohol; m.p. 260–262°, $(\alpha)_D^{20}$ −73.6° (alcohol, c = 0.94).

Anal. Calc'd for $C_{19}H_{25}ClINO_3$: C, 47.8; H, 5.27.
Found: C, 47.6; H, 5.59.

1-Bromo-6-methyldihydrocodeine. This compound, prepared from 1-bromodihydrocodeinone like the chloro analog, was obtained in 86% yield as an amorphous solid, m.p. 60–70°, exceedingly soluble in organic media. The *hydrochloride* was also very soluble, and hygroscopic. The *hydriodide* was prepared with 10% aqueous hydriodic acid, and purified from water, m.p. 248–249°, $(\alpha)_D^{20}$ −64.6° (alcohol, c = 1.05).

Anal. Calc'd for $C_{19}H_{25}BrINO_3$: C, 43.7; H, 4.83.
Found: C, 43.3; H, 5.06.

The *methiodide*, from methanol-ether, melted at 235–237°, $(\alpha)_D^{20}$ −73.1° (alcohol, c = 1.20).

Anal. Calc'd for $C_{20}H_{27}BrINO_3$: C, 44.8; H, 5.08.
Found: C, 45.1; H, 5.05.

6-Methyldihydromorphine (VI). This was prepared like the codeine analog from 12 g. (0.042 mole) of dihydromorphinone and 120 ml. of 0.9 *M* methyllithium (0.11 mole). It precipitated crystalline on addition of solid potassium carbonate to the HCl solution; chloroform extracted an additional amount; after recrystallization from acetone 8.7 g. was obtained, 69%. It sublimed at 150°/0.1 mm., m.p. 209–211°, $(\alpha)_D^{20}$ −147° (alcohol, c = 1.02). It adsorbed about 1% moisture avidly.

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.7; H, 7.69.
Found: C, 71.8; H, 7.69.

The *hydrochloride* crystallized from alcohol-ether, m.p. 308–309°, $(\alpha)_D^{20}$ −121° (alcohol, c = 1.04).

Anal. Calc'd for $C_{18}H_{24}ClNO_3$: C, 64.0; H, 7.16.
Found: C, 63.8; H, 6.94.

The *methiodide* crystallized from methanol, m.p. 277–278°, $(\alpha)_D^{20}$ −86.8° (alcohol, c = 0.53). It turned yellow quite rapidly.

Anal. Calc'd for $C_{19}H_{26}INO_3$: C, 51.5; H, 5.91.
Found: C, 51.7; H, 6.15.

The base was allowed to stand with excess ethereal diazomethane and methanol for two days. The product was 6-methyldihydrocodeine, m.p. 112–113°, no depression in mixture.

6-Ethyldihydrocodeine. The petroleum ether (b.p. 28–38°) was evaporated under reduced pressure from 380 ml. of 0.27 *M* ethyllithium (0.103 mole) to a volume of about 10 ml., and 150 ml. of abs. ether was added. The reaction with 10 g. (0.034 mole) of dihydrocodeinone was carried out as with the methyl analog, and after decomposition with HCl, basifying with NaOH, and ether extraction, an oily residue was obtained from which 0.5 g. of dihydrocodeinone was isolated; the ethyl derivative could not be crystallized. Most salts were oily or very soluble.

The *picrate* was prepared with alcoholic picric acid and purified from 75% alcohol, m.p. 217–219°, $(\alpha)_D^{20}$ −73.0° (75% alcohol, c = 0.60).

Anal. Calc'd for $C_{26}H_{30}N_4O_{10}$: C, 55.9; H, 5.41.
Found: C, 56.3; H, 5.64.

The *methiodide*, from methanol-ether, was purified from abs. alcohol, m.p. 238–240°, $(\alpha)_D^{20}$ −82.0° (alcohol, c = 1.11).

Anal. Calc'd for $C_{21}H_{30}INO_3$: C, 53.5; H, 6.42.
Found: C, 53.4; H, 6.43.

6-n-Amyldihydrocodeine. The reaction of dihydrocodeinone (5 g.) with *n*-amyllithium was carried out as for the ethyl compound. The product was 5.8 g. of oil, from which *N* alcoholic $HClO_4$ precipitated 0.6 g. (9%) of dihydrocodeinone perchlorate. The regenerated amyl derivative did not crystallize or give crystalline salts. Repeated distillation of the base at 140°/0.2 mm. gave a viscous, faintly yellow oil, having $(\alpha)_D^{20}$ −108° (alcohol, c = 0.88).

Anal. Calc'd for $C_{23}H_{33}NO_3$: C, 74.5; H, 8.95.
Found: C, 73.8; 73.7; H, 9.15, 8.90.

6- Phenyldihydrocodeine. To 60 ml. of 0.84 *M* ethereal phenyllithium (0.05 mole) was added, at 0°, 10 g. (0.033 mole) of dihydrocodeinone. After 10 min. the mixture was poured into 500 ml. of cold 3% acetic acid. The acid layer was washed with ether, basified, and extracted with ether, from which a liquid product was obtained. This was dissolved in 300 ml. of alcohol and treated with 50 ml. of *N* alcoholic perchloric acid, yield of crystalline salt 13.7 g. (86%). The salt was recrystallized four times from alcohol; the base liberated did not crystallize, and was distilled at 130°/0.1 mm. yielding an amorphous solid, m.p. 62–72°, $(\alpha)_D^{20}$ −155° (alcohol, c = 1.08).

Anal. Calc'd for $C_{24}H_{27}NO_3$: C, 76.4; H, 7.21.
Found: C, 76.2; H, 7.11.

The *perchlorate* melted at 246–248° and had $(\alpha)_D^{20}$ −126° (50% alcohol, c = 0.404).

Anal. Calc'd for $C_{24}H_{28}ClNO_7$: C, 60.3; H, 5.91.
Found: C, 60.4; H, 5.91.

The *hydrochloride* was prepared in 2.5 *N* aqueous hydrochloric acid and recrystallized from 1:1 abs. alcohol-ether; m.p. 190–191°, $(\alpha)_D^{20}$ −131° (alcohol, c = 1.04).

Anal. Calc'd for $C_{24}H_{28}ClNO_3$: C, 69.6; H, 6.82.
Found: C, 69.5, H, 7.18.

The *acid oxalate* was prepared with alcoholic oxalic acid and ether, and recrystallized from alcohol-ether; it retained one-half molecule of ethanol after vacuum-drying at 100°; m.p. 126–127°, $(\alpha)_D^{20}$ −117° (alcohol, c = 1.00).

Anal. Calc'd for $C_{26}H_{29}NO_7 + 0.5\ C_2H_6O$: C, 66.1; H, 6.58.
Found: C, 66.2; H, 6.84.

SUMMARY

The reaction of some ketones of the morphine series with organolithium compounds is described. In contrast to RMgX, the reagent adds at the carbonyl to give 6-substituted tertiary alcohols.

Degradation of 6-methyldihydrocodeine to a nitrogen-free product is described.

Thionyl chloride dehydrates 6-methyldihydrocodeine to 6-methyldesoxycodeine-C, whereas phosphorus pentachloride chlorinates at the 1-position in addition.

6-Methyldesoxycodeine-C undergoes reduction to a phenolic tetrahydro derivative, like its unmethylated analog.

BETHESDA—14, MD.

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