[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Preparation of Some 6-Methylated Dihydrodesoxymorphines[1]

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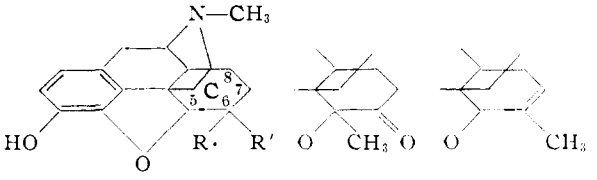
With the objective of finding a more effective morphine drug, several new alkyl derivatives of dihydrodesoxymorphine (III) have been prepared. Attempts to introduce an alkyl group into ring C by reaction of *p*-toluenesulfonylcodeine (VII) with alkyl lithiums led only to oxide-ring opening and the formation of $\Delta^{5,7}$-thebainone enol *p*-toluenesulfonate (VIII). On the other hand, the action of triphenylphosphinemethylene on dihydrocodeinone (I) gave an excellent yield of 6-methylenedihydrodesoxycodeine (XVIIc), and this was successfully hydrogenated to 6-methyldihydrodesoxycodeine (VIc). Both compounds were then cleaved with pyridine hydrochloride to the corresponding morphine derivatives. 6-Methyl-7-hydroxydihydrodesoxymorphine (XXVII) was prepared by a series of reactions starting with 6-methyl-Δ^6-desoxycodeine (Vc) and involving hydroxylation with osmium tetroxide, acetylation of the 7-hydroxyl, dehydration to 6-methylene-7-acetoxydihydrodesoxycodeine (XXIII), hydrolysis of the 7-acetyl group, hydrogenation, and ether cleavage. When 6-methyl-7-hydroxydihydrodesoxycodeine was oxidized, the expected ketone underwent β-elimination to the oxide-ring opened compound (XXVIII), affording another example of the instability of this ring when a carbonyl group is present at position 7.

Numerous derivatives of morphine have been prepared and their pharmacology has been investigated in the quest for an analgetic with low addiction liability. Although none have been completely satisfactory, a number seem to have distinct advantages over morphine for application under certain conditions and give indication at least that analgesia and addiction are not necessarily completely parallel activities.[2] Among the more interesting compounds may be mentioned dihydromorphinone (dilaudid) (I),[3] 5-methyldihydromorphinone (metopon) (II),[4] dihydrodesoxymorphine (desomorphine) (III),[5] 6-methyldihydromorphine (IV)[6] and 6-methyl-Δ^6-desoxymorphine (V).[7] However, either their advantage has been insufficient or their preparation has been difficult, and their use *vis-a-vis* morphine has been limited.[8]

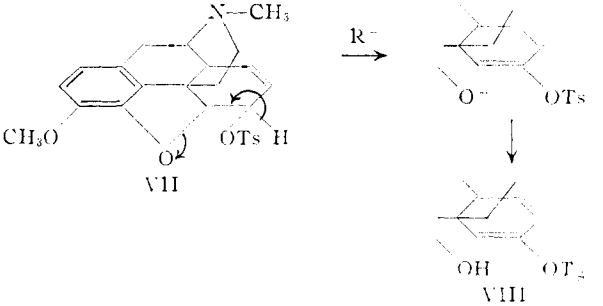


I, R,R′ = O[9]
III, R = R′ = H
IV, R = OH, R′ = CH_3
VI, R = H, R′ = CH_3

Examination of these five more interesting morphine derivatives indicates a certain pattern in structure–activity relationships that might be worth pursuing, namely, all have ring C either reduced or methylated or both, and the secondary hydroxyl at carbon six is absent. With the objective of exploring this further and possibly obtaining a more efficacious drug, some additional examples of these structural variants have been prepared.

The first compound sought was 6-methyldihydrodesoxymorphine (VI), and the obvious method of preparing it, reduction of 6-methyl-Δ^6-desoxymorphine (V), was explored exhaustively. As with the codeine analog,[6] hydrogenation under a large variety of conditions and with a number of catalysts led always to hydrogenolysis of the oxide ring. If the corresponding 6-methyl-Δ^7 compound were available, its hydrogenation should take the desired course since it would not be an allylic ether.

In an attempt to prepare 6-methyl-Δ^7-desoxymorphine, the action of methyllithium on *p*-toluenesulfonylcodeine (VII) was investigated. When methyllithium prepared from methyl iodide was used, the chief product was β-iodocodide[10] accompanied by a small amount of pseudocodeine, both undoubtedly resulting from displacement of the 6-*p*-toluenesulfonate group. The iodide ion was supplied by the high solubility of lithium iodide in ether, and the pseudocodeine most probably was formed during the isolation. Methyllithium free of other displacing anions then was prepared from methyl chloride, since lithium chloride is very insoluble in ether. From the reaction of this reagent and *p*-toluenesulfonylcodeine, a crystalline product still retaining the tosyl group was isolated in good yield. It was phenolic, as evidenced by coupling with diazotized sulfanilic acid and an



VII VIII

(1) Supported in part by a grant from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.

(2) For a recent and general review of the pharmacological aspects of this subject see the chapter by H. Krueger in R. H. F. Manske, "The Alkaloids," Vol. V, Academic Press, Inc., New York, N. Y., 1955.

(3) (a) Knoll and Co., German Patent 623,821 and previous patents; (b) H. Rapoport, R. Naumann, E. R. Bissell and R. M. Bonner, *J. Org. Chem.*, **15**, 1103 (1950).

(4) L. F. Small, H. M. Fitch and W. E. Smith, THIS JOURNAL, **58**, 1457 (1936); G. Stork and L. Bauer, *ibid.*, **75**, 4373 (1953).

(5) L. F. Small, K. C. Yuen and L. K. Eilers, *ibid.*, **55**, 3863 (1933).

(6) L. F. Small and H. Rapoport, *J. Org. Chem.*, **12**, 284 (1947).

(7) H. D. Brown, I. M. Rasmussen, G. B. Payne and K. Pfister, 3rd, THIS JOURNAL, **75**, 6238 (1953).

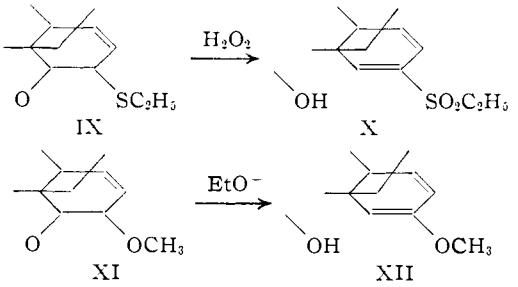
(8) For example, the 1953 consumption in the United States was 53,071 oz. of morphine and 3,662 oz. of dihydromorphinone, the most widely used of the derivatives mentioned above [M. H. Seevers, *Bull. Narcotics*, **8**, 28 (1956)].

(9) We have used the same structural formulas for the corresponding morphine (free phenol at position 3) and codeine (methoxyl group at position 3) derivatives, designated by the roman numeral alone and the roman numeral plus suffix c, respectively, in those cases where both occur.

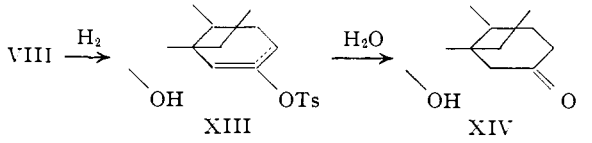
(10) L. F. Small and F. L. Cohen, THIS JOURNAL, **53**, 2214 (1931); G. Stork and F. H. Clarke, *ibid.*, **78**, 4619 (1956).

hydroxyl band in the infrared, and isomeric with the starting material VII. However, the tosyl group was now stable to displacement by halide or acetate ion. There was no evidence for a methyl group having entered the molecule, and this was confirmed by isolating the same product, in better yield, from the reaction with butyllithium.

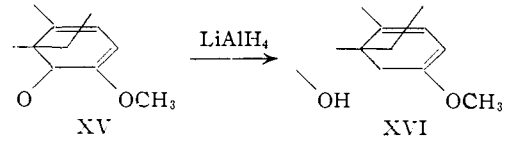
A reasonable postulate for the structure of this product was VIII, arising by *trans*-elimination initiated by attack of the strongly basic alkyl carbanion on the somewhat acidic 6-hydrogen. This reaction path is similar to the oxide-ring opening that occurs when β-ethylthiocodide (IX) is oxidized to the sulfone X,[11] and when codeine methyl ether (XI) is isomerized by ethoxide to $\Delta^{5,7}$-thebainone enol methyl ether (XII).[12]



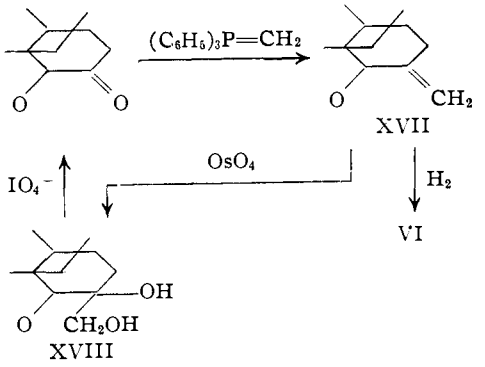
Hydrogenation of the alkyl lithium reaction product gave a dihydro compound XIII from which on alkaline hydrolysis the known dihydrothebainone (XIV) was isolated. This together with the previous data, establishes $\Delta^{5,7}$-thebainone enol *p*-toluenesulfonate (VIII) as the structure of this *p*-toluenesulfonylcodeine isomer, except for the position of the double bonds. A $\Delta^{6,8}$-diene, although unlikely considering the mechanism of its formation would also be consistent with the data.



To establish the position of the double bonds in VIII, the ultraviolet spectra of a number of dienes of the morphine series were examined. Two known $\Delta^{6,8}$-dienes are thebaine (XV) and $\Delta^{6,8}$-thebainone enol methyl ether (XVI), the product resulting from the action of lithium aluminum hydride on thebaine.[13] Both these compounds have very strong absorption, the extinction coefficient of thebaine being 7500 at 283 mμ while that of $\Delta^{6,8}$-thebainone enol methyl ether is 11,000 at 284 mμ.[13] Those morphine derivatives which have the guaiacol moiety as the only chromophore have an extinction coefficient of about 1500 in this region, whereas the $\Delta^{5,7}$-dienes are intermediate between these extremes. $\Delta^{5,7}$-Thebainone enol methyl ether's (XII) extinction at 281 mμ is 3480[13b,14] and that of the sulfone X is 3350 at 272 mμ. Thus the ultraviolet absorption clearly distinguishes the $\Delta^{6,8}$-dienes fully conjugate with a substituent at carbon 6 from the $\Delta^{5,7}$-dienes cross conjugate with such a substituent. The product resulting from the action of alkyl lithiums on *p*-toluenesulfonylcodeine has an ε of 3440 at 274 mμ and thus clearly has the structure VIII.



Returning to our original purpose, the preparation of 6-methyldihydrodesoxymorphine (VI), the triphenylphosphinemethylene reagent recently found[15] to replace carbonyl oxygen by methylene offered a strong possibility. Such a reaction with dihydrocodeinone might give 6-methylenedihydrodesoxycodeine (XVIIc), isomeric with 6-methyl-Δ^6-desoxycodeine (Vc), and although the latter could not be hydrogenated without hydrogenolysis, this is not necessarily so for the former.

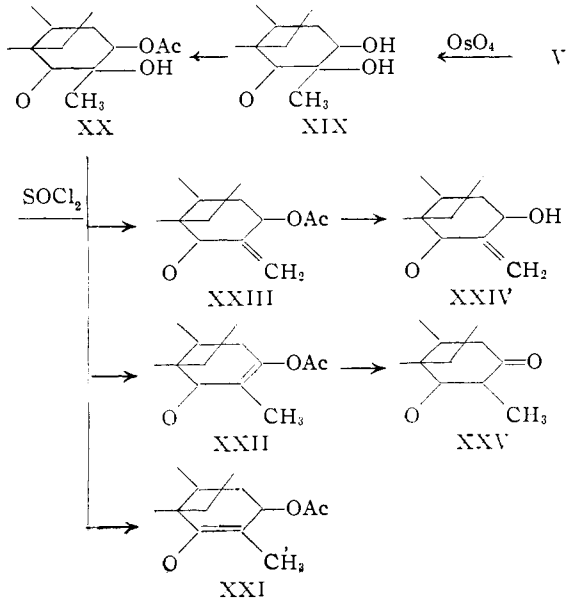


When dihydrocodeinone was treated with triphenylphosphinemethylene, an 85% yield of nonketonic material was isolated. That this material was indeed the methylene compound XVIIc was conclusively shown by hydroxylation with osmium tetroxide and periodate cleavage of the resulting glycol, 6-hydroxmethyldihydrocodeine (XVIII), to give formaldehyde and dihydrocodeinone. From the hydrogenation of the methylene compound XVII under the acidic conditions found to give the least hydrogenolysis,[16] the known phenolic compound, 6-methyltetrahydrodesoxycodeine, was obtained but at the same time a 44% yield of the non-phenolic 6-methyldihydrodesoxycodeine (VIc) was isolated. This was then cleaved with pyridine hydrochloride, and 6-methyldihydrodesoxymorphine resulted in reasonably good over-all yield. Ether cleavage also was applied to the 6-methylenedihydrodesoxycodeine (XVIIc), and both morphine derivatives were characterized by their typical shift in ultraviolet absorption upon addition of alkali and by re-etherification with diazomethane.

The derivatives sought next were those with a methyl at carbon 6 and an oxygen function (either carbonyl or hydroxyl) at 7. For this purpose the known 6-methyl-Δ^6-desoxycodeine (Vc) was con-

(11) H. Rapoport and R. M. Bonner, THIS JOURNAL, **73**, 2872 (1951).
(12) L. F. Small and G. L. Browning, Jr., *J. Org. Chem.*, **3**, 618 (1939).
(13) (a) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **33**, 863 (1950); (b) G. Stork, THIS JOURNAL, **74**, 768 (1952).
(14) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **34**, 1948 (1951).
(15) G. Wittig and U. Schöllkopf, *Ber.*, **87**, 1318 (1954).
(16) R. E. Lutz and L. F. Small, THIS JOURNAL, **56**, 2466 (1934).

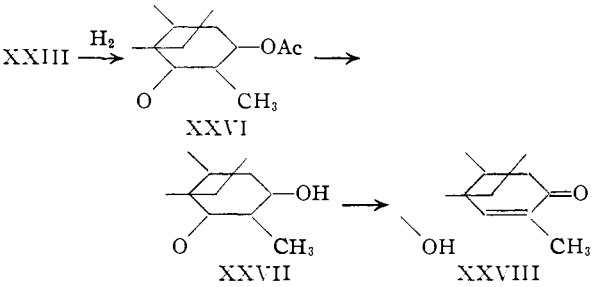
sidered as starting material according to the scheme



Hydroxylation of 6-methyl-Δ^6-desoxycodeine to the glycol and conversion of the 6-methyl-7-hydroxydihydrocodeine XIX to its O^7-monoacetate XX were, as expected, quite straightforward. However, the thionyl chloride dehydration of XX might take all or any of the three courses shown, and these possibilities were considered. Formation of the Δ^5-compound XXI seemed least likely since introduction of a double bond at this position with the oxide ring intact appears to introduce a prohibitive strain into the molecule and no such compound is known. However, both XXII and XXIII, and any of their hydrolytic products resulting from the isolation procedure, were anticipated as potential products of the dehydration.

By careful chromatography on alumina, the crude product from dehydration of XX was separated into three compounds in 27, 32 and 17% yield. These compounds, as shown by their infrared and ultraviolet absorption, were an alcohol, an acetate ester and an α,β-unsaturated ketone, respectively. The alcohol, on acetylation, formed the acetate, and the acetate, on hydrolysis, gave the alcohol. Since this behavior could not obtain for the enol acetate XXII, it was assumed that the acetate was XXIII and the alcohol was XXIV, arising from XXIII by hydrolysis during the isolation. To prove this the acetate was hydroxylated with osmium tetroxide and the resulting glycol was cleaved with periodate to give formaldehyde. The alcohol showed the absence of any C-methyl groups, thus confirming the structural assignments as XXIII and XXIV.

The α,β-unsaturated ketone had a hydroxyl band in the infrared as well as its unsaturated ketone absorption, and it gave a strong coupling test with diazotized sulfanilic acid, characteristic of morphine derivatives with the oxide-ring opened. On this basis, a reasonable structure for this ketone is XXVIII, arising as a result of β-elimination from ketone XXV, and this assignment receives support from similar observations of oxide-ring opening in other morphine derivatives upon introduction of a carbonyl function at carbon 7.[17]



Although hydrogenation of the alcohol XXIV gave mostly phenolic material by hydrogenolysis, the acetate XXIII could be hydrogenated to the non-phenolic 6-methyl-7-acetoxydihydrodesoxycodeine (XXVI), and this was hydrolyzed to the 6 - methyl - 7 - hydroxydihydrodesoxycodeine (XXVIIc). On subjecting this alcohol to Oppenauer oxidation, the α,β-unsaturated ketone XXVIII, identical with that isolated from the dehydration of XX, was obtained. Apparently the saturated ketone of structure XXV has no real existence, undergoing immediate β-elimination.[18]

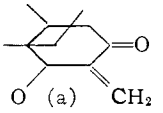
The usual ether cleavage with pyridine hydrochloride gave the corresponding 6-methyl-7-hydroxydihydrodesoxymorphine (XXVII); and this morphine derivative as well as 6-methyldihydrodesoxymorphine (VI), and 6-methylenedihydrodesoxymorphine (XVII) all displayed powerful analgetic activity in preliminary animal testing.[19]

Experimental[20]

$\Delta^{5,7}$-Thebainone Enol *p*-Toluenesulfonate (VIII).—Methyllithium was prepared from methyl chloride using a small amount of methyl iodide for entrainment. In this way an ethereal solution 0.37 *M* in methyllithium and 0.015 *M* in iodide resulted. To a solution of 4.5 g. (10 mmoles) of *p*-toluenesulfonylcodeine[11] in 30 ml. of tetrahydrofuran, cooled to 0°, was added 28 ml. (10 mmoles) of this methyllithium solution over 30 minutes, and the reaction mixture was kept at 0° in a nitrogen atmosphere for 12 hours. Ice-water (100 ml.) was added after evaporating most of the solvent *in vacuo* and the aqueous phase was extracted with four 50-ml. portions of methylene chloride. The alkaloidal material was then extracted into aqueous acid and back-extracted into methylene chloride after alkalization. This gave 3.2 g. of crude material from which pure $\Delta^{5,7}$-thebainone enol *p*-toluenesulfonate was obtained by crystallization from benzene; m.p. 208–210°, $[\alpha]^{21}D$ +18° (*c* 0.96, chloroform); λ_{max}^{EtOH} 274 mμ, ϵ 3440.

(17) H. Rapoport, M. S. Chadha and C. H. Lovell, THIS JOURNAL, **79**, 4694 (1957).

(18) Various attempts to prepare the non-phenolic unsaturated ketone (a) by oxidation of XXIV with silver carbonate, manganese dioxide or chromic anhydride in pyridine all failed.



(19) We are indebted to Drs. H. Elliott and T. Adler of the Department of Pharmacology, University of California, San Francisco, for these results which will be published in detail elsewhere.

(20) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley. Optical rotations were measured on ethanolic solutions in one-decimeter tubes, unless otherwise specified, and infrared spectra were measured in chloroform.

Anal. Calcd. for $C_{25}H_{27}O_5NS$: C, 66.2; H, 6.0; N, 3.1; S, 7.0. Found: C, 66.2; H, 6.3; N, 3.3; S, 7.1.

From the reaction of butyllithium and *p*-toluenesulfonylcodeine, carried out in the same manner as above except that the reaction mixture was maintained two hours at 0°, 12 hours at room temperature and then boiled under reflux for six hours, was isolated a 50% yield of $\Delta^{5,7}$-thebainone enol *p*-toluenesulfonate, m.p. 208–210°.

Δ^5-Dihydrothebainone Enol *p*-Toluenesulfonate (XIII).—A 200-mg. (0.44 mmole) sample of $\Delta^{5,7}$-thebainone enol *p*-toluenesulfonate (VIII) was dissolved in 10 ml. of glacial acetic acid, one drop of concentrated hydrochloric acid and 10 mg. of platinum oxide were added, and the mixture was hydrogenated at room temperature and atmospheric pressure. Hydrogenation ceased after four hours and the absorption of 270 mole % of hydrogen, and the solution then was filtered. Addition of 50 ml. of water and alkalization with concentrated ammonium hydroxide caused precipitation of a solid from the filtrate, and chloroform extraction removed more material. From a total of 160 mg. of crude, two crystallizations from methanol gave 100 mg. of Δ^5-dihydrothebainone enol *p*-toluenesulfonate,[21] m.p. 222–224° $[\alpha]^{21}D$ −69° (*c* 0.85, chloroform); λ_{max}^{EtOH} 273 mμ, ε 2190.

Anal. Calcd. for $C_{25}H_{29}O_5NS$: C, 65.9; H, 6.4; S, 7.0. Found: C, 66.3; H, 6.1; S, 6.8.

To a solution of 100 mg. of Δ^5-dihydrothebainone enol *p*-toluenesulfonate in 10 ml. of ethanol was added 300 mg. of potassium hydroxide in 1 ml. of water, and the solution was boiled on the steam-bath for six hours. After being concentrated almost to dryness, the hydrolyzate was distributed between water and methylene chloride. Evaporation of the methylene chloride left 64 mg. of crude product which was crystallized from ethyl acetate and sublimed. It was identical with a sample of dihydrothebainone (XIV), prepared from thebaine by hydrogenation,[12] in infrared spectrum, optical rotation, m.p. and mixed m.p.

6-Methylenedihydrodesoxycodeine (XVIIc).—To 400 ml. (90 mmoles) of a standardized solution of triphenylphosphinemethylene in ether[22] was added 270 ml. of purified tetrahydrofuran and the ether was removed by fractional distillation. The solution was cooled to 0°, 26.7 g. (90 mmoles) of dihydrocodeinone dissolved in 150 ml. of tetrahydrofuran was added dropwise during 30 minutes, and the reaction mixture then was heated under reflux for 38 hours with stirring and in a nitrogen atmosphere. The residue from evaporation of the tetrahydrofuran was dissolved in chloroform, and the chloroform, after being washed with alkali, was extracted thoroughly with *M* phosphoric acid. Concentrated ammonium hydroxide liberated the free bases from the combined phosphoric acid extracts, and these were taken into benzene and separated into ketonic and nonketonic fractions by extraction with bisulfite–sulfite buffer (*p*H 7). Dihydrocodeinone was recovered to the extent of 4 g. (15%), and 22.2 g. (84% yield) of 6-methylenedihydrodesoxycodeine, m.p. 126–128°, was obtained. Crystallization from heptane gave material of m.p. 127–129°, $[\alpha]^{21}D$ −123° (*c* 0.87); λ_{max}^{EtOH} 284 mμ, ε 1300.

Anal. Calcd. for $C_{19}H_{23}O_2N$: C, 76.8; H, 7.7. Found: C, 77.0; H, 8.0.

6-Hydroxymethyldihydrocodeine (XVIII).—A solution of 236 mg. (0.79 mmole) of 6-methylenedihydrodesoxycodeine (XVIIc) in 15 ml. of absolute ether was treated with 200 mg. (0.79 mmole) of osmium tetroxide in 5 ml. of ether. Immediately upon addition of pyridine (260 λ, 3.4 mmoles) precipitation commenced. After five hours at room temperature, the reaction mixture was centrifuged and the precipitate was washed several times with ether. For hydrolysis, the precipitated osmate ester was dissolved in 25 ml. of ethanol and heated with a solution of sodium sulfite (2 g. in 12 ml. of water) for two hours. On evaporation of the ethanol, 116 mg. of the glycol was obtained. Evaporation of the combined ether solution and washes above left a residue which was hydrolyzed in the same way and was separated into recovered olefin (29 mg.) and glycol (64 mg.) by fractional sublimation. Crystallization from methanol gave pure 6-hydroxymethyldihydrocodeine, m.p. 202–204°.

Anal. Calcd. for $C_{19}H_{25}O_4N$: C, 68.9; H, 7.6. Found: C, 68.6; H, 8.0.

A solution buffered at *p*H 5 and containing 83 mg. of the glycol XVIII and 76 mg. of metaperiodic acid was allowed to stand at room temperature for 90 minutes after which arsenious acid was added to destroy excess oxidant. The *p*H was adjusted to 8.5 with potassium carbonate, and the solution was extracted exhaustively with methylene chloride. From the aqueous portion, formaldehyde was isolated as the dimedone derivative in 61 mg. (84%) yield, m.p. 188–189°. From the methylene chloride portion, by extracting with *p*H 7 bisulfite–sulfite buffer, basifying and re-extracting into methylene chloride, 66 mg. (88% yield) of dihydrocodeinone was obtained, identical with an authentic sample.

6-Methyldihydrodesoxycodeine (VIc).—Hydrogenation of 5 g. of 6-methylenedihydrodesoxycodeine (XVIIc) in 120 ml. of glacial acetic acid, to which 1.5 ml. of concd. hydrochloric acid and 100 mg. of platinum oxide had been added, ceased after 27 hours and the absorption of 135 mole % of hydrogen. Filtration using a water wash, addition of excess aqueous ammonia, and extraction with methylene chloride gave crude alkaloidal material which was chromatographed on alumina. 6-Methyldihydrodesoxycodeine was obtained as the non-phenolic fraction (negative diazotized sulfanilic acid test) by elution with benzene–hexane (1:1) and crystallization from heptane; 2.2 g. (44% yield), m.p. 126–127°, $[\alpha]^{21}D$ −160° (*c* 1.1); λ_{max}^{EtOH} 284 mμ, ε 1690.

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.3; H, 8.4; C-CH_3, 5.0. Found: C, 76.5; H, 8.4; C-CH_3, 4.2.

Further elution with chloroform gave 6-methyltetrahydrodesoxycodeine, m.p. 156–158°, $[\alpha]^{25}D$ −5.3° (*c* 0.8) [reported[8] m.p. 157.5–158.5°, $[\alpha]^{20}D$ −4.5° (*c* 0.6)].

6-Methyldihydrodesoxymorphine.—A mixture of 2 g. of 6-methyldihydrodesoxycodeine and 6 g. of pyridine hydrochloride were heated in a nitrogen atmosphere for seven minutes in a bath pre-heated to and maintained at 220°. The reaction mixture was immediately cooled in an ice-bath, 30 ml. of water containing a pinch of sodium hydrosulfite was added and the cold solution, to which an equal volume of ether had been added, was adjusted to *p*H 12 with sodium hydroxide. The ether layer was separated, the aqueous phase was extracted with three additional equal volume portions of ether, and the combined and dried ether extracts on evaporation gave 980 mg. of recovered 6-methyldihydrodesoxycodeine. Cooling the aqueous phase and adding acid to *p*H 9 caused precipitation of a brown solid which was combined with the chloroform extract of the filtrate, and the total phenolic material thus obtained was crystallized from ethanol. Sublimation at 100° (0.3 mm.) gave 608 mg. of 6-methyldihydrodesoxymorphine, m.p. 224–226°, $[\alpha]^{21}D$ −166° (*c* 1.0); λ_{max}^{EtOH} 287 mμ (ε 1680), λ_{max} 300 mμ (ε 2690) in ethanolic sodium hydroxide.

Anal. Calcd. for $C_{18}H_{23}O_2N$: C, 75.8; H, 8.1. Found: C, 76.0; H, 7.8.

When a methanolic solution of 6-methyldihydrodesoxymorphine was treated with ethereal diazomethane, 6-methyldihydrodesoxycodeine resulted in quantitative yield.

6-Methylenedihydrodesoxymorphine.—Cleavage of the O^3-methyl ether was effected with pyridine hydrochloride as in the case of the 6-methyl analog except that heating was maintained for six minutes. Separation into non-phenolic and phenolic fractions gave a 5% recovery of starting ether and a 22% yield of 6-methylenedihydrodesoxymorphine, crystallized from acetone and sublimed, m.p. 196–198°, $[\alpha]^{21}D$ −140° (*c* 1.0); λ_{max}^{EtOH} 287 mμ (ε 1470), λ_{max} 298 mμ (ε 2470) in ethanolic sodium hydroxide.

Anal. Calcd. for $C_{18}H_{21}O_2N$: C, 76.3; H, 7.4. Found: C, 76.0; H, 7.3.

6-Methylenedihydrodesoxycodeine, identical with authentic material, was obtained when the morphine derivative in methanol was etherified with diazomethane.

6-Methyl-7-hydroxydihydrocodeine (XIX).—To a solution of 1.16 g. (3.9 mmoles) of 6-methyl-Δ^6-desoxycodeine

(21) Although this compound has been assigned, arbitrarily, the Δ^5-structure, it may just as well be the Δ^6-enol tosylate. The former would arise by 1,2-hydrogenation and the latter would result from 1,4-hydrogen addition. At this time, we have no definitive evidence on either the course of hydrogenation or the position (Δ^5 or Δ^6) of the remaining double bond.

(22) See ref. 15. To estimate the amount of triphenylphosphinemethylene reagent present, an aliquot was treated with excess cyclohexanone and the intensity of the infrared carbonyl absorption was compared with that of standard cyclohexanone solutions.

(V)[6] in 75 ml. of ether, 1.0 g. (3.9 mmoles) of osmium tetroxide dissolved in 20 ml. of ether and 1.3 ml. (16.8 mmoles) of pyridine was added. Precipitation began immediately and, after being kept at room temperature for five hours, the reaction mixture was centrifuged. The precipitated osmate ester was washed with ether and then was boiled with ethanol (125 ml.) and sodium sulfite solution (13 g. in 60 ml. of water) for three hours. Filtering, washing with hot ethanol, and concentrating the combined filtrate and washes gave a crystalline residue which was crystallized from methanol–water (2:1) and benzene. The yield of 6-methyl-7-hydroxydihydrocodeine was 86%, m.p. 184–186°, $[\alpha]^{21}D$ −116° (*c* 1.0). It was hygroscopic and was best analyzed as the hemihydrate.

Anal. Calcd. for $C_{19}H_{25}O_4N \cdot {}^1/_2H_2O$: C, 67.1; H, 7.6. Found: C, 67.2; H, 7.7.

Acetylation of 6-Methyl-7-hydroxydihydrocodeine.—The glycol XIX (493 mg., 1.5 mmoles) in a solution of 15 ml. of acetic anhydride and 2 ml. of pyridine was heated for two hours at 80°. Concentration at reduced pressure left a residue which was crystallized twice from benzene giving 450 mg., 80%, of 6-methyl-7-acetoxydihydrocodeine (XX), m.p. 150–151°, $[\alpha]^{26}D$ −118° (*c* 0.83).

Anal. Calcd. for $C_{21}H_{27}O_5N$: C, 67.6; H, 7.2; acetate, 11.5. Found: C, 67.7; H, 7.1; acetate, 11.8.

An acetylation was carried out as above except that the reaction mixture was heated at 120°, and the residue was distributed between water (*p*H 10.5) and chloroform. Evaporation of the chloroform and crystallization of this residue gave material which was obviously a mixture, m.p. 165–175°. Repeated crystallization from benzene and then from methanol finally gave 200 mg. of **acetyl-6-methyl-7-acetoxydihydrocodeine** (from 2.5 g. of glycol XIX), m.p. 203–204°, $[\alpha]^{26}D$ −84° (*c* 1.0).

Anal. Calcd. for $C_{23}H_{29}O_6N$: C, 66.5; H, 7.0; acetate, 20.8. Found: C, 66.7; H, 7.1; acetate, 20.7.

Dehydration of 6-Methyl-7-acetoxydihydrocodeine (XX).—To a solution of 17.9 g. (48 mmoles) of 6-methyl-7-acetoxydihydrocodeine in 65 ml. of absolute chloroform was added 5.6 ml. of thionyl chloride in 20 ml. of chloroform, and the mixture was heated under reflux for 3.5 hours. Concentration *in vacuo* left a residue which was suspended in 200 ml. of water and extracted with methylene chloride after alkalization with concentrated ammonium hydroxide. The methylene chloride was evaporated, the residue was digested with benzene, and the benzene solution, after being filtered to remove a small amount of insoluble material, was chromatographed on 400 g. of alumina. Elution with benzene removed 6.0 g. of material and benzene–chloroform (1:1) removed an additional 0.6 g., giving a total of 6.6 of fraction A. Elution was then continued with chloroform to obtain 7.1 g. of fraction B. Finally, washing the column with methanol led to the recovery of 1.5 g. (8%) of **6-methyl-7-hydroxydihydrocodeine (XIX).**

Fraction A (strong absorption at 5.80 μ) was crystallized from methanol–water and 5.5 g. (32% yield) of **6-methylene-7-acetoxydihydrodesoxycodeine (XXIII)** was obtained; m.p. 103–104°, $[\alpha]^{21}D$ −139° (*c* 1.2).

Anal. Calcd. for $C_{21}H_{25}O_4N$: C, 71.0; H, 7.0; acetate, 12.1. Found: C, 71.3; H, 7.2; acetate, 12.8.

Fraction B was crystallized from benzene several times to give 4.1 g. (27% yield) of **6-methylene-7-hydroxydihydrodesoxycodeine (XXIV)**, m.p. 192–193°, $[\alpha]^{21}D$ −156° (*c* 1.0), broad absorption at 2.8–3.2 μ.

Anal. Calcd. for $C_{19}H_{23}O_3N$: C, 72.8; H, 7.3. Found: C, 72.6; H, 7.0.

Evaporation of the mother liquors from crystallization of XXIV from fraction B left a residue which gave a strong coupling test with diazotized sulfanilic acid and showed strong absorption at 6.00 μ. This material was dissolved in benzene and chromatographed on alumina. After benzene and then ether had removed small amounts of material, the bulk of the material was eluted with chloroform and was crystallized three times from benzene. This resulted in 2.5 g. (17% yield) of **6-methyl-7-oxo-Δ⁵-dihydrodesoxycodeine (XXVIII)**, m.p. 177–178°, $[\alpha]^{22}D$ −36° (*c* 1.0); λ_{max}^{EtOH} 234 (ε 16,250), 280 (ε 2,150) mμ.

Anal. Calcd. for $C_{19}H_{21}O_3N$: C, 72.8; H, 7.3; C–CH_3, 4.8. Found: C, 73.0; H, 7.4; C–CH_3, 4.8.

Hydrolysis of 6-methylene-7-acetoxydihydrodesoxycodeine (XXIII) isolated from fraction A was achieved on standing at room temperature overnight with 2 *N* aqueous ethanolic potassium hydroxide, and 6-methylene-7-hydroxydihydrodesoxycodeine (XXIV), identical with that isolated from fraction B, was obtained in nearly quantitative yield.

Acetylation of 6-methylene-7-hydroxydihydrodesoxycodeine with acetic anhydride in pyridine proceeded at room temperature for 18 hours and isolation by the usual procedure gave an 85% yield of 6-methylene-7-acetoxydihydrodesoxycodeine, m.p. 100–102°.

Hydroxylation of 6-methylene-7-acetoxydihydrodesoxycodeine with osmium tetroxide was carried out exactly as in the previous case with 6-methylenedihydrodesoxycodeine (XVII) above, and the resulting glycol was cleaved with periodate. From this cleavage, formaldehyde was isolated as the dimedone derivative, m.p. 188–189°.

6-Methyl-7-acetoxydihydrodesoxycodeine (XXVI).—Hydrogenation of 5.3 g. (15 mmoles) of 6-methylene-7-acetoxydihydrodesoxycodeine (XXIII) in 100 ml. of glacial acetic acid containing 1.5 ml. of concentrated hydrochloric acid and 150 mg. of platinum oxide proceeded at room temperature and atmospheric pressure. Hydrogen absorption ceased after 20 hours and an uptake of 194 mole % of hydrogen. The platinum was removed by filtration, the filtrate was concentrated *in vacuo*, the residue was suspended in cold aqueous ammonia, and the suspension was extracted with methylene chloride. Evaporation of the methylene chloride left a residue from which phenolic material was removed[11] and the non-phenolic fraction (2.3 g.) was chromatographed on alumina (60 g.). Elution with benzene removed 1.74 g. of the crude acetate and continued elution with methanol gave 400 mg. of 6-methyl-7-hydroxydihydrodesoxycodeine (XXVII), identical with the material obtained below by hydrolysis. The acetate was purified by crystallization from heptane and 6-methyl-7-acetoxydihydrodesoxycodeine (XXVI) thus obtained melted at 100–102°, $[\alpha]^{21}D$ −170° (*c* 0.9).

Anal. Calcd. for $C_{21}H_{27}O_4N$: C, 70.6; H, 7.6. Found: C, 70.7; H, 7.6.

Hydrolysis.—A 1.5-g. portion of 6-methyl-7-acetoxydihydrodesoxycodeine (XXVI) was dissolved in 100 ml. of ethanol, a solution of 1 g. of potassium hydroxide in 10 ml. of water was added, and the solution was allowed to stand overnight at room temperature. Concentration at reduced pressure removed most of the ethanol, and a crystalline solid separated. Cooling, filtration and crystallization from ethanol–water (1:1) gave 1.2 g. of **6-methyl-7-hydroxydihydrodesoxycodeine (XXVIIc)**, m.p. 147–149°, $[\alpha]^{21}D$ −154° (*c* 0.92).

Anal. Calcd. for $C_{19}H_{25}O_3N$: C, 72.4; H, 7.9; C–CH_3, 4.8. Found: C, 72.3; H, 7.8; C–CH_3, 4.5.

Oppenauer Oxidation of 6-Methyl-7-hydroxydihydrodesoxycodeine.—Oxidation of 6-methyl-7-hydroxydihydrodesoxycodeine (XXVIIc), using the same conditions as in the oxidation of dihydrocodeine,[3b] gave almost a quantitative yield of material whose infrared spectrum was identical with that of 6-methyl-7-oxo-Δ⁵-dihydrodesoxycodeine (XXVIII), isolated from the dehydration of 6-methyl-7-acetoxydihydrodesoxycodeine (above). On crystallization from benzene, it melted at 90–93°, $[\alpha]^{21}D$ −39° (*c* 1.0), apparently a dimorphic modification since recrystallization from ethyl acetate gave material of m.p. 177–178°, identical with that isolated from the dehydration.

6-Methyl-7-hydroxydihydrodesoxymorphine.—Conversion of XXVIIc to the corresponding morphine derivative was accomplished by heating 315 mg. of XXVII and 1 g. of pyridine hydrochloride at 220° for six minutes. Distribution of the product between ether and aqueous alkali led to the recovery of 110 mg. of XXVII from the ether layer, and chloroform extraction of the aqueous phase, adjusted to *p*H 9, gave the phenolic material. This was crystallized from ethanol and sublimed at 185° (0.01 mm.), yielding 6-methyl-7-hydroxydihydrodesoxymorphine, m.p. 270–273° (with dec. in a nitrogen-filled capillary), $[\alpha]^{21}D$ −163° (*c* 0.93); λ_{max}^{EtOH} 286 mμ (ε 1680), λ_{max} 298 mμ (ε 2980) in ethanolic sodium hydroxide.

Anal. Calcd. for $C_{18}H_{23}O_3N$: C, 71.8; H, 7.6. Found: C, 71.9; H, 7.4.

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