0.003 mole) was added to a mixture of methanol (5 ml.) and 10% sodium hydroxide (3.5 ml., 0.009 mole). To the resulting solution, was added dropwise 15% hydrogen peroxide (4 ml., 0.009 mole) with stirring and ice cooling. Yellow needles gradually separated from the red solution which finally turned to a thick paste. After standing overnight in a refrigerator, it was filtered, and acidified with dilute hydrochloric acid to give a yellow crystalline product (0.6 g., 57.4%), m.p. > 320°.

Upon crystallization from glacial acetic acid, light yellow needles separated which gave a brown color with ferric chloride in ethanol and an orange-red color in concentrated sulfuric acid; they were difficultly soluble in hot ethanol or acetone.

Anal. Calcd. for $C_{17}H_{10}O_7$: C, 62.58; H, 3.07. Found: C, 62.49; H, 3.08.

3′,4′-Dihydroxy-6-carboxyflavonol.—Ozawa's[3] method was used in this preparation. To a solution of aluminum chloride (1 g., 0.007 mole) in nitrobenzene (20 ml.) was added 3′,4′-methylenedioxy-6-carboxyflavonol (1 g., 0.003 mole) in small portions with shaking at room temperature. After standing overnight (calcium chloride tube), the resulting dark orange viscous mass was decomposed by the addition of water (20 ml.) and concentrated hydrochloric acid (3 ml.). After removal of the nitrobenzene by steam distillation, a yellow solid (0.9 g.) was formed which was crystallized from ethanol to give yellow plates, m.p. > 320° with darkening around 310° and sintering at 316°. The compound gave a deep dark brown color with ferric chloride in ethanol and an orange red color in concentrated sulfuric acid, it was very slightly soluble in hot water but readily soluble in aqueous sodium carbonate. It was adsorbed upon silicic acid in ethanol with decomposition and the decomposed matter eluted by glacial acetic acid. On treatment with magnesium in ethanolic concentrated hydrochloric acid, it developed a red color and in ethanolic acetic acid, a greenish-yellow color.

Anal. Calcd. for $C_{16}H_{10}O_7$: C, 61.15; H, 3.18. Found: C, 61.02; H, 3.49.

Triacetyl Derivative.—The above flavonol (0.2 g.) was acetylated with acetic anhydride (0.5 ml.) in the presence of pyridine (1 ml.) by standing for 15 hours in a refrigerator. The product was crystallized from 80% acetic acid to give colorless prisms, m.p. 218–220° (dec. with foaming), which gave no color with ferric chloride.

Anal. Calcd. for $C_{22}H_{16}O_{10}$: C, 60.00; H, 3.64. Found: C, 60.25; H, 4.12.

(3) H. Ozawa, T. Okuda, M. Kawanishi and K. Fujii, *J. Pharm. Soc. Japan*, **71**, 1182 (1951).

Beckmann Rearrangement of the Oxime.—A solution of 0.4 g. of the oxime of 2-hydroxy-5-carboxyacetophenone in 4 ml. of concentrated sulfuric acid was heated at 100° for one-half hour, and the cooled solution was poured into ice-water. The resulting precipitate was collected, washed with water and dried.

The crude product A (0.36 g.) began to sinter at 140° and melted completely at 215°. A portion of A (0.20 g.) was repeatedly recrystallized from 50% acetic acid to yield colorless prisms (0.03 g.), which gave no color reaction with ferric chloride and which melted at 186–188° alone or on admixture with a sample of 2-methyl-5-carboxybenzoxazole.

Anal. Calcd. for $C_9H_7NO_3$: N, 7.91. Found: N, 7.95.

The filtrate from the recrystallizations was evaporated to dryness, and the residue was recrystallized repeatedly from 50% acetic acid to yield colorless prisms (0.09 g.) which gave a yellowish-brown color with ferric chloride and melted at 258° (dec. with foaming). A mixture with a sample of 3-acetamino-4-hydroxybenzoic acid showed no depression of melting point.

Anal. Calcd. for $C_9H_9NO_4$: N, 7.18. Found: N, 7.19.

The remaining portion of the crude product was refluxed with 15% hydrochloric acid for one hour to give prismatic crystals melting at 275° dec. They were identified as the hydrochloride of 3-amino-4-hydroxybenzoic acid by the mixed m.p. method.

Anal. Calcd. for $C_7H_7NO_3 \cdot HCl$: N, 7.47. Found: N, 7.52.

The hydrochloride was made alkaline with sodium sulfide in water to give the free base, m.p. 205°, a mixture with a sample of 3-amino-4-hydroxybenzoic acid, m.p. 202°, showed no depression of the melting point.

Anal. Calcd. for $C_7H_7NO_3$: N, 9.15. Found: N, 9.26.

3-Acetamino-4-hydroxybenzoic Acid.—3-Amino-4-hydroxybenzoic acid (0.15 g.) was acetylated with acetic anhydride (0.2 ml.) in 50% acetic acid at room temperature. On crystallization from 50% acetic acid, colorless prisms, melting at 258° (dec. with foaming), were produced.

Anal. Calcd. for $C_9H_9NO_4$: N, 7.18. Found: N, 7.29.

2-Methyl-5-carboxybenzoxazole.—A small portion of 3-acetamino-4-hydroxybenzoic acid was carefully distilled by heating in a free flame at atmospheric pressure, and the distillate was crystallized from benzene to give colorless prisms, m.p. 186–188°.

Anal. Calcd. for $C_9H_7NO_3$: N, 7.91. Found: N, 7.97.

TOKYO, JAPAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

6-Substituted Δ^6-Desoxymorphines

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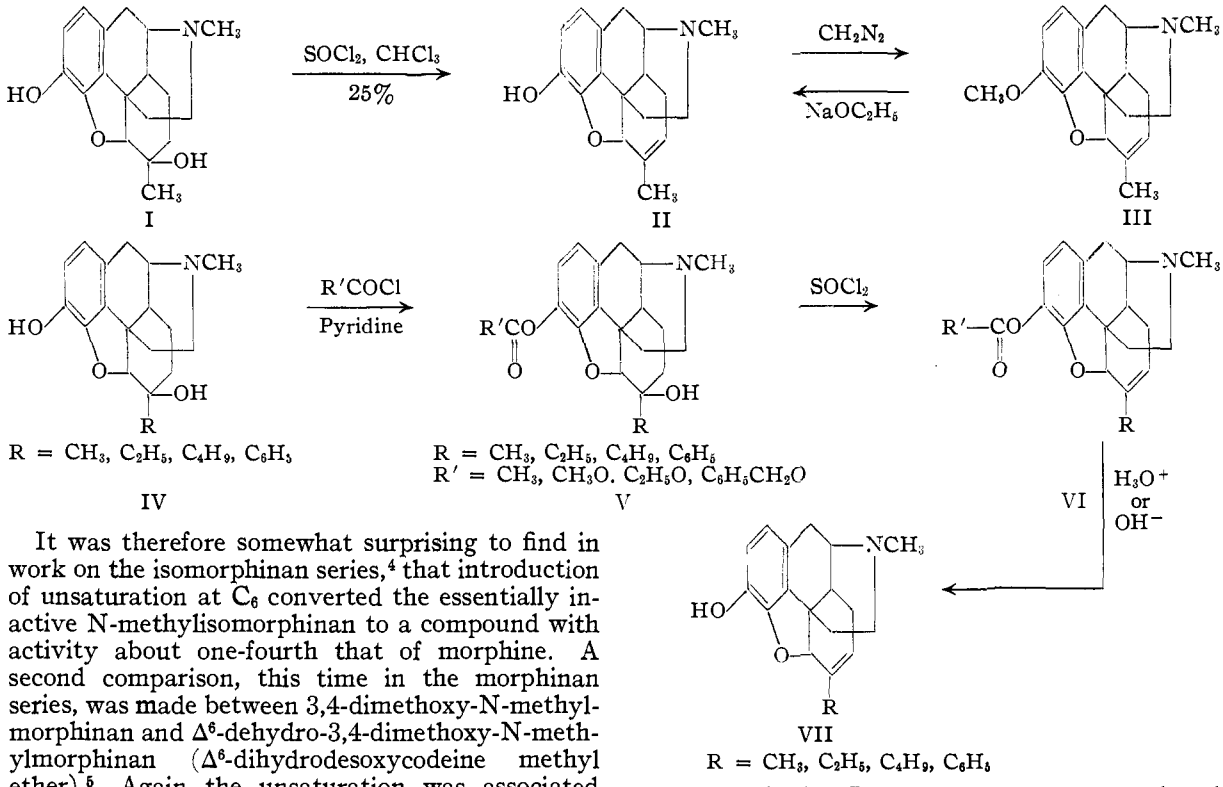
A series of pharmacologically interesting 6-substituted Δ^6-desoxymorphines (VII) has been synthesized. Although only small yields of the desired olefins were obtained by dehydration of the corresponding 6-substituted dihydromorphines and by demethylation of suitable Δ^6-desoxycodeines, the new analgetics were readily produced by acylation of the dihydromorphines (IV) followed by thionyl chloride dehydration and hydrolysis of the protecting groups.

In the morphine series of analgetics it is well known that "muzzling" or eliminating the 6-hydroxyl increases potency though frequently at the expense of other desirable properties such as duration of action, minimal respiratory depression and relative freedom from convulsant and emetic actions.[1] Thus O,O′-diacetylmorphine, dihydromorphinone and dihydrodesoxymorphine-D ("Desomorphine") are all considerably more potent analgetics than the parent alkaloid. No particular effect has been ascribed to unsaturation in the oxygen-free alicyclic ring, and in fact the pair "Desomorphine" and Δ^7-desoxymorphine show very similar activity,[2] while Δ^6-desoxymorphine (desoxymorphine-C) was reported to be less active.[3]

(1) N. B. Eddy, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 245 (1950); Small, Eddy, Mosettig and Himmelsbach, "Studies on Drug Addiction," Supplement No. 138 to the Public Health Reports, U. S. Gov't. Printing Office, Washington, 1938.

(2) (a) Personal communication from Dr. N. B. Eddy; (b) synthesis by H. Rapoport and R. M. Bonner, THIS JOURNAL, **73**, 5485 (1951).

(3) N. B. Eddy and H. A. Howes, *J. Pharm. Expt. Ther.*, **55**, 257 (1935).



It was therefore somewhat surprising to find in work on the isomorphinan series,[4] that introduction of unsaturation at C_6 converted the essentially inactive N-methylisomorphinan to a compound with activity about one-fourth that of morphine. A second comparison, this time in the morphinan series, was made between 3,4-dimethoxy-N-methylmorphinan and Δ6-dehydro-3,4-dimethoxy-N-methylmorphinan (Δ6-dihydrodesoxycodeine methyl ether).[5] Again the unsaturation was associated with change from a substantially inactive material to an analgetic, in this case about one-half as potent as morphine. The present report describes the preparation of a number of Δ6-desoxymorphines which were made in an extension of the above described finding to the morphine (4,5-epoxymorphinan) type of analgetic.

The 6-alkyldihydrocodeines and 6-methyldihydromorphine described by Small and Rapoport[6] appeared to present a possible entry to the desired compounds. These workers had in fact already dehydrated the dihydrocodeine analog to obtain 6-methyl-Δ6-desoxycodeine. However, it was immediately evident that dehydration of 6-methyldihydromorphine (I) was far more difficult than with the corresponding codeine compound. Thus the mild conditions used by Small and Rapoport, thionyl chloride in refluxing chloroform for two hours, had no effect while higher temperatures caused extensive attack on the aromatic ring. At optimum conditions a 20–30% yield of difficultly purified 6-methyl-Δ6-desoxymorphine (II) could be obtained. Preliminary testing indicated very high analgetic activity for this compound and created a need for a better route to this and related substances.

With the failure of a series of dehydrating agents other than thionyl chloride (see Experimental section), cleavage of the methoxyl group in 6-methyl-Δ6-desoxycodeine (III) was tried by a variety of methods and widely varied conditions. Pyridine hydrochloride[2b] at 175–225° and reaction times of 5–30 minutes gave at best only negligible amounts of II. Lower temperatures produced little cleavage and above 210° the dihydrofuran ring opened to give products sensitive to alkali. Sodium ethoxide at 140° under nitrogen produced cleavage and yielded the desired olefin in 20–30% yields with nearly 50% of the starting material recoverable for recycling. More stringent conditions only reduced the yield and recovery of starting material, while a switch to potassium *t*-butoxide was not helpful.

By contrast, dehydration of the phenolic esters V was achieved in good yield. Derivatives of several types, acetyl, carboalkoxy or carbobenzoxy, were found to be useful and easily prepared using the anhydrides or chlorocarbonates in pyridine solutions. Thionyl chloride in cold pyridine or refluxing chloroform gave satisfactory dehydration, and hydrolysis of the protecting group then yielded high quality 6-methyl-Δ6-desoxymorphine in overall yield of 60–70%. Treatment with diazomethane gave 6-methyl-Δ6-desoxycodeine (III) identical with that from dehydration of 6-methyldihydrocodeine. This procedure was used to obtain other 6-substituted-Δ6-desoxymorphines (VII), usually without isolation of the olefin esters VI but with isolation of the tertiary carbinol esters V and purification of the final products.

Esterification of the tertiary hydroxyl group in the 6-substituted derivatives was not readily achieved, as was to be expected from the previous work of Small and Rapoport[6] with the codeine analogs. Prior conversion to the lithium salt, however, yielded the desired 3,6-diacetyl-6-methyldihydromorphine. Acetylation of the Δ6-derivatives, of course, was readily achieved by standard methods.

Hydrogenation of II with a platinum catalyst in dilute sulfuric acid resulted in uptake of two moles

(4) Epimeric with the morphines or morphinans at C_{14}; *cf.* M. Gates, *et al.*, THIS JOURNAL, **72**, 1141 (1950).

(5) M. Gates and G. Tschudi, *ibid.*, **72**, 4839 (1950). We are indebted to Dr. Gates for a sample of this compound.

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

of hydrogen and the formation of an alkali sensitive product which was isolated only as the hydrochloride.

Analgetic Activity.—Although details of the pharmacological studies will be reported elsewhere, it is in order to indicate approximate activity relationships at this time.[7] The most potent compound investigated was 6-methyl-Δ^6-desoxymorphine (II), which gave complete analgesia of rather short duration in all the rats at doses as low as 63 γ/kg. Acetylation of II did not greatly alter the activity but did shorten the duration for a given dosage. The 6-ethyl and 6-butyl homologs of II were still extremely potent analgetics but slightly less active than II while the 6-phenyl olefin was significantly less active. Despite these encouraging results following introduction of unsaturation at C_6–C_7 in morphine type structures, results to be published later will show that this structural alteration is far from being an invariably successful method of boosting analgetic potency.

Of the intermediates 3-acetyl-6-methyldihydromorphine was potent but quite toxic. The corresponding 3,6-diacetyl compound was only about one-eighth as active as the monoacetate. Substitution of phenyl for alkyl in the dihydromorphines markedly reduced the activity.

Experimental[8]

6-Methyldihydromorphine (I).—The procedure of Small and Rapoport[6] was followed, with 2.2 to 2.5 equivalents of methyl lithium being used for each mole of dihydromorphinone. Yields of 50 to 60% of recrystallized (acetone) product (m.p. 209–210°) were obtained in several runs.

Several attempts were made to dehydrate 6-methyldihydromorphine with thionyl chloride in refluxing chloroform. At best yields of 20–30% of 6-methyl-Δ^6-desoxymorphine were obtained. Separation of impurities and the *t*-alcohol was difficult—several recrystallizations from isopropyl alcohol and finally ethyl acetate being necessary to obtain a colorless product melting above 220°. $POCl_3$ in pyridine (25°) with and without a trace of water converted the phenol to water-soluble derivatives from which none of the desired olefin was obtained. Concentrated HCl did not dehydrate the 6-alkyldihydromorphines but was successful with the 6-phenyl compound (see below). Attempted azeotropic removal of water in refluxing toluene (iodine, *p*-toluenesulfonic acid or oxalic acid as catalysts) was ineffective. $KHSO_4$ in tetralin (190°) destroyed the compound. Refluxing acetic anhydride gave only the 3-acetyl derivative (see below).

6-Ethyldihydromorphine (IV, R = C_2H_5).—As described above for the methyl derivative, 10 g. of dihydromorphinone and 0.11 mole of ethyllithium gave 6 g. of the crude tertiary alcohol which after recrystallization from acetone melted at 212–213°, $\alpha^{25}D$ −141° (*c* 1, alc.).

Anal. Calcd. for $C_{19}H_{25}O_3N$ (315.4): C, 72.35; H, 7.99; N, 4.44. Found: C, 72.76; H, 8.13; N, 4.48.

The hydrobromide salt was prepared from alcoholic HBr and ether, m.p. 291–297° dec.

Anal. Calcd. for $C_{19}H_{26}O_3NBr$ (396.3): C, 57.58; H, 6.61; N, 3.53. Found: C, 57.99; H, 6.61; N, 3.29.

6-Butyldihydromorphine (IV, R = C_4H_9).—*n*-Butyllithium (0.2 mole) when reacting with 17.1 g. (0.06 mole) of dihydromorphinone at 0° gave 3.5 g. of recovered ketone. The oily residue slowly crystallized and after washing with acetone melted at 175° (yield 4.5 g.). Recrystallization did not raise the melting point. The analytical sample was sublimed *in vacuo*, $[\alpha]^{25}D$ −150° (*c* 1, alc.).

Anal. Calcd. for $C_{21}H_{29}O_3N$ (343.5): C, 73.43; H, 8.51; N, 4.08. Found: C, 73.53; H, 8.11; N, 4.03.

The hydrochloride melted at 320–330° dec.

Anal. Calcd. for $C_{21}H_{29}O_3N\cdot HCl\cdot H_2O$: C, 63.41; H, 8.10. Found: C, 63.29; H, 6.71.

6-Phenyldihydromorphine (IV, R = C_6H_5).—Dihydromorphinone (18 g., 0.063 mole) was added to an excess of phenyllithium solution cooled in ice. Extraction of the base into chloroform and removal of the solvent gave a residue which was slurried with 75 ml. of alcohol, chilled and filtered to give 17 g. of solid, m.p. 130–145°. Leaching with 150 ml. of boiling alcohol, filtering from 4 g. of solid (unchanged ketone) and chilling precipitated 9.5 g. of 6-phenyldihydromorphine, m.p. 135–137°. A small sample recrystallized for analysis melted at 138–140° (gas evolution), $\alpha^{25}D$ −126° (*c* 1, alc.).

Anal. Calcd. for $C_{23}H_{25}O_3N\cdot{}^1/_2C_2H_5OH$ (386.5): C, 74.59; H, 7.30. Found: C, 74.27; H, 7.25.

The hydrochloride salt (from alcohol-ether) melted at 276–281° dec., $\alpha^{25}D$ −104° (*c* 0.5, alc.).

3-Carboethoxy-6-methyldihydromorphine (V).—Three grams of 6-methyldihydromorphine in 20 ml. of pyridine was treated dropwise with 1.5 ml. of ethyl chlorocarbonate with stirring and cooling in ice. After standing overnight at room temperature the solution was poured onto cracked ice containing an excess of $NaHCO_3$. Extraction with chloroform, removal of solvent and crystallization from ether yielded 3.0 g. of the ester, melting at 120–121° (unchanged on recrystallization), $\alpha^{25}D$ −216° (*c* 1, alc.).

Anal. Calcd. for $C_{21}H_{27}O_5N$ (373.4): C, 67.54; H, 7.28; N, 3.75. Found: C, 68.08; H, 7.26; N, 4.20.

3-Carbomethoxy-6-methyldihydromorphine (V).—Reaction of methyl chlorocarbonate and 6-methyldihydromorphine as described above for the ethoxy derivative gave the ester in good yield. After crystallization from ether it melted at 141°, $\alpha^{25}D$ −241° (*c* 1, alc.).

Anal. Calcd. for $C_{20}H_{25}O_5N$ (350.4): C, 66.83; H, 7.01; N, 3.90. Found: C, 67.42; H, 7.13; N, 3.96.

3-Carbethoxy-6-phenyldihydromorphine (V).—From 5 g. of 6-phenyldihydromorphine in 25 ml. of cold pyridine and 10% excess ethyl chlorocarbonate there was secured 5.08 g. of the "cathyl" derivative, m.p. 173–174°. Recrystallization from 60 ml. of boiling ether (filtering from a small residue) raised the melting point to 175–176°, $\alpha^{25}D$ −213° (*c* = 1, alc.).

Anal. Calcd. for $C_{26}H_{29}O_5N$: C, 71.69; H, 6.70; N, 3.22. Found: C, 71.73; H, 6.63; N, 3.24.

Since 6-phenyldihydromorphine dehydrated directly with hydrochloric acid, this derivative was not utilized in the dehydration.

Dehydration of 3-"Cathyl"-6-methyldihydromorphine (V → VII).—Two and seven-tenths grams of the carbonate in 100 ml. of absolute chloroform was treated dropwise with cooling with 3 ml. of thionyl chloride. After gentle refluxing overnight the solution was cooled, poured on ice, made *p*H 9 with ammonia, extracted with chloroform and concentrated *in vacuo*. The light yellow sirup did not readily crystallize and was, therefore, saponified to give 6-methyl-Δ^6-desoxymorphine using 1 g. of KOH in 50 ml. of 95% alcohol (30 min. gentle warming, nitrogen atmosphere, trace $NaHSO_3$). The olefin crystallized readily from ethyl acetate to give 1.27 g. of product, m.p. 225–229°, $\alpha^{25}D$ −215° (*c* 1, alc.). A second crop yield of 0.27 g. melted slightly lower. Further purification raised the melting point to 235–237°.

Anal. Calcd. for $C_{18}H_{21}O_2N$ (283.3): C, 76.28; H, 7.47; N, 4.94. Found: C, 76.31; H, 7.40; N, 4.81.

The hydrochloride salt melted 288–289°, $\alpha^{25}D$ −186° (*c* 1, alc.) and was anhydrous after crystallization from alcohol–ether and drying at 100° (1 mm.). The hydrobromide salt (from alcohol) decomposed at 293–297°, $\alpha^{25}D$ −167° (*c* 0.6, methanol). In refluxing benzene (3 hours) the methiodide of II was prepared from 0.28 g. of base and 0.1 ml. of CH_3I. The yield was quantitative. When recrystallized from alcohol containing a trace of ether it melted at 290–291°. For analysis a portion was dried at 100° (1 mm.).

(7) For these results we are indebted to Drs. C. A. Winter and P. D. Orahovats and their associates of the Merck Institute for Therapeutic Research. The d'Amour-Smith procedure for measuring analgesia in rats was used.

(8) Melting points were taken on a Fisher–Johns microblock and are corrected. We are indebted to Mr. R. N. Boos and his associates for the microanalytical data reported herein.

Anal. Calcd. for $C_{19}H_{24}O_2NI$ (425.3): C, 53.65; H, 5.69. Found: C, 53.86; H, 5.39.

Phase solubility studies on the sample of II indicated a purity of 99.2 ± 0.5%. The pK_a was found to be 9.3 (9.85 for morphine). Comparison of the infrared spectra[9] with morphine indicated the complete absence of a normal hydroxyl band—the phenolic hydroxyl of this and related morphine compounds (without an aliphatic hydroxyl) is apparently shifted by bonding.

Dehydration of 3-Carbomethoxy-6-methyldihydromorphine (V → VI).—A pyridine (25 ml.) solution of 2.4 g. of the carbonate was treated dropwise (cooling in ice) with 2 ml. of thionyl chloride and then allowed to stand overnight. Isolation of the base by decomposition on ice–$NaHCO_3$, extraction into chloroform, thorough washing with water and removal of solvent *in vacuo* gave **3-carbomethoxy-6-methyl-Δ^6-desoxymorphine**. One and eight-tenths grams of the olefin was secured as a solid melting at 135–140°.

Further purification was not attempted. Instead the ester was saponified (dilute alcoholic NaOH) to produce 1.33 g. of II, melting at 228–232°. One further crystallization from ethyl acetate raised the melting point to 236–237°, $\alpha^{25}D$ −227° (*c* 1, alc.).

Anal. Calcd. for $C_{18}H_{21}O_2N$ (283.3): C, 76.28; H, 7.47; N, 4.94. Found: C, 76.43; H, 7.40; N, 5.14.

The above carbomethoxy derivative was also dehydrated by seven hours refluxing with a slight excess of thionyl chloride in absolute chloroform. After removal of the protecting group by warming on a steam-bath with 2 *N* HCl for one hour, conversion back to the base and crystallization from ethyl acetate the yield of II was 60%.

In a similar fashion the carbobenzoxy group was used as a protecting group for the phenol during dehydration. Purification of the intermediates was not attempted and the over-all yield of 6-methyl-Δ^6-desoxymorphine was lower than described above.

Alkaline Cleavage of 6-Methyl-Δ^6-desoxycodeine (III).—6-Methyl-Δ^6-desoxycodeine[6] (1 g.) was dissolved in a solution containing 4 g. of sodium in 100 ml. of absolute alcohol. In a glass-lined bomb the solution was heated at 150° for 30 hr. under 500 p.s.i. nitrogen. Removal of the alcohol <40° and separation of the alkali-soluble portion yielded 0.2 g. of crystalline phenol, melting at 231–233° (from acetone). Recrystallization raised the melting point to 239° (no depression on admixture with material obtained above by dehydration). A 0.4-g. fraction of 6-methyl-Δ^6-desoxycodeine was recovered from the alkali-insoluble fraction above.

6-Ethyl-Δ^6-desoxymorphine (VII, R = C_2H_5).—6-Ethyldihydromorphine (1.7 g.) was converted to the carbonate ester with 1 ml. of ethyl chlorocarbonate in pyridine. The oily product was dehydrated by refluxing overnight in 50 ml. of absolute chloroform with 1 ml. of $SOCl_2$. Isolation of the crude olefin and saponification (1 g. KOH in 30 ml. 80% alcohol) resulted in a 40% over-all yield of VII (R = C_2H_5), m.p. 122–124° (from ethyl acetate), $\alpha^{25}D$ −185° (*c* 1, alc.). The hydrobromide salt (from alcohol–ether) melted at 277–284° dec. The analytical sample was dried at 78° (1 mm.).

Anal. Calcd. for $C_{19}H_{24}O_2NBr$ (378.3): C, 60.32; H, 6.39. Found: C, 59.62; H, 6.13.

6-Butyl-Δ^6-desoxymorphine (VII, R = C_4H_9).—Four and five-tenths grams of 6-butyldihydromorphine was converted to the 3-carbethoxy derivative (4 g., oil) which was dehydrated with 3 ml. of $SOCl_2$ in pyridine (overnight, 25°). Isolation by the above described procedure gave a 71% yield of the crude olefinic ester (viscous oil). After saponification (3 g. of NaOH in 70 ml. of 50% alcohol, trace $NaHSO_3$) and crystallization from ethyl acetate the phenol melted at 167 to 169°, $\alpha^{25}D$ −215° (*c* 1, alc.). Analysis of a sample dried *in vacuo* indicated solvation. Hence a small portion was sublimed at 180° (1 mm.).

Anal. Calcd. for $C_{21}H_{27}O_2N$ (325.4): C, 77.50; H, 8.36; N, 4.30. Found: C, 77.59; H, 8.40; N, 4.56.

The base was titrated with 0.1 *N* H_2SO_4 to yield a solution for analgetic testing.

6-Phenyl-Δ^6-desoxymorphine (VII, R = C_6H_5).—One gram of 6-phenyldihydromorphine was added in small portions with stirring to 10 ml. of concd. HCl (*T*, 15–20°). Most of the base dissolved and after 20 to 30 minutes a sticky gum separated. After standing for two days in a cold room the acid was neutralized and a chloroform extraction was made at *p*H 9. Removal of the solvent followed by two recrystallizations from alcohol yielded 0.4 g. of the olefin which melted at 152–154°, with slight preliminary softening, $\alpha^{25}D$ −341° (*c* 1, alc.). After sublimation (165° (0.1 mm.)) the sample was analyzed.

Anal. Calcd. for $C_{23}H_{23}O_2N$ (345.4): C, 79.97; H, 6.71. Found: C, 80.13; H, 6.45.

The hydrochloride (dec. 271–276°) contained two moles of water of hydration (Karl Fischer titration).

3-Acetyl-6-methyldihydromorphine.—Preferential acetylation of the phenolic hydroxyl of 6-methyldihydromorphine (1 g.) with acetic anhydride (0.36 ml.) in dry pyridine (15 ml.) was readily achieved in high yield. The product (sometimes melting ~ 142° when first isolated) was recrystallized from a small volume of ether, m.p. 166°, $\alpha^{25}D$ −231° (*c* 1, abs. alcohol).

Anal. Calcd. for $C_{20}H_{25}O_4N$ (343.4): C, 69.93; H, 7.34; N, 4.08. Found: C, 70.18; H, 7.65; N, 4.01.

3,6-Diacetyl-6-methyldihydromorphine.—6-Methyldihydromorphine (1 g., 0.0033 mole, vacuum dried, 70°) was treated dropwise with an excess (0.065 m.) of methyllithium at 0–5°. After the addition of an excess of acetic anhydride (cooling and stirring) the tacky gum was heated to reflux for 30 minutes and allowed to stand overnight. Decomposition on cold 2% acetic acid, extraction of the base (*p*H *ca.* 8.5—$NaHCO_3$) into chloroform, removal of the solvent and trituration with ethyl acetate produced the crystalline diacetate 0.54 g., m.p. 181–183°. Two recrystallizations from ethyl acetate gave a fraction melting 181–182°, $\alpha^{25}D$ − 82° (*c* 1, abs. alc.).

Anal. Calcd. for $C_{22}H_{27}O_5N$ (385.5): C, 68.55; H, 7.06; N, 3.63. Found: C, 69.04; H, 7.19; N, 4.11.

The hydrochloride (alcohol–ether) melted at 283–286° dec.

Anal. Calcd. for $C_{22}H_{27}O_5 \cdot HCl$ (421.9): C, 62.63; H, 6.69; N, 3.32. Found: C, 62.89; H, 6.98; N, 3.61.

3-Acetyl-6-methyl-Δ^6-desoxymorphine.—A 0.64-g. sample of VII (R = CH_3) in 20 ml. of cold pyridine was treated with 3 ml. acetic anhydride dropwise. Isolation by standard procedures gave 0.44 g. of the ester, m.p. 161–165°. Recrystallization from ether raised the m.p. to 169°, $\alpha^{25}D$ −229° (*c* 1, alc.).

Anal. Calcd. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12; N, 4.31. Found: C, 73.76; H, 7.13; N, 3.92.

The hydrochloride melted (dec.) at 285–290° (and depressed the melting point of I hydrochloride). Dehydration of V, (R = CH_3, R′ = CH_3) using $SOCl_2$ in pyridine also gave 3-acetyl-6-methyl-Δ^6-desoxymorphine (*ca.* 50%), m.p. 170°.

Anal. Found: C, 73.83; H, 7.04.

Alkaline saponification removed the 3-acetyl group to give 6-methyl-Δ^6-desoxymorphine, m.p. 236–237°.

Methylation of 6-Methyl-Δ^6-desoxymorphine (II → III).—An alcohol solution of 6-methyl-Δ^6-desoxymorphine (0.125 g.) was treated (0°) with excess ether solution of diazomethane. After standing overnight (25°) the solvents were removed to give 0.14 g. of an amorphous powder, melting at 150–165°. The solid in chloroform solution was extracted with 2.5 *N* NaOH, solvent was removed and the residue was triturated with methanol (82 mg. of crystals). Following recrystallization from methanol the melting point and mixed melting point with an authentic sample[6] was 171–172°. For analysis the base was sublimed at 115° (0.1 mm.).

Anal. Calcd. for $C_{19}H_{23}O_2N$ (297.4): C, 76.74; H, 7.81; N, 4.72. Found: C, 76.87; H, 7.52; N, 4.35.

Hydrogenation of 6-Methyl-Δ^6-desoxymorphine (II).—When 0.283 g. of 6-methyl-Δ^6-desoxymorphine in 25 ml. of 5% H_2SO_4 was hydrogenated at 25° in the presence of 100 mg. of Adams catalyst, 77.8 ml. of hydrogen was absorbed in 2.25 hr. (theory for 2 moles is 75 ml.). Extraction with $CHCl_3$ at *p*H 9 gave a colorless solution which rapidly colored. No crystalline base could be readily isolated. A crystalline hydrochloride (from *wet* alcoholic HCl) melting at 253–257° was obtained but the product was not studied further. Under similar conditions and in about the same yield the reduction of 6-methyl-Δ^6-desoxycodeine was carried out.[6]

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