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

ETHERS AND HETERO-ETHERS OF MORPHINE AND ITS ISOMERS*

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It has long been known that the pharmacodynamic result of methylation of the phenolic hydroxyl group of morphine is an increase in toxicity and convulsant action, accompanied by a marked decrease in analgesic, depressant, and other effects. The comparison of a long series of morphine derivatives with their methylated analogs which has been made in recent years[1] shows that with occasional exceptions (principally among hydrogenated derivatives) the change in physiological action produced by inactivation of the phenolic hydroxyl through methyl ether formation is quite uniform.[2] Although numerous other phenol ethers of morphine have been described,[3] with the exception of the ethyl and benzyl ethers, little is known of their pharmacology. Of the isomers of morphine, only the phenol methyl ethers (*i.e.*, the codeine isomers) have been previously prepared, and only recently have any extensive studies been made of the physiological action of this series of ethers.[4]

It is possible to etherify the secondary alcoholic hydroxyl of morphine, while leaving the phenolic hydroxyl intact, by utilizing the ingenious device

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[1] By the pharmacological unit associated with us at the University of Michigan; EDDY, *J. Pharmacol.*, **49**, 319 (1933); EDDY AND RIED, *ibid.*, **52**, 468 (1934).

[2] EDMUNDS, EDDY, AND SMALL, *J. Am. Med. Assoc.*, **103**, 1417 (1934).

[3] SMALL AND LUTZ, "Chemistry of the Opium Alkaloids," Supplement 103 to the Public Health Reports, **1932**, p. 156.

[4] EDDY, *J. Pharmacol.*, **45**, 361 (1932); **51**, 35 (1934); EDDY AND AHRENS, *Am. J. Psychol.*, **47**, 614 (1935); FOSTER, *J. Pharmacol.*, **51**, 153, 170 (1934); WRIGHT, *ibid.*, **51**, 327, 343 (1934); KRUEGER, *ibid.*, **50**, 254 (1934); KRUEGER, HOWES, AND GAY, *ibid.*, **55**, 288 (1935).

of Mannich.[5] Heterocodeine (I, R = CH_3) is the only ether of this type known. As we were led to predict from the extraordinary increase in activity (especially in respect to analgesia and depression) observed in other morphine types where the alcoholic hydroxyl is masked or removed (codeine methyl ether, monoacetylmorphine, desoxymorphine-C, dihydrodesoxymorphine-D[6]), heterocodeine is much more effective in the animal body than morphine.[7] Dihydroheterocodeine, which we have prepared not only by hydrogenation of heterocodeine but also by methylation of dihydromorphine, is approximately as potent a narcotic in man as dihydrodesoxymorphine-D, although open to the same objections in respect to habituation and brevity of action as the latter drug.[8]

It is evident from the above-cited examples that the phenolic and alcoholic hydroxyl groups in the morphine series exert a profound influence on physiological action, and we regard it as important to extend our pharmacological knowledge of the phenolic and especially of the alcoholic ethers not only of morphine but of its isomers and related compounds. We have, accordingly, prepared the series of derivatives listed in Table I, which is arranged with respect to the type of morphine isomer and type of etherification. Several previously known ethers, listed here to indicate the extent of the comparative studies being conducted by the pharmacological unit, are designated by literature references.

Comparison of the physiological action of the numerous phenol ethyl ethers with the unalkylated morphines and with the codeines should yield information on the effect of ethylation in a series where thus far only morphine, codeine, and ethylmorphine have been studied. The methoxymethyl and benzyl ethers represent interesting types in which the phenolic hydroxyl is covered with groups easily removed (especially the methoxymethyl) by hydrolytic processes, and which may liberate the phenolic base at the site of hydrolysis in the body. In the case of benzyldihydrodesoxymorphine-D, it was believed that by benzylation the powerful but disadvantageously evanescent analgesic action of dihydrodesoxymorphine-D might be prolonged, an expectation which has been realized to some extent. Similarly, benzylmorphine methyl ether may be expected to liberate heterocodeine slowly in the body, as it does on hydrolysis *in vitro*.

The alcoholic methyl and ethyl ethers of the morphine isomers are important because of striking observations already reported for γ-isomor-

[5] MANNICH, *Arch. Pharm.*, **254**, 349 (1916).

[6] EDMUNDS, EDDY, AND SMALL, *J. Am. Med. Assoc.*, **103**, 1417 (1934); EDDY AND HOWES, *J. Pharmacol.*, **53**, 430 (1935); **55**, 257 (1935); WRIGHT AND BARBOUR, *ibid.*, **54**, 25 (1935).

[7] EDDY, *ibid.*, **55**, 127 (1935).

[8] C. K. HIMMELSBACH, unpublished results.

TABLE I

MORPHINE ISOMER DERIVATIVES PREPARED

PHENOLIC ETHER	ALCOHOLIC ETHER
Morphine	
Codeine[9]	Heterocodeine[5]
Ethylmorphine[9]	Heteroethylmorphine
Benzylmorphine[9]	Heterodihydrocodeine
Methoxymethylmorphine[5]	Heteroethyldihydromorphine
Dihydrocodeine[9]	
Ethyldihydromorphine	
Benzyldihydromorphine	
Methoxymethyldihydromorphine	
α-Isomorphine	
Isocodeine[10]	Heteroisocodeine
Ethyl-α-isomorphine	Heteroethyl-α-isomorphine
Dihydroisocodeine[11]	Heterodihydroisocodeine
Ethyldihydro-α-isomorphine	Heteroethyldihydro-α-isomorphine
β-Isomorphine	
Allopseudocodeine[10]	Heteroethyl-β-isomorphine(?)
Ethyl-β-isomorphine	
Dihydroallopseudocodeine[12]	
Ethyldihydro-β-isomorphine	
γ-Isomorphine	
Pseudocodeine[10]	Heteropseudocodeine
Ethyl-γ-isomorphine	Heteroethyl-γ-isomorphine
Dihydropseudocodeine[13]	Heterodihydropseudocodeine
Ethyldihydro-γ-isomorphine	Heteroethyldihydro-γ-isomorphine
Miscellaneous	
Benzyldihydrodesoxymorphine-D	Benzylmorphine methyl ether
	Benzyldihydromorphine methyl ether

phine and pseudocodeine, and their respective dihydro derivatives.[14] These four substances exert moderate analgesic action, with low toxicity and complete lack of any convulsant action, even in fatal doses. If the

[9] Literature abundant. See SMALL AND LUTZ, "Chemistry of the Opium Alkaloids," pp. 156, 174.

[10] SPEYER AND KRAUSS, *Ann.*, **432**, 233 (1923).

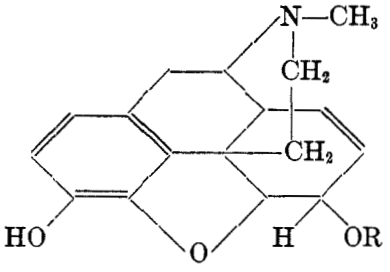
[11] SPEYER AND WIETERS, *Ber.*, **54**, 2647 (1921).

[12] LUTZ AND SMALL, *J. Am. Chem. Soc.*, **54**, 4715 (1932).

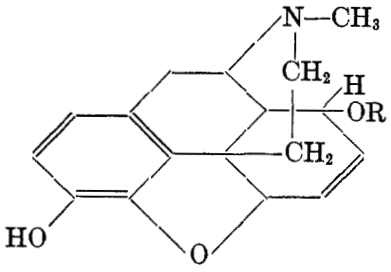
[13] LUTZ AND SMALL, *ibid.*, **56**, 2466 (1934).

[14] EDDY, *J. Pharmacol.*, in press.

analgesic action of this series can be heightened by alkylation of the alcoholic hydroxyl group (formula II) to a degree comparable with that reported for heterocodeine and dihydroheterocodeine, a group of valuable narcotics may be obtained. The same considerations apply to some extent to the compounds of the α-isomorphine series.

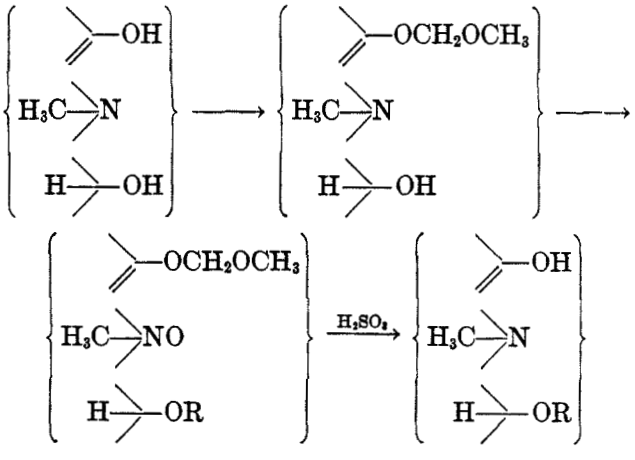


I. Morphine hetero-ethers



II. γ-Isomorphine hetero-ethers

The ethylation of the phenolic hydroxyl group throughout the series (with the exception of ethylmorphine) was accomplished by the use of diazoethane; methoxymethylation and benzylation, by the usual procedures. Alkylation of the alcoholic hydroxyl was carried out by the method of Mannich,[5] through the methoxymethyl ether, methoxymethyl ether-*N*-oxide alcoholic alkyl ether, followed by simultaneous reduction at the *N*-oxide group and hydrolysis at the methoxymethyl ether group by means of sulfurous acid. The operation may be represented by the following equations, in which the three principal functional groups of morphine (the phenolic hydroxyl, the basic nitrogen, and the secondary alcoholic hydroxyl) are joined by brackets:



For the heteromethyl- and heteroethyl-γ-isomorphine types, we were able to spare effort by applying an alcoholysis of the type discovered by

Knorr and Hartmann[15] for the conversion of α-chlorocodide to pseudocodeine methyl ether by heating with methanol. In the cases under discussion, heteropseudocodeine (γ-isomorphine alcoholic methyl ether) was first synthesized on a small scale by the Mannich method, in order that we might be certain of the structure of our alcoholysis product. The compound obtained in good yield by comparatively large scale methyl alcoholysis of α-chloromorphide was found identical with the substance obtained by Mannich's procedure. Heteroethyl-γ-isomorphine, from ethyl alcoholysis of α-chloromorphide is assumed, without further proof, to have the same structure.

An attempt to prepare the heteromethyl and heteroethyl ethers of β-isomorphine by prolonged alkylation of methoxymethyl-β-isomorphine-*N*-oxide resulted only in unchanged material. Hydrolysis of bromomorphide results, to a large extent, in formation of β-isomorphine, and by analogy, alcoholysis of bromomorphide might be expected to yield the desired 8-alkyl ether. We have obtained in fact from ethyl alcoholysis of bromomorphide a new ethyl ether which we believe to be heteroethyl-β-isomorphine, but the structural proof is as yet not complete.

The preparation of the hydrogenated β- and γ-isomorphine ethers involves overcoming the well known tendency shown by all pseudocodeine types to undergo scission of the ether linkage with formation of 4-phenolic tetrahydro derivatives. In the cases of ethyldihydro-β- and ethyldihydro-γ-isomorphines the most convenient method lay in the ethylation of the already available dihydro-β-[16] and dihydro-γ-isomorphines.[17] For heterodihydropseudocodeine and heteroethyldihydro-γ-isomorphine, the respective unhydrogenated hetero-alkyl derivatives were first prepared and then hydrogenated according to the Lutz and Small technique,[12] establishing two more cases in which this method has been successfully applied to the preparation of otherwise inaccessible derivatives.

EXPERIMENTAL

I. Morphine Series

Ethyldihydromorphine.—Ethylmorphine[18] in dilute hydrochloric acid with platinum oxide, absorbed one mole of hydrogen. The product was a colorless oil, which was distilled in a high vacuum at 170°. In absolute alcohol $[\alpha]_D^{24}$ −135.9° (c = 1.004).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99.
Found: C, 72.13; H, 8.22.

The only crystalline salt obtainable was the acid tartrate, of m.p. 167° (sinters

[15] KNORR AND HARTMANN, *Ber.*, **45**, 1354 (1912).
[16] SMALL AND FARIS, *J. Am. Chem. Soc.*, **57**, 364 (1935).
[17] SMALL AND LUTZ, *ibid.*, **56**, 1928 (1934).
[18] Prepared by the method of MERING, U. S. Patent 629,264 (July 18, 1899).

with loss of water at 93°) and $[\alpha]_D^{25}$ −59.4° (water, c = 1.095), which gave inconsistent analyses.

The methiodide crystallizes from ethanol and has the m.p. 260° (evac. tube); $[\alpha]_D^{25}$ −66.9° (water, c = 1.001).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.76. Found: I, 27.92.

Benzyldihydromorphine.—Hydrogenation of benzylmorphine in dilute acetic acid solution (faintly acid) resulted in considerable hydrolysis, as evidenced by the appearance of much dihydromorphine. A solution of 13.4 g. of benzylmorphine (m.p. 126–128°, prepared by the method of Mering[19]) in methanol with 50 mg. of platinum oxide absorbed one mole of hydrogen in 3 hours. The yield was 13 g.; the product crystallizes best from its own weight of ethyl acetate as a monohydrate of m.p. 95–97°. In alcohol $[\alpha]_D^{24}$ −88.1° (c = 1.028).

Anal. Calc'd for $C_{24}H_{27}NO_3 + H_2O$: C, 72.87; H, 7.40; H_2O, 4.5.
Found: C, 73.20; H, 7.67; H_2O, 4.1.

The hydrochloride monohydrate (dihydroperonin), prepared with 3 *N* hydrochloric acid, avoiding any excess, can be recrystallized from water without hydrolysis; it is soluble to the extent of 4% at 25°. The salt melts at 233–235° (evac. tube); $[\alpha]_D^{20}$ −52.1° (water, c = 0.960).

Anal. Calc'd for $C_{24}H_{28}ClNO_3 + H_2O$: H_2O, 4.2; Cl, 8.21.
Found: H_2O, 3.8; Cl, 7.90.

The hydrobromide monohydrate (from water) melts at 193–195° (evac. tube); $[\alpha]_D^{24}$ −44° (water, c = 0.981).

Anal. Calc'd for $C_{24}H_{28}BrNO_3 + H_2O$: H_2O, 3.8; Br, 16.78.
Found: H_2O, 3.8; Br, 16.75.

The hydriodide can be recrystallized from water with very slow cooling, and melts at 215–217° (evac. tube, gas); $[\alpha]_D^{24}$ −45.3° (water, c = 1.036).

Anal. Calc'd for $C_{24}H_{28}INO_3$: I, 25.13. Found: I, 25.22.

The perchlorate crystallizes from water containing 20% alcohol. It melts at 188–192° and has $[\alpha]_D^{23}$ −59.5° (alcohol, c = 1.008).

Anal. Calc'd for $C_{24}H_{28}ClNO_7$: Cl, 7.42. Found: Cl, 7.23.

The methiodide crystallizes in beautiful flakes from methanol (very sparingly soluble). It melts at 242–244° (evac. tube, gas); $[\alpha]_D^{24}$ −43.2° (methanol, c = 1.041).

Anal. Calc'd for $C_{25}H_{30}INO_3$: I, 24.45. Found: I, 24.40.

Methoxymethyldihydromorphine.—Hydrogenation of methoxymethylmorphine in alcohol with platinum (oxide) yielded a low-melting base which was best purified from acetone (very soluble). It melts at 99–101°; $[\alpha]_D^{24}$ −154.5° (alcohol, c = 1.133).

Anal. Calc'd for $C_{19}H_{25}NO_4$: C, 68.84; H, 7.61.
Found: C, 68.99; H, 7.89.

Methoxymethyldihydromorphine is exceedingly sensitive to hydrolysis in the presence of acids, but salts can be prepared by working slightly on the basic side. The hydrochloride was prepared in absolute alcohol by adding an insufficient quantity of alcoholic hydrogen chloride and precipitating the salt with absolute ether. It was purified in similar fashion. M.p. 124–126° (gas evolution); $[\alpha]_D^{24}$ −71.8° (water, c = 1.020).

Anal. Calc'd for $C_{19}H_{26}ClNO_4 + H_2O$: H_2O, 4.6. Found: H_2O, 4.6.
Calc'd for $C_{19}H_{26}ClNO_4$: Cl, 9.64. Found: Cl, 9.81.

The sulfate was prepared in alcohol with insufficient 10% sulfuric acid, and precipitated crystalline when absolute ether was added. It was purified by reprecipitation. It melts at 49° (gas evolution at 118°); $[\alpha]_D^{24}$ −72.8° (water, c = 1.098).

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[19] MERING, U. S. Patent, 584,388 (June 15, 1897).

Anal. Calc'd for $C_{38}H_{52}N_2O_{12}S + 5H_2O$: H_2O, 10.6. Found: H_2O, 10.8.
Calc'd for $C_{38}H_{52}N_2O_{12}S$: SO_4, 12.63. Found: SO_4, 12.91.

The methiodide was purified by crystallization from ethanol. It melted at 201–203° (evac. tube, gas); $[\alpha]_D^{24}$ −61.8° (water, c = 1.020).

Anal. Calc'd for $C_{20}H_{28}INO_4$: I, 26.83. Found: I, 26.43.

Heterodihydrocodeine (*Dihydromorphine alcoholic methyl ether*).—A solution of 43.5 g. of heterocodeine[5] in 95 cc. of 10% acetic acid was made up with water to 150 cc. and hydrogenated in the presence of 2 g. of palladium-barium sulfate. In 3 days 3480 cc. of hydrogen was absorbed, and the solution was made ammoniacal and extracted with 2.5 liters of ether; crystallization of the new base from the ether causes some difficulty at this point. The yield is nearly quantitative. After recrystallization from alcohol, the base melts at 216.5–217° (evac. tube); $[\alpha]_D^{26}$ −178.0° (alcohol, c = 1.000).

In the preparation from dihydromorphine, the crystalline sodium salt of dihydromorphine was converted to methoxymethyldihydromorphine (*q. v.*); the latter was converted to the *N*-oxide in the usual way, and the *N*-oxide was methylated as previously described.[5] The product from hydrolysis and reduction was identical with the above heterodihydrocodeine, but the over-all yield was only about 10% of the calculated amount, chiefly because of losses (incomplete etherification) in the preparation of methoxymethyldihydromorphine.

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.72; H, 7.70.
Found: C, 71.68; H, 7.93.

The hydrochloride was prepared in absolute alcohol with alcoholic hydrogen chloride; m.p. 299–299.5° (evac. tube, gas); $[\alpha]_D^{26}$ −136.5° (water, c = 1.000).

Anal. Calc'd for $C_{18}H_{24}ClNO_3$: Cl, 10.50. Found: Cl, 10.75.

The hydriodide, prepared in the usual way, crystallized after several weeks. It was purified from water; m.p. 269° (evac. tube); $[\alpha]_D^{25}$ −98.9° (water, c = 1.001).

Anal. Calc'd for $C_{18}H_{24}INO_3$: I, 29.58. Found: I, 29.73.

The perchlorate, prepared with 25% perchloric acid, crystallized from water; m.p. 258–260° (evac. tube, decomp.); $[\alpha]_D^{28}$ −110.0° (water, c = 1.042).

Anal. Calc'd for $C_{18}H_{24}ClNO_7$: Cl, 8.83. Found: Cl, 8.80.

The acid fumarate was prepared with alcoholic fumaric acid and recrystallized from 95% alcohol; m.p. 215–216° (evac. tube, gas); $[\alpha]_D^{28}$ −110.0° (water, c = 1.046).

Anal. Calc'd for $C_{22}H_{27}NO_7$: C, 63.28; H, 6.52.
Found: C, 63.37; H, 6.91.

The methiodide crystallizes from methanol; m.p. 260–261° (evac. tube, gas); $[\alpha]_D^{28}$ −91.4° (methanol, c = 1.023).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.64. Found: I, 28.93.

Heteroethylmorphine (*Morphine alcoholic ethyl ether*).—Treatment of 108 g. of methoxymethylmorphine with 65 cc. of 30% hydrogen peroxide as described by Mannich gave a viscous yellow oil, which on treatment with hot acetone yielded 116 g. of the hitherto unknown crystalline form of methoxymethylmorphine-*N*-oxide, containing a molecule of acetone. This material was alkylated with 180 cc. of ethyl sulfate and 180 cc. of 10 *N* sodium hydroxide during 10 hours. After hydrolysis and reduction, the residue from the ether extracts was most advantageously converted to the very insoluble salicylate; the base was liberated, and transformed to the hydrochloride with 3 *N* hydrochloric acid. Yield of hydrochloride, 55 g. Heteroethylmorphine crystallizes best from ethyl acetate, as the monohydrate; m.p. 110–112°; $[\alpha]_D^{23}$ −178.8° (alcohol, c = 1.012).

Anal. Calc'd for $C_{19}H_{23}NO_3 + H_2O$: C, 68.84; H, 7.61; OC_2H_5, 13.6; H_2O, 5.4.
Found: C, 68.68; H, 7.60; OC_2H_5, 13.3; H_2O, 4.8.

The hydrochloride (heterodionin), prepared as above and recrystallized from water contains 3 molecules of hydrate water and melts at 241–243° (evac. tube); $[\alpha]_D^{24}$ −134.9° (water, c = 1.004).

Anal. Calc'd for $C_{19}H_{24}ClNO_3 + 3H_2O$: H_2O, 13.4. Found: H_2O, 13.4.
Calc'd for $C_{19}H_{24}ClNO_3$: Cl, 10.14. Found: Cl, 10.22.

The hydrobromide dihydrate was prepared with 20% hydrobromic acid and recrystallized from water; m.p. 285–287° (evac. tube, sintering at 170–180°); $[\alpha]_D^{23}$ −119.2° (water, c = 1.081).

Anal. Calc'd for $C_{19}H_{24}BrNO_3 + 2H_2O$: H_2O, 8.3; Br, 18.58.
Found: H_2O, 8.3; Br, 18.53.

The hydriodide crystallizes from water as the dihydrate, melts at 171–174°, solidifies, and remelts at 282° (evac. tube, decomp.); $[\alpha]_D^{24}$ −115.8° (water, c = 1.027).

Anal. Calc'd for $C_{19}H_{24}INO_3 + 2H_2O$: H_2O, 7.6; I, 26.60.
Found: H_2O, 7.6; I, 26.60.

The perchlorate, prepared with 25% perchloric acid and purified from water, melts at 249–250° (evac. tube, decomp.); $[\alpha]_D^{24}$ −126° (alcohol, c = 1.103).

Anal. Calc'd for $C_{19}H_{24}ClNO_7$: Cl, 8.57. Found: Cl, 8.63.

The methiodide was recrystallized from water; it melts with decomp. at 255–265° (evac. tube); $[\alpha]_D^{24}$ −104.6° (water, c = 1.060). It lost 2.5% in weight on drying, but does not appear to be hydrated.

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.89. Found: I, 27.75.

Heteroethyldihydromorphine.—A solution of 17 g. of heteroethylmorphine in 200 cc. of water with 1 g. of palladium-barium sulfate took up 1150 cc. of hydrogen in one hour. By evaporation of the solvent under diminished pressure the new hydrochloride was obtained in nearly quantitative yield. The base was precipitated crystalline by ammonia in the presence of a little ether (in which it is practically insoluble) and purified from ethyl acetate. It melts at 189–190°; $[\alpha]_D^{23}$ −164.8° (alcohol, c = 1.017).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 7.99.
Found: C, 72.48; H, 8.04.

The hydrochloride trihydrate (dihydroheterodionin) was prepared with 3 *N* hydrochloric acid and purified from water, in which it is very soluble. It melts in an open tube at 95–110° (gas), in an evacuated tube at 165–170°, solidifies and remelts at 274–276°; $[\alpha]_D^{24}$ −121.7° (water, c = 1.00).

Anal. Calc'd for $C_{19}H_{26}ClNO_3 + 3H_2O$: H_2O, 13.3. Found: H_2O, 13.2.
Calc'd for $C_{19}H_{26}ClNO_3$: Cl, 10.08. Found: Cl, 10.02.

The hydrobromide crystallizes from water, probably as the dihydrate, but appears to lose part of its hydrate water readily (calc'd for $2H_2O$, 8.3; found, 7.5). It melts in a vacuum at 282–284°; $[\alpha]_D^{25}$ −125.1° (water, c = 1.00).

Anal. Calc'd for $C_{19}H_{26}BrNO_3$: Br, 20.18. Found: Br, 20.37.

The hydriodide crystallizes from water, and melts at 291–293° (evac. tube); $[\alpha]_D^{20}$ −110.6° (water, c = 1.066).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.65. Found: I, 28.75.

The perchlorate crystallizes from water, and melts in a vacuum at 234–235°; $[\alpha]_D^{23}$ −98° (alcohol, c = 1.020).

Anal. Calc'd for $C_{19}H_{26}ClNO_7$: Cl, 8.53. Found: Cl, 8.18.

The methiodide was prepared by heating the base in methanol with methyl iodide under reflux for 20 minutes, precipitated crystalline with ether, and was purified from methanol by addition of ether. It melts at 250–251° (evac. tube); $[\alpha]_D^{25}$ −79.4° (methanol, c = 1.026).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.76. Found: I, 27.76.

II. α-Isomorphine Series

Ethyl-α-isomorphine (α-Codethylin).—Pure α-isomorphine base (from hydrolysis of bromomorphide) was suspended in a mixture of 3 parts of absolute ether with 1 part of absolute ethanol, and diazoethane in 100% excess of the calculated amount was distilled into the suspension. After the reaction mixture had stood for 24 hours in the dark, the solvent was distilled off, the residue dissolved in normal hydrochloric acid, made alkaline with excess of normal sodium hydroxide, and the ethylated base was extracted into ether. The material obtained after removal of the ether was best purified by conversion to the hydrobromide and recrystallization of the salt from water after decolorizing with Norit. The base regenerated from the hydrobromide was finally purified by distillation in a high vacuum at 140°. The yield of crystalline ethyl-α-isomorphine of m.p. 128–130° was 40% of the calculated amount. The compound shows in alcohol $[\alpha]_D^{23}$ −143.7° (c = 1.030).

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40: OC_2H_5, 14.7.
Found: C, 72.75; H, 7.46; OC_2H_5, 13.6.

The salts of ethyl-α-isomorphine with the common acids were not crystalline. The methiodide, prepared in the usual way and recrystallized from absolute alcohol has the m.p. 243° (evac. tube), and $[\alpha]_D^{21}$ −91.6° (water, c = 0.999).

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.89. Found: I, 27.73.

Ethyldihydro-α-isomorphine.—An ethereal suspension of dihydro-α-isomorphine[16] was treated with excess of diazoethane. After 24 hours the solution was washed with dilute sodium hydroxide and the ether was removed. The resulting pale yellow oil crystallized when ethyl acetate was added, and could be purified from this solvent, in which it is quite soluble; the yield is 90% of the calculated amount. The base crystallizes with one molecule of water; m.p. 86–91° (gas evolution at 105°); $[\alpha]_D^{24}$ −110° (methanol, c = 0.970). It distills in a high vacuum at 130°, yielding the anhydrous crystalline form of m.p. 104°.

Anal. Calc'd for $C_{19}H_{25}NO_3 + H_2O$: H_2O, 5.44. Found: H_2O, 5.38.
Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 8.00.
Found: C, 72.15; H, 8.23.

Of the salts, only the acid tartrate could be obtained crystalline. This crystallized after several days from a solution of the base in excess of alcoholic tartaric acid, and was purified from acetone, yield 70%. It is very soluble in water or alcohol. The hydrated salt has the m.p. 109–112° (gas evolution), and $[\alpha]_D^{23}$ −66° (water, c = 0.932).

Anal. Calc'd for $C_{23}H_{31}NO_9 + H_2O$: H_2O, 3.73. Found: H_2O, 3.55.
Calc'd for $C_{23}H_{31}NO_9$: C, 59.32; H, 6.72.
Found: C, 59.22; H, 6.52.

The methiodide, prepared in the usual way, is very soluble in water, nearly insoluble in alcohol, and was crystallized from 80% alcohol. It melts at 277° (evac. tube) with gas evolution; $[\alpha]_D^{23}$ −76.2° (water, c = 1.233).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.76. Found: I, 27.56.

Heteroisocodeine (α-Isomorphine alcoholic methyl ether).—Twenty grams of α-isomorphine were added to a cold solution of 1.5 g. of sodium in 50 cc. of absolute alcohol. A crystalline sodium salt could not be obtained by precipitation with ether; the solution was evaporated to dryness at 60° under diminished pressure, and the residue was converted to the methoxymethyl ether by treatment with chloromethyl ether in absolute chloroform, as described by Mannich.[5] Methoxymethyl-α-isomorphine was obtained as a viscous oil, as was its N-oxide. The latter compound, in 20 cc. of water, was methylated under vigorous stirring and ice-cooling

by dropwise addition of 30 cc. of dimethyl sulfate and 30 cc. of 10 *N* sodium hydroxide over a period of 6 hours. The mixture was acidified with sulfuric acid, and sulfur dioxide was bubbled through it at 40° until the odor no longer disappeared after an hour's standing. The solution was made alkaline with ammonia, and extracted with ether. Heteroisocodeine was purified by crystallization from absolute alcohol, followed by high-vacuum sublimation at 155°; m.p. 206.5–207° (evac. tube); $[\alpha]_D^{22}$ −185.5° (methanol, c = 0.973).

Anal. Calc'd for $C_{18}H_{21}NO_3$: C, 72.19; H, 7.08; OCH_3, 10.4.
Found: C, 72.01; H, 7.17; OCH_3, 11.1.

Heteroisocodeine methiodide crystallizes from absolute alcohol, and has the m.p. 227–228° (evac. tube, gas evolution); $[\alpha]_D^{22}$ −105.4° (water, c = 1.110).

Anal. Calc'd for $C_{19}H_{24}INO_3$: I, 28.78. Found: I, 28.65.

Heterodihydroisocodeine (*Dihydro-α-isomorphine alcoholic methyl ether*).—Five grams of heteroisocodeine dissolved to neutral solution in 200 cc. of very dilute hydrochloric acid, with 50 mg. of platinum oxide, took up one mole of hydrogen in two hours. The new base precipitated crystalline when ammonia was added, and was purified from absolute alcohol; m.p. 198–200°; $[\alpha]_D^{25}$ −118.1° (alcohol, c = 1.004).

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.72; H, 7.70.
Found: C, 71.69; H, 7.88.

The hydrochloride was prepared with 3 *N* hydrochloric acid, purified from water; m.p. 273–275° (evac. tube); $[\alpha]_D^{24}$ −111.1° (water, c = 1.026).

Anal. Calc'd for $C_{18}H_{24}ClNO_3$: Cl, 10.50. Found: Cl, 10.72.

The hydriodide was prepared in 10% acetic acid with potassium iodide, purified from water; m.p. 287–288° (evac. tube, gas evolution); $[\alpha]_D^{24}$ −85.2° (water, c = 0.416).

Anal. Calc'd for $C_{18}H_{24}INO_3$: I, 29.58. Found: I, 29.52.

The methiodide, crystallized from ethanol, melts at 245–248° (evac. tube, sintering at 170–180°); $[\alpha]_D^{24}$ −77.9° (water, c = 1.078).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.64. Found: I, 28.93.

Heteroethyl-α-isomorphine.—The ethylation of methoxymethyl-α-isomorphine-*N*-oxide was carried out like the methylation, but with ethyl sulfate at room temperature, and the product was isolated in the same way. The yield was 6 g. from 20 g. of α-isomorphine; the base was obtained crystalline by high vacuum distillation at 170°. It melts at 161–162° (evac. tube); $[\alpha]_D^{22}$ −205.1° (methanol, c = 0.946).

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40; OC_2H_5, 14.4.
Found: C, 72.77; H, 7.43; OC_2H_5, 14.0.

The hydrochloride (heteroisodionin) was prepared with alcoholic hydrogen chloride and washed with absolute alcohol; m.p. 247–248° (evac. tube, decomp.); $[\alpha]_D^{24}$ −164.2° (water, c = 1.102).

Anal. Calc'd for $C_{19}H_{24}ClNO_3$: Cl, 10.14. Found: Cl, 10.15.

The hydriodide (from acetic acid and potassium iodide) crystallizes from water; m.p. 264° (evac. tube, decomp.); $[\alpha]_D^{24}$ −132.7° (water, c = 1.168).

Anal. Calc'd for $C_{19}H_{24}INO_3$: I, 28.77. Found: I, 28.70.

The hydrobromide, prepared with 20% hydrobromic acid, crystallizes from water; m.p. 255–258° (evac. tube, decomp.); $[\alpha]_D^{24}$ −150.2° (water, c = 1.051).

Anal. Calc'd for $C_{19}H_{24}BrNO_3$: Br, 20.28. Found: Br, 20.67.

The methiodide crystallizes from alcohol and has the m.p. 229–231° (evac. tube, gas); $[\alpha]_D^{24}$ −131.3° (water, c = 1.050).

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.89. Found: I, 28.10.

Heteroethyldihydro-α-isomorphine.—The preparation of this base by hydrogenation of heteroethyl-α-isomorphine is parallel to that of heterodihydroisocodeine. It crystallizes from absolute alcohol; m.p. 210–212°; $[\alpha]_D^{24}$ −128° (alcohol, c = 1.031).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 7.99.
Found: C, 72.07; H, 8.20.

The hydrochloride (dihydroheteroisodionin), prepared with alcoholic hydrogen chloride and washed with absolute alcohol, melts at 300° (evac. tube, gas); $[\alpha]_D^{24}$ −125.7° (water, c = 1.034).

Anal. Calc'd for $C_{19}H_{26}ClNO_3$: Cl, 10.08. Found: Cl, 10.04.

The hydriodide was prepared by adding potassium iodide solution to a saturated aqueous solution of the hydrochloride, and was recrystallized from water; m.p. 287° (evac. tube, gas); $[\alpha]_D^{24}$ −99.5° (water, c = 0.467).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.65. Found: I, 28.59.

The methiodide, crystallized from absolute ethanol, has the m.p. 256–258° (evac. tube) and shows $[\alpha]_D^{24}$ −86.1° (water, c = 1.034).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.76. Found: I, 27.82.

III. β-Isomorphine Series

Ethyl-β-isomorphine (β-Codethylin).—Ethylation of β-isomorphine with diazoethane was carried out as for α-isomorphine. The resulting base was a viscous oil, which was purified by distillation in a high vacuum at 170°. It was brought to analysis in the form of its salts.

The acid sulfate was prepared with 20% sulfuric acid, and was recrystallized from water; m.p. 195–198° (evac. tube); $[\alpha]_D^{24}$ −136.3° (water, c = 1.027).

Anal. Calc'd for $C_{19}H_{25}NO_7S$: C, 55.44; H, 6.27; SO_4, 23.36.
Found: C, 55.20; H, 6.37; SO_4, 23.53.

The perchlorate crystallizes from water, in which it is only sparingly soluble; m.p. 264–266° (evac. tube, decomp.); $[\alpha]_D^{25}$ −113.2° (40% alcohol, c = 0.733).

Anal. Calc'd for $C_{19}H_{24}ClNO_7$: Cl, 8.57. Found: Cl, 8.26.

The fumarate, of m.p. 172–175° (evac. tube) and $[\alpha]_D^{24}$ −100.3° (alcohol, c = 0.723) was exceedingly difficult to burn, and gave inconsistent analyses.

Ethyldihydro-β-isomorphine.—Ethylation of dihydro-β-isomorphine with diazoethane gave an 80% yield of glass-like solid, which was distilled in a high vacuum at 210°.

The perchlorate crystallizes from water; m.p. 231–234° (evac. tube); $[\alpha]_D^{25}$ −64.3° (water, c = 1.057).

Anal. Calc'd for $C_{19}H_{26}ClNO_7$: C, 57.43; H, 6.31; Cl, 8.53.
Found: C, 57.26; H, 6.62; Cl, 8.37.

The picrate was prepared with alcoholic picric acid, and recrystallized from 50% alcohol; m.p. 187–189° (evac. tube); $[\alpha]_D^{25}$ −64.8° (alcohol, c = 0.617).

Anal. Calc'd for $C_{25}H_{28}N_4O_{10}$: N, 10.29. Found: N, 10.39.

Heteroethyl-β-isomorphine (?).—Five grams of bromomorphide in 100 cc. of absolute ethanol was heated in a pressure bottle at 100° for 6 hours. The solution was evaporated to dryness, the residue was dissolved in dilute acid, ammonia was added, and the precipitate was extracted into ether. The product was found to contain halogen; it was brought into ether, and extracted with tenth-normal hydrochloric acid in six fractions. The base obtained from the first two fractions was halogen-free, and was purified by crystallization from alcohol; yield 20%; m.p. 209–211° (evac. tube); $[\alpha]_D^{24}$ −60.1° (abs. alcohol, c = 1.015).

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40; OC_2H_5, 13.6.
Found: C, 72.69; H, 7.74; OC_2H_5, 14.1.

The new base is different from heteroethyl-α-isomorphine and from heteroethyl-γ-isomorphine, and reasoning from the course taken by hydrolysis of bromomorphide, we believe it to be the desired heteroethyl-β-isomorphine.

IV. γ-Isomorphine Series

Ethyl-γ-isomorphine (γ-Codethylin).—Ten grams of γ-isomorphine suspended in 100 cc. of absolute ether and 100 cc. of absolute alcohol was ethylated with diazoethane and the product isolated as described for the α-series. The product, 7 g., was purified from absolute alcohol; m.p. 183–184°; $[\alpha]_D^{22}$ −75° (methanol, c = 0.967).

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40; OC_2H_5, 14.3.
Found: C, 72.64; H, 7.53; OC_2H_5, 14.2.

The hydrochloride (γ-isodionin) was prepared with alcoholic hydrogen chloride and washed with absolute alcohol; m.p. 298–300° (evac. tube, decomp.); $[\alpha]_D^{24}$ −62.7° (water, c = 1.005).

Anal. Calc'd for $C_{19}H_{24}ClNO_3$: Cl, 10.14. Found: Cl, 10.24.

The methiodide, recrystallized from 70% alcohol, melts at 252–253° (evac. tube, gas); $[\alpha]_D^{21}$ −40.8° (water, c = 1.005).

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.89. Found: I, 27.43.

Ethyldihydro-γ-isomorphine.—Dihydro-γ-isomorphine,[17] suspended in absolute ether was ethylated with diazoethane and the product was isolated as described above; it crystallized best from ethyl acetate. Yield 80%; m.p. 158–159°; $[\alpha]_D^{23}$ −36.2° (methanol, c = 0.985).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.16; H, 7.98.
Found: C, 72.33; H, 8.00.

The neutral fumarate was the only salt which could be obtained crystalline; it was prepared with absolute alcoholic fumaric acid and recrystallized from absolute alcohol; m.p. 180–192° (evac. tube. In open tube it develops an intense magenta color before melting); $[\alpha]_D^{23}$ −23.7° (water, c = 0.992).

Anal. Calc'd for $C_{40}H_{46}N_2O_{10}$: C, 67.52; H, 7.29.
Found: C, 67.04; H, 7.23.

The methiodide, prepared as usual and crystallized from 70% alcohol has the m.p. 252–253° (evac. tube, gas); $[\alpha]_D^{21}$ −40.8° (water, c = 1.005).

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.89. Found: I, 27.43.

Heteropseudocodeine (γ-Isomorphine alcoholic methyl ether).—Twenty grams of γ-isomorphine was dissolved in 50 cc. of alcohol containing 1.5 g. of dissolved sodium; addition of 100 cc. of ether caused precipitation of the crystalline sodium salt. This salt was converted to the methoxymethyl ether, which was likewise crystalline. Methoxymethyl-γ-isomorphine-*N*-oxide crystallized when acetone was added to the resinous mass resulting from vacuum evaporation of the hydrogen peroxide solution. The methylation was carried out as described for heteroisocodeine, and the product was crystallized from absolute alcohol; yield 8 g.; m.p. 239–241° (evac. tube); $[\alpha]_D^{23}$ −79.5° (methanol, c = 0.880).

Anal. Calc'd for $C_{18}H_{21}NO_3$: C, 72.19; H, 7.08; OCH_3, 10.4.
Found: C, 72.02; H, 6.88; OCH_3, 9.3.

The same compound was obtained when 15 g. of α-chloromorphide in 100 cc. of absolute methanol was heated in a pressure bottle at 100° for 6 hours. The methanol was removed in a vacuum, the residue dissolved in a liter of water, decolorized with Norit, made ammoniacal, and extracted; yield about 40%.

The hydrochloride was prepared with 3 *N* hydrochloric acid and purified from water, in which it is very soluble. It melts at 274–276° (evac. tube, decomp.); $[\alpha]_D^{22}$ −48.6° (water, c = 1.161).

Anal. Calc'd for $C_{18}H_{22}ClNO_3$: Cl, 10.56. Found: Cl, 10.37.

The hydriodide crystallizes from water and melts at 185–188° (decomp.); $[\alpha]_D^{21}$ −48.7° (water, c = 1.036).

Anal. Calc'd for $C_{18}H_{22}INO_3$: I, 29.72. Found: I, 29.63.

Heterodihydropseudocodeine (Dihydro-γ-isomorphine alcoholic methyl ether).—A suspension of 5 g. of heteropseudocodeine with 0.1 g. of platinum oxide in 200 cc. of glacial acetic acid took up 1.3 moles of hydrogen. Enough water was added to dissolve the new hydrochlorides, catalyst was removed, and the solution was distilled to dryness at 40° under diminished pressure. The residue, in water, was made ammoniacal and extracted into ether. The residue from the ether was dissolved in dilute hydrochloric acid, made ammoniacal and again extracted. The tetrahydro derivative is not appreciably dissolved by the ether. The dihydro base was recrystallized from absolute alcohol and sublimed at 175° in a high vacuum; yield 40%. Heterodihydropseudocodeine has the m.p. 235–237° (evac. tube); $[\alpha]_D^{25}$ −83.4° (alcohol, c = 0.857).

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.72; H, 7.70.
Found: C, 71.96; H, 7.89.

The hydrobromide (from 20% hydrobromic acid) was purified from water; m.p. 256–258° (evac. tube); $[\alpha]_D^{25}$ −55.4° (water, c = 0.884).

Anal. Calc'd for $C_{18}H_{24}BrNO_3$: Br, 21.71. Found: Br, 21.45.

The hydriodide, prepared as usual, and purified from water, melts at 185–187° (evac. tube); $[\alpha]_D^{25}$ −52.8° (water, c = 0.776).

Anal. Calc'd for $C_{18}H_{24}INO_3$: I, 29.58. Found: I, 29.86.

Heteroethyl-γ-isomorphine.—Ten grams of α-chloromorphide in 100 cc. of absolute alcohol was heated in a pressure bottle at 100° for 6 hours. The product was isolated as in the methyl alcoholysis of α-chloromorphide and crystallized from absolute ethanol; yield, 30%. The compound melts at 215–220° (evac. tube, decomp.); $[\alpha]_D^{23}$ −43.5° (methanol, c = 0.827).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.80; H, 7.40; OC_2H_5, 14.4.
Found: C, 72.56; H, 7.56; OC_2H_5, 13.5.

The hydrochloride dihydrate (heteropseudodionin) was prepared with 3 *N* hydrochloric acid and recrystallized from water in which it is very soluble; m.p. 287–290° (evac. tube, decomp.); $[\alpha]_D^{23}$ −30.5° (water, c = 1.114).

Anal. Calc'd for $C_{19}H_{24}ClNO_3 + 2H_2O$: H_2O, 9.3. Found: H_2O, 8.8.
Calc'd for $C_{19}H_{24}ClNO_3$: Cl, 10.14. Found: Cl, 10.25.

The hydriodide monohydrate was prepared in the usual way and purified from water; m.p. 276–277° (evac. tube, decomp.); $[\alpha]_D^{22}$ −23.2° (water, c = 0.906).

Anal. Calc'd for $C_{20}H_{24}INO_3 + H_2O$: H_2O, 3.9. Found: H_2O, 3.6.
Calc'd for $C_{20}H_{24}INO_3$: I, 26.60. Found: I, 26.44.

Heteroethyldihydro-γ-isomorphine.—Six grams of heteroethyl-γ-isomorphine in 200 cc. of 1.5 *N* hydrochloric acid with 50 mg. of platinum oxide absorbed 1.54 moles of hydrogen. The catalyst was removed, and the crystalline mixed hydrochlorides obtained by concentration under diminished pressure. The hydrochlorides of the mixed dihydro and tetrahydro derivatives could not be separated, but the free heteroethyldihydro-γ-isomorphine proved to be much more soluble in ether than the tetrahydro base, and was separated from the latter by this means. It crystallized in contact with absolute ethanol, and was sublimed in a high vacuum at 175°; yield 30%. It melts at 220–223° (evac. tube); $[\alpha]_D^{25}$ −20.2° (ethanol, c = 0.692).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 7.99.
Found: C, 72.25; H, 7.85.

The hydrochloride and sulfate are not crystalline. The hydriodide, prepared

in the usual way and recrystallized from water, melts at 277–281° (evac. tube) and has $[\alpha]_D^{25}$ −9.1° (water, c = 0.551).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.65. Found: I, 28.45.

The methiodide crystallizes from 80% alcohol, and melts at 250–252° (evac. tube); $[\alpha]_D^{25}$ −7.2° (water, c = 0.552).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.76. Found: I, 28.04.

V. Miscellaneous

Benzylmethylmorphine (*Benzylmorphine alcoholic methyl ether*).—Benzylmorphine (100 g.) was warmed with 100 cc. of 30% hydrogen peroxide; the vigorous reaction was controlled with ice. The clear yellow solution crystallized rapidly when water was added, and the sparingly soluble *N*-oxide separated as a white mass of short thick prisms; yield, 84 g. The product can be recrystallized from alcohol; m.p. 236–238° (evac. tube, decomp.); $[\alpha]_D^{23}$ −53.2° (alcohol, c = 0.2112).

Anal. Calc'd for $C_{24}H_{25}NO_4$: C, 73.62; H, 6.44.
Found: C, 73.55; H, 6.73.

This product, suspended in water, was methylated by the Mannich procedure for 24 hours, but, due to the extremely slight solubility of the *N*-oxide, methylation was incomplete. The unchanged oxide was filtered out, and the mother liquor was acidified and treated with sulfur dioxide. Sodium hydroxide and ether yielded about 10% of the calculated amount of an oily base, which was purified as the hydrochloride.

Because of these difficulties, the preparation from heterocodeine is to be preferred. Five grams of heterocodeine and 2.1 g. of benzyl chloride were added to a solution of 0.4 g. of sodium in 50 cc. of absolute alcohol. This was heated under reflux for an hour, sodium chloride was filtered out, and the alcohol was removed under diminished pressure. An oily base was obtained and was converted to the hydrochloride with 3 *N* hydrochloric acid, after distillation in a high vacuum at 180°. The salt crystallizes from water; m.p. 233–236° (evac. tube); $[\alpha]_D^{28}$ −88.9° (water, c = 1.080).

Anal. Calc'd for $C_{25}H_{28}ClNO_3$: Cl, 8.33. Found: Cl, 8.50.

The acid sulfate forms with 20% sulfuric acid, and crystallizes well from water; m.p. 247–249° (evac. tube); $[\alpha]_D^{25}$ −90.1° (water, c = 0.910).

Anal. Calc'd for $C_{25}H_{29}NO_7S$: C, 61.57; H, 6.00; SO_4, 19.72.
Found: C, 61.78; H, 6.33; SO_4, 19.45.

The methiodide crystallizes from 50% alcohol, and has the m.p. 155–157° (evac. tube); $[\alpha]_D^{24}$ −75.8° (50% alcohol, c = 0.448).

Anal. Calc'd for $C_{26}H_{30}INO_3$: I, 23.90. Found: I, 23.69.

Benzylmethyldihydromorphine.—This derivative was prepared by benzylation of heterodihydrocodeine as described above for benzylmethylmorphine. The base is not crystalline, nor does it yield crystalline salts. It was purified by distillation in a high vacuum at 210°. In alcohol it shows $[\alpha]_D^{25}$ −89.1° (c = 0.942).

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.68; H, 7.47.
Found: C, 76.45; H, 7.72.

The methiodide crystallizes readily from ethanol and has the m.p. 155–157° (evac. tube); $[\alpha]_D^{24}$ −54.60° (water, c = 1.034).

Anal. Calc'd for $C_{26}H_{32}INO_3$: I, 23.81. Found: I, 23.72.

Benzyldihydrodesoxymorphine-D.—To a solution of 1.1 g. of sodium in 100 cc. of absolute alcohol, 12.7 g. of dihydrodesoxymorphine-D[20] was added under hy-

[20] Prepared by the method of SMALL, YUEN, AND EILERS, *J. Am. Chem. Soc.*, **55**, 3863 (1933), and *U. S. Patent* 1,980,972 (Nov. 13, 1934); we are indebted to Merck and Co., Rahway, N. J. for the quantity preparation of this material.

drogen, and the red solution was then treated with 6.05 g. of benzyl chloride. The mixture was heated under reflux (hydrogen stream) for 2 hours, sodium chloride was filtered out, and alcohol was removed by distillation. The residue was taken up in 10% acetic acid, excess of dilute sodium hydroxide was added, and the precipitated base was extracted into ether. The aqueous layer, with ammonium chloride, gave 2.3 g. of unchanged dihydrodesoxymorphine-D. The ether yielded a pale yellow oil which could not be induced to crystallize. It was taken up in absolute alcohol, and treated with alcoholic hydrogen chloride to faint acidity. The yield of white crystalline hydrochloride was 11 g. It was recrystallized from 35 cc. of alcohol; m.p. 249° (evac. tube, gas); $[\alpha]_D^{23}$ −34.4° (alcohol, c = 1.060).

Anal. Calc'd for $C_{24}H_{28}ClNO_2$: Cl, 8.92. Found: Cl, 8.94.

The hydrobromide was prepared in 10% acetic acid with potassium bromide, and recrystallized from alcohol; m.p. 226–227° (evac. tube); $[\alpha]_D^{23}$ −29.8° (alcohol, c = 1.074).

Anal. Calc'd for $C_{24}H_{28}BrNO_2$: C, 65.13; H, 6.38; Br, 18.07.
Found: C, 64.92; H, 6.65; Br, 17.85.

The perchlorate crystallizes in sparkling flakes from alcohol and melts at 223–224° (evac. tube, gas); $[\alpha]_D^{24}$ −51.5° (alcohol, c = 1.068).

Anal. Calc'd for $C_{24}H_{28}ClNO_6$: Cl, 7.68. Found: Cl, 7.71.

The methiodide, prepared in the usual way, separates from methanol in brilliant yellow crystals having a decomposition point at about 70°; $[\alpha]_D^{24}$ −25.8° (methanol, c = 1.00). It is so unstable that it had largely decomposed before it could be brought to analysis.

SUMMARY

As part of an investigation on the relationship between constitution and physiological action, a series of 21 new ethers of morphine, of α-, β-, and γ-isomorphines, and of their dihydro derivatives has been synthesized. This series includes both phenolic and alcoholic ethers (heteroethers). New ethers of benzylmorphine, benzyldihydromorphine, and of dihydrodesoxymorphine-D are described.