Anal. Calcd. for $C_{12}H_{22}$: C, 86.73; H, 13.27. Found: C, 86.48; H, 13.38.

This compound solidified when cooled in dry ice. The crystals were separated from the liquid by filtering through a cooled filter, and after recrystallization from methyl alcohol gave a pure white substance with a melting point of 46–47°.

Anal. Calcd. for $C_{12}H_{22}$: C, 86.73; H, 13.27. Found: C, 86.55; H, 13.30.

This compound corresponds exactly to dimethyldicyclopentyl isolated by Nenitzescu and Ionescu.[5]

Another portion of this product was dehydrogenated over palladium catalyst at 320°, according to Zelinsky and Borisoff.[6] After the dehydrogenation, the refractive index of the product increased from n_{16} 1.4675 to n_{18} 1.4815, and the following treatment by fuming sulfuric acid (15% SO_3 content) showed an aromatic content of 25%. The residue after sulfuric acid treatment could not be further dehydrogenated over palladium, and its analysis gave C, 86.78; H, 13.28. This investigation shows that 25% of the compound $C_{12}H_{22}$ is dicyclohexyl, the other 75% of this compound being dimethyldicyclopentyl, which could not be dehydrogenated over palladium.

Summary

1. The reaction of aluminum chloride on benzene has been confirmed and the formation of ethylbenzene and diphenyl has been studied quantitatively.

2. The action of aluminum chloride on cyclohexane has been investigated and the formation of dimethylcyclohexane and polycyclic hydrocarbons, $C_{12}H_{22}$, has been found.

3. The formation of ethylbenzene from benzene and dimethylcyclohexane from cyclohexane has been explained by assuming a simultaneous decomposition and alkylation designated by the term "Destructive Alkylation."

CHICAGO, ILLINOIS RECEIVED MARCH 22, 1934

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, NO. 137]

Reduction Studies in the Morphine Series. III. Dihydro-γ-isomorphine[1]

BY LYNDON SMALL AND ROBERT E. LUTZ

The extraordinary tendency of morphine derivatives of the pseudocodeine type, having a double linkage in the 6,7-position, to undergo "abnormal" reduction with addition of four hydrogen atoms, has heretofore made the normal dihydro derivatives of such bases inaccessible for pharmacological study. In the first paper of this series[2] it was demonstrated that the course of hydrogenation of pseudocodeine can be influenced by the reduction conditions in such a way that reductive scission of the ether ring is largely suppressed, and the principal product is a non-phenolic dihydropseudocodeine. This communication deals with the application of the special reduction conditions to γ-isomorphine and the development of a feasible preparative method for dihydro-γ-isomorphine.

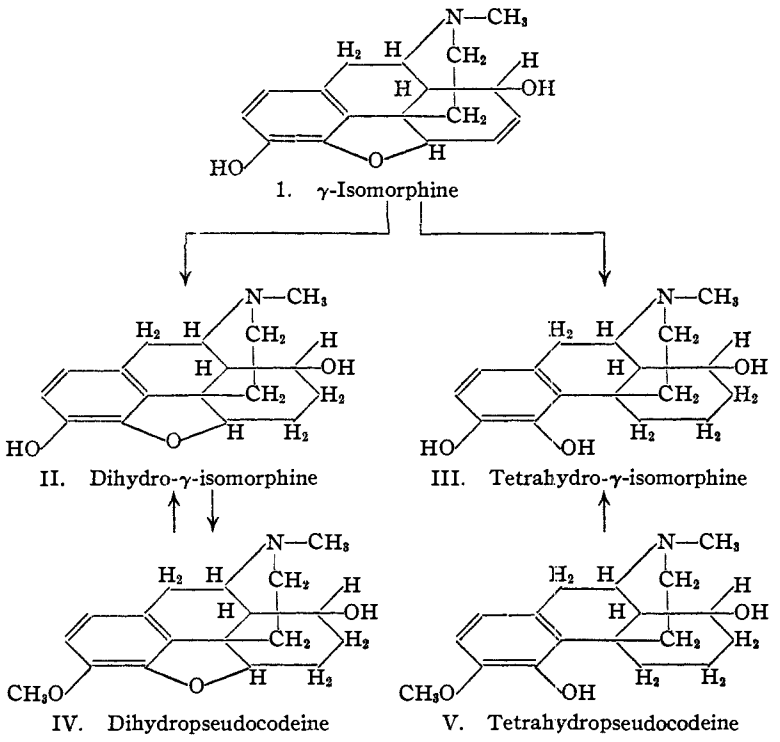
As would be anticipated from the structural features present in ring III, γ-isomorphine is reduced catalytically under ordinary conditions with absorption of two moles of hydrogen, one of which is used in opening the ether ring, the other in saturating the alicyclic double linkage. The product is the diphenolic base tetrahydro-γ-isomorphine (III), which is very sensitive in neutral or alkaline solution, but so stable toward acids that it may be prepared by demethylation of tetrahydropseudocodeine (V) with boiling concentrated hydriodic acid.

By catalytic hydrogenation of γ-isomorphine under the conditions described in our previous communication, reductive scission of the ether linkage is diminished and the product consists of nearly equal amounts of tetrahydro-γ-isomorphine and the desired dihydro-γ-isomorphine (II). It is noteworthy that for γ-isomorphine the tendency to "abnormal" reduction appears to be much greater than for pseudocodeine under similar conditions.

The new dihydro-γ-isomorphine can be methylated with diazomethane, giving the known non-phenolic dihydropseudocodeine (IV).[2] The preparation of γ-isomorphine and the separation of the products obtained in its hydrogenation is an arduous process. As a preparative method it was found more advantageous to demethylate the relatively accessible dihydropseudocodeine with concentrated hydriodic acid, a reaction which gives an 84% yield of practically pure dihydro-γ-isomorphine.

(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) Lutz and Small, THIS JOURNAL, 54, 4715 (1932).



The transition from γ-isomorphine to dihydro-γ-isomorphine results in a general increase in physiological activity, comparable to the increase observed in the analogous pair pseudocodeine–dihydropseudocodeine. Like the latter pair, γ-isomorphine and dihydro-γ-isomorphine appear to be entirely lacking in convulsant action. Analgesic, emetic and exciting effects in the γ-series are low in comparison with morphine and dihydromorphine. More complete data on the physiological action of dihydro-γ-isomorphine will be presented in a communication from the Pharmacological Laboratory of the University of Michigan.

Experimental

Tetrahydro-γ-isomorphine.—The γ-isomorphine used for hydrogenation was prepared by hydrolysis of α-chloromorphide. It had the m. p. 278–279° (corr., evac. tube) and $[\alpha]_D^{25}$ −93.6° (methanol, c = 1.293) and yielded a hydrochloride showing the value $[\alpha]_D^{25}$ −74.8°; Oppé observed the m. p. 278°, $[\alpha]_D^{15}$ −94°, hydrochloride $[\alpha]_D^{15}$ −76°. Reduction favoring conversion to tetrahydro-γ-isomorphine was carried out in dilute acetic acid. A solution of 1.5 g. of γ-isomorphine in 15 cc. of 16% acetic acid with 0.5 g. of palladium–barium sulfate absorbed 236 cc. of hydrogen (2.2 moles). The filtered solution was acidified with a few drops of concentrated hydrochloric acid, evaporated in vacuum to a small volume, taken up in glacial acetic acid, and again concentrated to a sirup. On addition of glacial acetic acid containing 10% hydrogen chloride, an amorphous precipitate separated and slowly formed balls of microscopic hair-like needles. The yield was 1.2 g. (76%) of tetrahydro-γ-isomorphine hydrochloride of $[\alpha]_D^{27}$ −3.5° (water, c = 1.14). No dihydro-γ-isomorphine could be isolated from the filtrate.

A solution of 3 g. of tetrahydropseudocodeine in 10 cc. of hydriodic acid (sp. gr. 1.7, containing 3% hypophosphorous acid) was boiled gently for two minutes, cooled, and diluted slowly with 18 cc. of water. The crystalline tetrahydro-γ-isomorphine hydriodide which separated weighed 2.9 g.; from the hydriodic acid mother liquor 0.4 g. of demethylated base was obtained, yield 84%. Tetrahydro-γ-isomorphine is stable in acid solution or in the form of its salts, exceedingly sensitive in alkaline solution or in organic solvents excepting ethyl acetate. It is insoluble in benzene or chloroform, sparingly soluble in hot ethyl acetate or acetone, very soluble in ethanol and turns red rapidly. It could not be obtained crystalline. The derivatives obtained from the hydrogenation and demethylation products were identical in properties.

Dihydro-γ-isomorphine.—A solution of 2 g. of γ-isomorphine hydrochloride in 50 cc. of glacial acetic acid with 0.065 g. of platinum oxide absorbed 185 cc. of hydrogen (corr.) or 1.3 moles. During the reduction a white precipitate of hydrochlorides appeared. The solution was warmed until this dissolved. It was then filtered and frozen. After the acetic acid had melted slowly, there remained in suspension the characteristic balls of crystals of tetrahydro-γ-isomorphine hydrochloride; yield 0.45 g. (21%), m. p. 260–265°, $[\alpha]_D^{27}$ −1.8°. The filtrate was evaporated in vacuum and the residue taken up in hot absolute alcohol, from which 0.75 g. (35% yield) of nearly pure dihydro-γ-isomorphine hydrochloride crystallized. The base melted at 127° (frothing), solidified, and remelted at 221°; $[\alpha]_D^{25}$ −35°. It did not depress the melting point of the material prepared by demethylation of dihydropseudocodeine, and yielded the same salts. The filtrate from the above hydrochloride yielded 0.65 g. of mixed di- and tetra-hydro derivatives.

Five grams of non-phenolic dihydropseudocodeine suspended in 15 cc. of hydriodic acid (sp. gr. 1.7, containing 3% hypophosphorous acid) was warmed to a clear solution and boiled gently for three minutes; copious evolution of methyl iodide was observed. The nearly colorless solution was cooled quickly and diluted with 20 cc. of water, whereupon the hydriodide of dihydro-γ-isomorphine separated as sparkling white crystals. The crude hydriodide has a tendency to become yellow or brown on drying, hence it was suspended in hot water, treated with a slight excess of sodium carbonate containing a trace of sodium hydrosulfite, and heated until no more carbon dioxide was evolved; in the absence of the hydrosulfite the product is faintly pink. The base as thrown out by hot carbonate consisted of radiating clumps of thick white prisms and weighed 4.0 g., a yield of 84%. It is hydrated and melts at 128–130° with gas

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,	2.70	2.90	Cl,	10.66	10.63
						Cl,	10.95[h]	11.12[h]			
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.