DIHYDRO-γ-ISOMORPHINE DERIVATIVES

Substance	$[\alpha]_D$	t, °C.	c (water)	M. p., °C. (corr.)	Formula		Calcd.	Found		Calcd.	Found
Hydriodide[a]	−21.7	25	1.037	285–288	$C_{17}H_{22}O_3NI$	I,	30.58	30.64			
Hydrochloride[b]	−27.4	28	0.78	300–302	$C_{17}H_{22}O_3NCl + 0.5H_2O$	H_2O, Cl,	2.70 10.95[h]	2.90 11.12[h]	Cl,	10.66	10.63
Salicylate[c]	−22.8	27	1.163	131.5–132.5	$C_{24}H_{27}O_6N + 0.5H_2O$	C,	66.33	66.40	H,	6.49	6.40
Perchlorate[d]	−24.0	25	1.020		$C_{17}H_{22}O_7NCl + H_2O$	H_2O,	4.44	4.28	Cl,	9.19[h]	9.34[h]
Methiodide[e]	−21.0	27	1.117	255–257	$C_{18}H_{24}O_3NI$	I,	29.58	29.33			

TETRAHYDRO-γ-ISOMORPHINE DERIVATIVES

Hydrochloride				275–280	$C_{17}H_{24}O_3NCl$	Cl,	10.88	11.09			
Hydriodide	− 1.8	27	0.58	280–290	$C_{17}H_{24}O_3NI + 0.5H_2O$	I,	30.43[h]	30.57[h]	H_2O,	2.1	2.6
Perchlorate[g]	0	25	0.49	215–220	$C_{17}H_{24}O_7NCl + H_2O$	Cl,	9.10[h]	9.39[h]	H_2O,	4.44	3.8

[a] Hydriodide from the demethylation, purified from water; crystallizes in very thin sharp-pointed colorless needles. [b] Prepared by treating a solution of the base in absolute alcohol with alcoholic hydrogen chloride. Very soluble in water, purified from 95% alcohol, thin diamond-shaped scales. [c] Prepared in absolute alcohol with alcoholic salicylic acid, precipitating with absolute ether. Purified from absolute alcohol. It turns green on melting, and dec. in attempted water determinations. [d] Prepared by treating solid base with 20% perchloric acid and warming to solution; purified from water. It crystallizes in bundles of very long hair-like needles. [e] Prepared by heating the base with methyl iodide in methanol, and boiling off excess methyl iodide; recrystallized from methanol, fine sparkling flakes. The oxalate and sulfate crystallize poorly, the maleinate, succinate, picrate and benzoate are amorphous. [f] Fine needles from glacial acetic acid. [g] Crystallized from water. [h] Anhydrous.

evolution, solidifies at 160–170° as large white radiating prisms, and remelts at 222–223°. In 95% alcohol, $[\alpha]_D^{22}$ −35.4° (c = 1.554). The hydrated base is sparingly soluble in boiling acetone, more soluble in ethyl acetate, and separates anhydrous from both solvents; from alcohol the hydrate is obtained.

Anal. Calcd. for $C_{17}H_{21}O_3N + H_2O$: C, 66.84; H, 7.59; H_2O, 5.9. Found: C, 66.71; H, 7.51; H_2O, 6.3.

Methylation of Dihydro-γ-isomorphine.—To an ethereal solution of 0.5 g. of diazomethane was added 0.5 g. of dihydro-γ-isomorphine hydrate and a few drops of methanol. After thirty hours the base had not dissolved completely, and 0.5 g. of diazomethane was added. After twelve hours longer the reaction was complete, and distillation of the ether yielded 0.48 g. of dihydropseudocodeine, m. p. 123° (hydrate) and 153–154°. Recrystallized from 60% alcohol, it melted at 124°, evolved gas at 126°, solidified, and remelted at 155°. It did not depress the melting point of dihydropseudocodeine-A.

Summary

1. By suitable control of the experimental conditions, γ-isomorphine may be hydrogenated to the monophenolic dihydro-γ-isomorphine, or to the diphenolic tetrahydro-γ-isomorphine.

2. A practicable preparative method of obtaining these two products through demethylation of dihydropseudocodeine-A and of tetrahydropseudocodeine is described.

UNIVERSITY, VIRGINIA RECEIVED MAY 2, 1934

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, No. 138]

Gamma-Pseudomorphine[1]

BY LYNDON SMALL AND BURT F. FARIS[2]

The dimolecular base pseudomorphine is formed on gentle oxidation of morphine by a variety of reagents. The point at which the two morphine nuclei join is not certain, but the fact that bromomorphine, in which bromine is believed to occupy position 2, cannot be oxidized to a dimolecular product has been advanced as evidence that the 2-position is involved in the union. Degradation experiments by Goto and Kitasato led to a similar assumption, supported only by analogy with the o,o'-union in β-dinaphthol. Pseudomorphine exhibits, however, peculiarities which are not explicable on the basis of the symmetrical 2,2′-dimorphine formula; notably, it appears to contain but one phenolic hydroxyl group, and the two nitrogen atoms show marked differences in behavior.[3] With a view to determining whether

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

(2) Squibb Fellow in Alkaloid Chemistry.

(3) For a literature review see Small and Lutz, "Chemistry of the Opium Alkaloids," 1932, pp. 170–174.

the formation of pseudomorphine types is limited to morphine itself, and whether related dimolecular products exhibit similar peculiarities, we have studied the oxidation of γ-isomorphine and other morphine analogs. This investigation will later be extended to the structural question.

Treatment of γ-isomorphine in alkaline solution with potassium ferricyanide results in formation of a new dimolecular base, $C_{34}H_{36}O_6N_2$, γ-pseudomorphine, which shows a striking similarity to pseudomorphine in physical and chemical properties. It contains four free (or potential) hydroxyl groups, for a tetraacetyl derivative can be prepared. Only one of these hydroxyls appears to be phenolic; methylation with alcoholic alkali and methyl iodide results in a monomethyl ether monomethiodide. Under conditions where even the alcoholic hydroxyl of morphine is methylated, γ-pseudomorphine gives only a monomethyl ether, which is not appreciably soluble in alkali and gives no ferric chloride test. The dimolecular nature of γ-pseudomorphine is demonstrated by the existence of the methyl ether monomethiodide, and by molecular weight values found for the tetraacetyl derivative.

The two nitrogen atoms of γ-pseudomorphine form stable salts with acids as weak as benzoic, but, like those in pseudomorphine, do not add methyl iodide even under extreme conditions. Gamma-pseudomorphine dimethiodide can be prepared only by oxidizing γ-isomorphine methiodide and treating the resulting γ-pseudomorphine methiodide methohydroxide with hydriodic acid. The fact that tetraacetyl-γ-pseudomorphine forms a dimethiodide with great ease suggests that the anomalous behavior of nitrogen and one phenolic hydroxyl in these dimolecular bases may arise from intramolecular saturation.

Each of the presumably identical halves of the γ-pseudomorphine molecule contains an allyl ether arrangement of the pseudocodeine type and should behave like pseudocodeine[4] or γ-isomorphine[5] under varying conditions of hydrogenation. Reduction of γ-pseudomorphine by the procedure which favors saturation of the alicyclic double linkage only, results in a good yield of tetrahydro-γ-pseudomorphine. This substance has the ether grouping in both halves of the molecule still intact, for it can also be prepared by oxidation of dihydro-γ-isomorphine, whose relationship to the non-phenolic dihydropseudocodeine is certain.[5] Hydrogenation of γ-pseudomorphine in dilute acetic acid, on the other hand, resulted in absorption of four moles of hydrogen, with formation of octahydro-γ-pseudomorphine. It was not possible to isolate this substance from the oxidation of tetrahydro-γ-isomorphine, the reaction perhaps proceeding in more than one way as might be predicted if Goto's speculations are valid.

Pseudomorphine itself, having in each half of the molecule an unsaturation located as in morphine, absorbs only two moles of hydrogen under any ordinary conditions of catalytic reduction. The tetrahydropseudomorphine so formed can likewise be prepared in good yield by oxidation of dihydromorphine.

The other morphine isomers, α-isomorphine and β-isomorphine, can be oxidized in somewhat lower yield to the corresponding dimolecular products, α-pseudomorphine and β-pseudomorphine. Extension of the oxidation process to heterocodeine yields a dimolecular product which represents the otherwise inaccessible (alcoholic) dimethyl ether of pseudomorphine. Dihydrodesoxymorphine-D gives similarly tetrahydrodidesoxypseudomorphine, resembling in physical properties the other dimolecular products described above. Experiments on the oxidation of an equimolecular mixture of morphine and γ-isomorphine indicate that pseudomorphine analogs with dissimilar halves can also be prepared. Of the three products which might be expected from such a reaction, the morphine-γ-isomorphine dimolecule greatly predominates. Morphine-γ-isomorphine is isomeric with pseudomorphine and γ-pseudomorphine, and resembles them in general physical properties. Its constitution could be demonstrated by hydrogenation; whereas pseudomorphine is saturated through absorption of two moles of hydrogen, and γ-pseudomorphine through four moles, in morphine-γ-isomorphine the morphine half of the molecule should require one mole, the γ-isomorphine half two moles. This expectation was confirmed experimentally, hydrogen absorption by the unsymmetrical base stopping completely at three moles.

Experimental

Gamma-pseudomorphine.—A solution of 1 g. of γ-isomorphine (of m. p. 274°, $[\alpha]_D$ −94°) in *N* sodium hydroxide was treated with a concd. solution of 1.2 g. of potassium ferricyanide, the mixture neutralized with carbon dioxide, and the dimolecular product crystallized

(4) Lutz and Small, THIS JOURNAL, **54**, 4715 (1932).
(5) Small and Lutz, *ibid.*, in press.

by dissolving in hot ammonium hydroxide and boiling off ammonia. The yield was 85%, white granular crystals, soluble in concd. ammonia, benzyl alcohol, pyridine, slightly soluble in aniline, insoluble in other organic solvents or water. It crystallizes from ammonia with three molecules of hydrate water, of which one and one-half molecules are lost in vacuum at 100°, the remainder very slowly at 156°. In normal hydrochloric acid the trihydrate shows $[\alpha]_D^{24}$ +44.8° (c = 0.864). The melting point (evac. tube) lies at 282–283°; ferric chloride test is very deep intense green.

Anal. Calcd. for $C_{34}H_{36}O_6N_2 + 3H_2O$: C, 65.56; H, 6.80; H_2O, 8.68. Found: C, 65.72; H, 6.87; H_2O, 8.89.

Tetraacetyl-γ-pseudomorphine.—A suspension of 3 g. of γ-pseudomorphine in 50 cc. of benzene with 10 cc. of acetic anhydride was refluxed until all material was in solution. The reaction mixture was poured into water, the tetraacetyl derivative thrown out with ammonia and extracted into ether, from which it crystallized in anhydrous prisms. It can be recrystallized from isopropyl ether, separating as a hydrate; extremely soluble in alcohol. The anhydrous base has the specific rotation $[\alpha]_D^{26}$ +57.5° (alcohol, c = 0.809), and the m. p. 189–191°.

Anal. Calcd. for $C_{42}H_{44}O_{10}N_2$: C, 68.45; H, 6.02. Found: C, 68.29; H, 6.06. Calcd. for $C_{34}H_{32}O_6N_2(COCH_3)_4$: $COCH_3$, 23.36. Found (Freudenberg): $COCH_3$, 23.40.

DERIVATIVES OF γ-PSEUDOMORPHINE

Substance	$[\alpha]_D^\circ$	Solvent	t, °C.	c	Formula	*, Anhydrous Calcd.		Found		Calcd.	Found
Monotartrate[a]	+43	Water	23	0.0872	$C_{38}H_{42}O_{12}N_2 + 7H_2O$	C,	63.48*	63.28*	H,	5.89*	5.96*
						H_2O,	14.93	14.99			
Disalicylate[b]	+40.4	60% EtOH	23	.0928	$C_{48}H_{48}O_{12}N_2$	C,	68.22	68.22	H,	5.73	5.85
Dibenzoate[c]	+42.5	Water	23	.0588	$C_{48}H_{48}O_{10}N_2$	C,	70.90	71.06	H,	5.95	5.99
Dihydrochloride[d]	+46.4	Water	23	.1042	$C_{34}H_{38}O_6N_2Cl_2 + 2.5H_2O$	Cl,	11.06*	11.28*	H_2O,	6.55	6.58
Dihydrobromide[e]	+39.0	Water	23	.0962	$C_{34}H_{38}O_6N_2Br_2 + 2H_2O$	Br,	21.89*	21.76*	H_2O,	4.70	4.93
Dihydriodide[f]	+35.3	Water	24	.0922	$C_{34}H_{38}O_6N_2I_2 + H_2O$	I,	30.80*	30.61*	H_2O,	2.14	2.00
Diperchlorate[g]	+49.4	Water	23	.0962	$C_{34}H_{38}O_{14}N_2Cl_2 + 2H_2O$	Cl,	9.22*	9.05*	H_2O,	4.47	4.18
Monosulfate[h]	+29.6	Water	25	.845	$C_{34}H_{38}O_{10}N_2S + 3H_2O$	SO_4,	14.43*	14.26*	H_2O,	7.50	7.24
Methiodidemethohydroxide[i]	+45.7	Water	25	.1804	$C_{36}H_{43}O_7N_2I + 5H_2O$	I,	17.10*	17.20*	H_2O,	10.82	10.70
Dimethiodide[j]	+31.1	Water	24	.466	$C_{36}H_{42}O_6N_2I_2 + 3H_2O$	I,	29.79*	29.51*	H_2O,	5.96	6.42

DERIVATIVES OF TETRAACETYL-γ-PSEUDOMORPHINE

Dihydrobromide[k]	+72.6	Water	22	.539	$C_{42}H_{46}O_{10}N_2Br_2 + 4H_2O$	Br,	17.80*	17.67*	H_2O,	7.42	7.56
Dihydriodide[l]	+62.4	Water	22	.200	$C_{42}H_{46}O_{10}N_2I_2 + 3H_2O$	I,	25.58*	25.45*	H_2O,	5.16	4.91
Diperchlorate[m]	+57.7	Water	25	.615	$C_{42}H_{46}O_{18}N_2Cl_2 + 3H_2O$	Cl,	7.57*	7.39*	H_2O,	5.45	5.03
Dimethiodide[n]	+61	Water	25	.639	$C_{44}H_{50}O_{10}N_2I_2 + 6H_2O$	I,	24.88*	24.74*	H_2O,	9.58	9.93

[a] Prepared in water with excess tartaric acid and precipitated crystalline with alcohol; purified from hot water. [b] Prepared in alcoholic salicylic acid, washed with alcohol and ether; not crystalline, anhydrous. [c] Prepared like the salicylate; amorphous, anhydrous. [d] Prepared from base with excess of warm 6 *N* hydrochloric acid; recrystallized from water. [e] Prepared with 20% hydrobromic acid, recrystallized from water. [f] Prepared in 10% acetic acid with excess potassium iodide, crystallized from water. [g] Prepared with 25% perchloric acid, crystallized from dilute alcohol. [h] Prepared in 20% sulfuric acid, heated to solution, and thrown out with alcohol; recrystallized from 70% alcohol. [i] Prepared by oxidation of γ-isomorphine methiodide in normal sodium hydroxide solution with potassium ferricyanide, and precipitation with carbon dioxide; purified by dissolving in dil. hydrochloric acid and precipitating with ammonia, crystallizing from water. Crystallizes in fine plates having the appearance of aluminum bronze, and when dry has a very faint blue metallic appearance. [j] Prepared by dissolving the methiodide methohydroxide in hot dilute hydriodic acid; separates as a yellow powder from hot water. Heating γ-pseudomorphine in a sealed tube with methyl iodide for five hours at 100° gave only unchanged material. [k] Prepared with 20% hydrobromic acid, recrystallized by addition of water to a suspension in boiling alcohol. [l] Prepared with 20% hydriodic acid, purified from water, light yellow crystals. [m] Precipitates crystalline when alcohol is added to a solution of the tetraacetyl base in 25% perchloric acid; purified like the hydrobromide. [n] Separates crystalline when methyl iodide is added to a cold solution of the base in methanol; purified like the hydrobromide.

For molecular weight, calcd. 736.35. Found (micro-Rast): 737; cryoscopic in *p*-chlorotoluene (K = 5.6), 645, 721.

Gamma-pseudomorphine Monomethyl Ether.—Methylation of γ-pseudomorphine under the conditions of Pschorr and Dickhäuser[6] resulted in a white, flaky precipitate, sparingly soluble in water or dilute alkali, precipitated from either solution by concd. alkali, soluble in absolute alcohol, ether, chloroform, giving no ferric chloride test; the purified base was not detectably more soluble in dilute alkali than in sodium carbonate. The hydrobromide and sulfate crystallize in needles, very soluble; the di-oxalate was prepared in absolute alcohol with alcoholic oxalic acid and recrystallized by precipitating slowly from absolute alcohol solution with absolute ether. It formed fine, white needles having $[\alpha]_D^{25}$ −5.6° (water, c = 0.704); decomposition products from the oxalic acid prevented a methoxyl determination.

Anal. Calcd. for $C_{39}H_{42}O_{14}N_2$ + $5H_2O$: C, 54.90; H, 6.15; H_2O, 10.44. Found: C, 55.01; H, 6.36; H_2O, 10.69.

γ-Pseudomorphine monomethyl ether monomethiodide was prepared by heating under reflux 3 g. of γ-pseudomorphine in 50 cc. of methanol with 25 cc. of water, 7 cc. of normal sodium hydroxide and 1.3 g. of methyl iodide. As the reaction proceeded, a precipitate separated. After twelve hours of standing, this was filtered off and recrystallized from hot water: yield 2.7 g. Its preparation by addition of methyl iodide to the above-described monomethyl ether was not attempted because of lack of material. It has in water the rotation $[\alpha]_D^{25}$ +13.1° (c = 0.1341).

Anal. Calcd. for $C_{36}H_{41}O_6N_2I$ + $2H_2O$: C, 56.82; H, 5.97; H_2O, 4.74. Found: C, 56.85; H, 6.03; H_2O, 4.56.

Tetrahydro-γ-pseudomorphine.—Five grams of γ-pseudomorphine was converted to the hydrochloride, and the salt hydrogenated in suspension in glacial acetic acid with 0.5 g. of palladium on barium sulfate. In seventy-five hours 485 cc. of hydrogen (2.14 moles) was absorbed. The solution was diluted with two volumes of water, partly neutralized with sodium hydroxide, and saturated sodium carbonate solution in excess added. The gelatinous precipitate was filtered, washed with water, and crystallized from ammonia; yield 60%. The base has the melting point (evac. tube) 254° (dec.), and shows $[\alpha]_D^{26}$ +34.3° (normal HCl, c = 1.035). The same substance was obtained in 65% yield when dihydro-γ-isomorphine[5] was oxidized in normal sodium hydroxide with potassium ferricyanide. After crystallization from ammonia the base from this source showed $[\alpha]_D^{26}$ +33.7° (normal HCl, c = 1.022).

Anal. Calcd. for $C_{34}H_{40}O_6N_2$ + $3H_2O$: C, 65.14; H, 7.40; H_2O, 8.63. Found: C, 64.98; H, 7.56; H_2O, 8.96.

Tetrahydro-γ-pseudomorphine sulfate crystallized after two days from a solution of the base in 20% sulfuric acid; recrystallized from very little water, in which it is very soluble. It shows in aqueous solution $[\alpha]_D$ +20.9° (c = 0.431).

Anal. Calcd. for $C_{34}H_{42}O_{10}N_2S$ + $2H_2O$: H_2O, 5.10. Found: H_2O, 5.51. Calcd. for $C_{34}H_{42}O_{10}N_2S$: SO_4, 14.33. Found (Carius): SO_4, 14.34.

Octahydro-γ-pseudomorphine.—Five grams of γ-pseudomorphine was dissolved in a slight excess of 10% acetic acid, the solution diluted to 150 cc., and hydrogenated in the presence of 0.5 g. of palladium–barium sulfate (0.025 g. of Pd). The hydrogenation proceeded slowly, and after five days stopped; calculated for 4 moles, 904 cc.; absorbed, 855 cc. The base was precipitated as a gelatinous mass with sodium carbonate; it could not be obtained crystalline, and came to analysis in the form of its salts. Oxidation of tetrahydro-γ-isomorphine in alkaline solution with ferricyanide gave a crude substance having similar properties, but from which no crystalline salts could be obtained; it is possibly a mixture resulting from union of two molecules in the 1,1′-, 1,2′- and 2,2′-positions.

Octahydro-γ-pseudomorphine gave a crystalline hydrochloride when warmed into solution in 6 N hydrochloric acid; after two crystallizations from water the salt showed $[\alpha]_D^{25}$ +8.9° (water, c = 0.356). The dihydrobromide was obtained in the same way and recrystallized from a small amount of water. It formed yellow crystals having $[\alpha]_D^{23}$ +8.2° (water, c = 0.306).

Anal. Calcd. for $C_{34}H_{46}O_6N_2Br_2$ + $2H_2O$: C, 52.70; H, 6.51; Br, 20.64; H_2O, 4.65. Found: C, 52.63; H, 6.71; Br, 20.50; H_2O, 4.49.

The diperchlorate crystallized from a solution of the octahydro base in warm 25% perchloric acid, and was purified by two crystallizations from the minimum amount of water. Like the other salts of the octahydro compound it is yellow; in water, $[\alpha]_D^{23}$ +6.3° (c = 0.398).

Anal. Calcd. for $C_{34}H_{46}O_{14}N_2Cl_2$ + $2H_2O$: H_2O, 4.43. Found: H_2O, 4.10. Calcd. for $C_{84}H_{46}O_{14}N_2Cl_2$: Cl, 9.12. Found: Cl, 9.19.

Alpha-pseudomorphine.—Oxidation of α-isomorphine (m. p. 247–248°, $[\alpha]_D^{21}$ −168°) and purification of the dimolecular product were carried out as described for the γ-isomer; yield 34%; white crystals, m. p. 276° (evac. tube), $[\alpha]_D^{24}$ +6.2° (N hydrochloric acid, c = 0.811), slightly soluble in water and organic media.

Anal. Calcd. for $C_{34}H_{36}O_6N_2$ + $3H_2O$: C, 65.56; H, 6.80; H_2O, 8.69. Found: C, 65.44; H, 6.77; H_2O, 8.41.

Beta-pseudomorphine.—β-Isomorphine of m. p. 179–181°, $[\alpha]_D^{26}$ −213°, was oxidized like the γ-isomer; the product does not crystallize from ammonia. It was purified by boiling for a few minutes in N hydrochloric acid, filtering through charcoal, adding excess of alkali and passing in carbon dioxide; the yield of crystalline base was 41%; m. p. 272° (evac. tube), $[\alpha]_D^{25}$ −77° (N hydrochloric acid, c = 0.649); solubility like α-pseudomorphine.

Anal. Calcd. for $C_{34}H_{36}O_6N_2$ + $3H_2O$: C, 65.56; H, 6.80; H_2O, 8.69. Found: C, 65.68; H, 6.61; H_2O, 8.35.

Tetrahydropseudomorphine.—Dihydromorphine of m. p. 156–157°, $[\alpha]_D^{25}$ −145° (alcohol, c = 1.589), was oxidized and the product purified as described for γ-pseudomorphine, yield, 60% of fine white crystals, m. p. 300–302° (dec., evac. tube), $[\alpha]_D^{26}$ −85.9° (N hydrochloric acid, c = 1.129). The same product was obtained in 90% yield when pseudomorphine ditartrate hexahydrate was hydro-

(6) Pschorr and Dickhäuser, *Ber.*, **44**, 2633 (1911).

genated in aqueous solution with palladium–barium sulfate; $[\alpha]_D^{26}$ −89.5° (*N* hydrochloric acid, c = 1.033).

Anal. Calcd. for $C_{34}H_{40}O_6N_2 + 2H_2O$: C, 67.07; H, 7.29; H_2O, 5.92. Found: C, 66.87; H, 7.41; H_2O, 6.26.

Tetrahydropseudomorphine monotartrate pentahydrate was obtained when the base was dissolved in an excess of concentrated aqueous tartaric acid and alcohol added slowly. The crystalline precipitate was dissolved in water and again crystallized by addition of alcohol; in aqueous solution, $[\alpha]_D^{25}$ −54.4° (c = 1.056).

Anal. Calcd. for $C_{38}H_{46}O_{12}N_2 + 5H_2O$: C, 56.13; H, 6.95; H_2O, 11.09. Found: C, 56.28; H, 7.06; H_2O, 11.92.

Tetrahydrodidesoxypseudomorphine.—Dihydrodesoxymorphine-D sulfate[7] of specific rotation −57° was oxidized according to the above procedure, and purified from ammonia. The doubtfully crystalline product was suspended in methanol and boiled for a few minutes, giving pure white fine crystals; yield, 75%. The base melted at 318° with dec. (evac. tube) and had in *N* hydrochloric acid $[\alpha]_D^{27}$ −13.4° (c = 1.083). Monomolecular dihydrodesoxymorphine-D has the m. p. 189° and $[\alpha]_D$ −66.8° (as hydrochloride).

Anal. Calcd. for $C_{34}H_{40}O_4N_2 + 2H_2O$: C, 70.79; H, 7.69; H_2O, 6.23. Found: C, 70.63; H, 7.85; H_2O, 6.45.

Pseudomorphine (Alcoholic) Dimethyl Ether (Pseudoheterocodeine).—Heterocodeine (morphine alcoholic methyl ether)[8] of m. p. 242° gave on oxidation a gelatinous precipitate which could be obtained as minute white crystals from ammonia, yield 68%. The base melts at 250–252° (evac. tube); its hydrochloride is so insoluble that the rotation was determined in 10% acetic acid, $[\alpha]_D^{27}$ −192° (c = 0.783).

Anal. Calcd. for $C_{36}H_{40}O_6N_2 + 2H_2O$: C, 68.32; H, 7.01; H_2O, 5.70. Found: C, 68.18; H, 7.18; H_2O, 5.91.

Morphine-γ-isomorphine.—One gram of morphine hydrate and the equivalent weight of γ-isomorphine gave on oxidation a gelatinous base which was crystallized from ammonia; yield 50%. The substance so obtained gave no trace of precipitate with 20% sulfuric acid (pseudomorphine sulfate is very insoluble), hence could have contained only minute quantities of pseudomorphine; if pseudomorphine was not formed, all of the morphine (and therefore of γ-isomorphine) must have gone into formation of the mixed dimolecule. Morphine-γ-isomorphine shows the melting point in vacuum 268–269°, and has $[\alpha]_D^{24}$ −26.4° (normal HCl, c = 0.875). On hydrogenation in dilute acetic acid pseudomorphine takes up 2 moles and γ-pseudomorphine takes up 4 moles of hydrogen; the mixed base should therefore absorb 3 moles. In the presence of 50 mg. of palladium–barium sulfate, 239 mg. of morphine-γ-isomorphine absorbed 30.4 cc. of hydrogen; calculated for 3 moles at 27.5°, 755 mm., 29.64 cc.

(7) Small, Yuen and Eilers, THIS JOURNAL, **55**, 3863 (1933).

(8) Mannich, *Arch. Pharm.*, **254**, 349 (1916).

Summary

1. Gentle oxidation of γ-isomorphine results in γ-pseudomorphine, a dimolecular base of the pseudomorphine type.

2. γ-Pseudomorphine shows the same abnormalities in the reactions of its phenolic hydroxyl groups and nitrogen atoms as does pseudomorphine. Tetraacetyl-γ-pseudomorphine gives a dimethiodide normally, indicating that the peculiarities of the parent base may be due to some form of intramolecular saturation.

3. Hydrogenation of γ-pseudomorphine proceeds with absorption of two or four moles of hydrogen, according to the conditions.

4. Dimolecular bases from the oxidation of dihydro-γ-isomorphine, dihydromorphine, α-isomorphine, β-isomorphine, heterocodeine and dihydrodesoxymorphine-D are described.

5. A dimolecular base containing one morphine and one γ-isomorphine nucleus is described and its unsymmetrical nature demonstrated through hydrogenation.

UNIVERSITY, VIRGINIA RECEIVED MAY 4, 1934