

THE ISOMERIZATION OF MORPHINE TO O-DESMETHYLTHEBAINONE¹

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Received June 11, 1948

The isomerization of morphine (I) to dihydromorphinone (II) (in acidic medium) in the presence of noble metal catalysts is well known (1). We have observed that in the course of this interconversion (1a) there is also produced a smaller amount of a hitherto unrecorded isomer of morphine. Under appropriate conditions we have been able to achieve about 60% conversion of morphine to this new isomer. Separation of the new compound from the accompanying dihydromorphinone is effected through their different solubilities in chloroform or pyridine. The work to be presented indicates almost unequivocally that the compound has the structure III. It could best be designated as O-desmethyl-thebainone.

The new compound is a homogeneous, well defined chemical individual, as demonstrated by the uniformity of the free base obtained from various fractions of the recrystallized hydrochloride. The analytical values agree well with those for the composition $C_{17}H_{19}NO_3$. With acetic anhydride it forms an easily saponified diacetate, indicating two actual or potential hydroxyl groups. Molecular weight determination on this compound cryoscopically in benzene or camphor (Rast) gave values corresponding to a diacetate of $C_{17}H_{19}NO_3$, whereas the parent compound III was too insoluble in the usual solvents for cryoscopic or ebullioscopic molecular weight measurements. Absorption of one mole of hydrogen in the presence of palladium to give compound IV with persistence of the original carbonyl group (formation of oximes and thiosemicarbazones of both compounds) demonstrates the presence of the double bond.

Evidence for placing the ethylenic double bond in the 7,8-position, in conjugation with the carbonyl group, was obtained in several different ways. With aqueous alkali, in the presence of sodium hydrosulfite, III produces a light yellow color. It has been shown (2) that, among ketonic morphine derivatives, this color reaction is given only by thebainone, 14-hydroxythebainone, and sinomenine, all α,β -unsaturated ketones.² Schöpf has considered this as a characteristic group reaction. Some small doubt may be cast upon this generalization by our observation that the dihydro derivative (IV), under the same conditions provides a solution which stays colorless for only a short time, rapidly becoming brown in spite of the presence of hydrosulfite. However, this color is easily distinguished from the yellow produced by III.

Speyer *et al.* (3) have observed that oximes of α,β -unsaturated ketones undergo catalytic hydrogenation and hydrogenolysis simultaneously to ammonia and the

¹ Presented before the Organic Division, 114th meeting of the American Chemical Society, St. Louis, Mo., Sept. 7, 1948.

² With those compounds which are less sensitive to oxygen than III or IV, no hydrosulfite was used.

saturated ketone. In conformity, the oxime of III upon catalytic hydrogenation gave ammonia and IV, isolated as the oxime hydrochloride.

It was hoped that a study of the ultraviolet absorption spectra of III and IV, and comparison with the spectra of other possibly related morphine derivatives

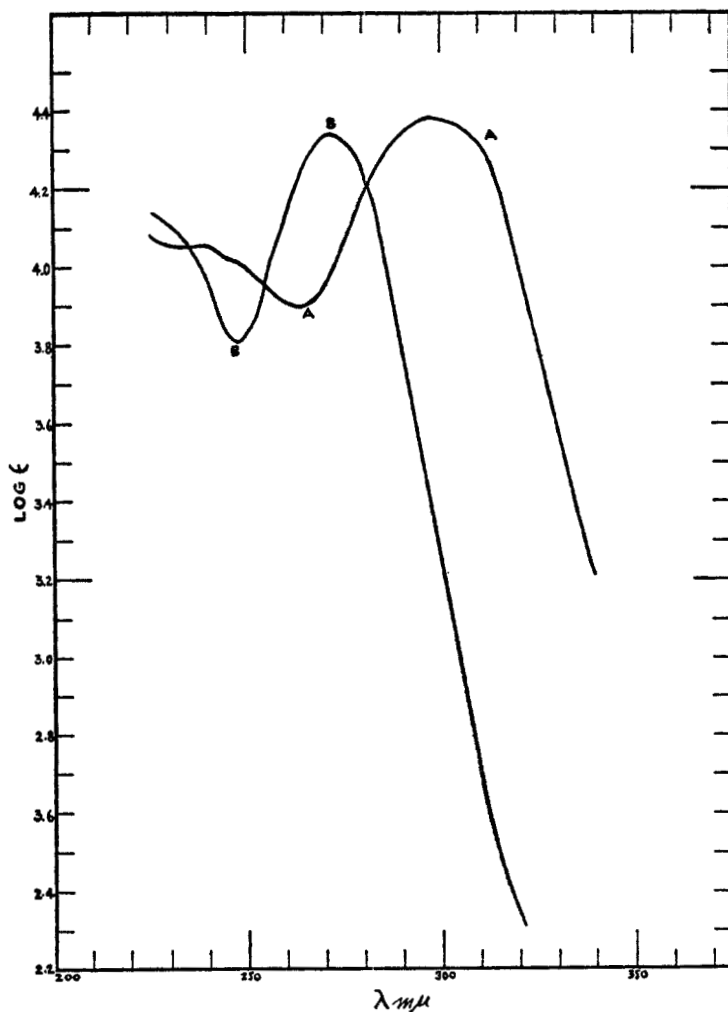


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA IN METHANOL OF THE THIOSEMICARBAZONE HYDROCHLORIDES OF O-DESMETHYLTHEBAINONE (III), (CURVE A) AND OF O-DESMETHYLDIHYDROTHEBAINONE (IV), (CURVE B)

would give supporting evidence for the conjugated system. Unfortunately, the significant band for such a conjugated system ($225 \pm 5 \text{ m}\mu$) (4) was completely obscured by the end absorption exhibited by all morphine derivatives. Examination of the absorption spectrum of the thiosemicarbazones³ of III and IV gave

³ We are indebted to Dr. R. B. Woodward of Harvard University for this suggestion and for the reference to the work of Gillam.

final and conclusive proof of the presence of the conjugated system. Evans and Gillam (5) found that thiosemicarbazones of unsaturated ketones are characterized by a very high absorption maximum at $301.5 \pm 2 \text{ m}\mu$ ($\epsilon = 20,000\text{--}30,000$) and a lesser one at $245 \pm 4 \text{ m}\mu$ ($\epsilon = 7,000\text{--}13,000$).

The semicarbazones of saturated ketones and of unsaturated ketones other than α,β , have maxima at 270 and 230 $\text{m}\mu$. The thiosemicarbazone hydrochlorides of III and IV fit very well into this pattern (see Fig. 1).

Indications that compound III resulted by opening of the oxygen bridge were first obtained from color reactions. Morphine, and many of its derivatives, in which the oxygen bridge is intact, give red to purple shades of varying intensities with Marquis' reagent (6), formalin in conc'd H_2SO_4 (7). In contrast, III and IV give blue-green colors with this reagent and resemble dihydrothebainone (V) in this respect. This point was unequivocally demonstrated by methylation of the dihydro derivative (IV) with diazomethane, resulting in the isolation of dihydrothebainone (V). A single attempt to convert III to the known thebainone, (8) VI, with diazomethane resulted in resins. This may not be surprising in view of the known reactivity of α,β -unsaturated ketones towards diazomethane. Additional confirmation for the *o*-diphenol structure of III and IV may be deduced from the sensitivity of the compounds to air in the presence of alkali, IV being more sensitive than III.

The optical activities of III and IV are in good agreement with the assigned structures, the $[\alpha]_D$ -values having the expected similarity with those of the respective methyl ethers, VI and V.

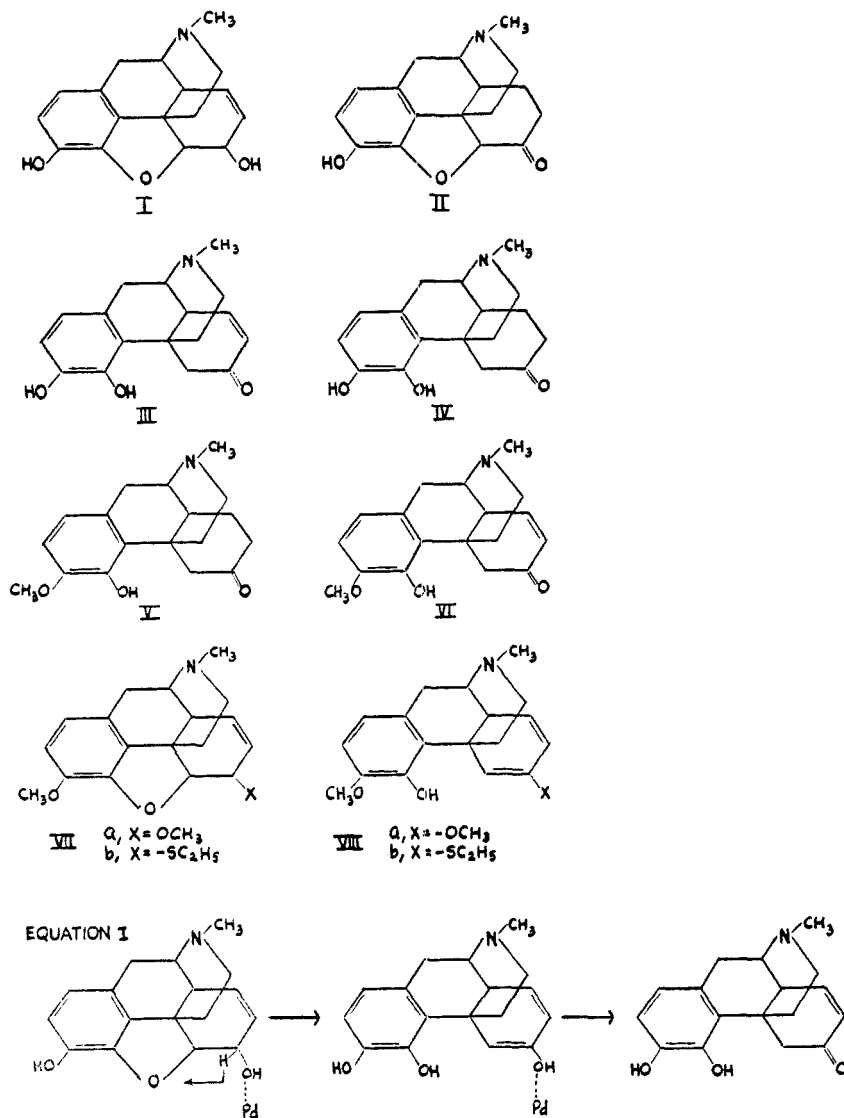
	III	VI (9a)	IV	V (9b)
$[\alpha]_D$	-34.3°	-42.5°	-68°	-72.5°

It may be interesting to speculate upon the mechanism by which this *O*-desmethylthebainone (III) may be formed. Formal analogies to such oxygen-bridge cleavages are available, but, in all probability, cannot be compared to the situation here described. Thus, codeine methyl ether VIIa can be transformed to thebainone methyl enolate VIIIa by the action of sodium alcoholate (10) and α -ethylthiocodide (VIIb) is similarly isomerized to β -ethylthiocodide (VIIIb) (10).

The same reaction with morphine should result in III (as its enol form), but opposed to this is the observation (10) that codeine does not undergo this transformation. In any case these reactions (VII \rightarrow VIII) are promoted by alkali whereas the formation of III takes place in acid solution.

The fact that a hydrogenation-dehydrogenation catalyst is necessary for the transformation leads us to suggest a hypothesis based on intra- and inter-molecular hydrogenation. Under all conditions examined both III and dihydromorphinone II are formed in varying proportions, dependent on the type and quantity of catalyst. The highest yield of III was obtained in the presence of a large amount of 10% palladium on charcoal catalyst, the proportion of dihydro-

morphinone increasing and that of III decreasing as the quantity of catalyst was decreased. When a less active palladium-black catalyst was used, the yield of



III was diminished, and a certain amount of dihydromorphine was obtained, in all probability by reduction of morphine with hydrogen occluded in the catalyst. This possibly indicates that in the presence of a small amount of catalyst many morphine molecules are adsorbed at a single active center, favoring an intermolecular hydrogen exchange resulting in dihydromorphinone, whereas in the presence of a large quantity of catalyst the possibility of single morphine molecules being adsorbed at single active centers would be favored (Equation I).

The electron deficient catalyst, sharing the free electrons of the hydroxyl oxygen would presumably mobilize the hydrogen on carbon atom 6 in a fashion analogous to the function of the aluminum in the Meerwein-Ponndorf-Verley reduction. The availability of an adjacent electron-rich center, the oxygen bridge, would, on this assumption, provide a proton-accepting atom quite similar to that furnished by the carbonyl group in the Meerwein-Ponndorf-Verley reduction. A similar case may be cited in the observations of Adkins and Folkers (11) on the thermal disproportionation of 2,2-dimethyl-3-butene-1-ol over alumina. In this case the products were 2,2-dimethyl-3-butene-1-al and 2,2-dimethylbutene.

Addition to proof, received Feb. 4, 1949: Further experimental work carried out since submission of this paper, has shown that codeine is converted in part to thebainone under similar conditions.

ACKNOWLEDGMENT

We wish to acknowledge the assistance of J. Braude in carrying out some of the experiments and of Joseph E. Machurek in the preparation of the drawing.

We are indebted to Dr. L. F. Small for a stimulating discussion of the findings herein reported.

EXPERIMENTAL

O-desmethylthebainone (III). Fifty g. of morphine hydrochloride trihydrate was dissolved in 250 cc. of water in a one-liter flask, 6.5 cc. of 2 *N* hydrochloric acid and 60 g. of 10% palladium on charcoal catalyst⁴ was added. The flask was flushed free of air with nitrogen and placed in an electrically heated shaking apparatus. The temperature was raised to 80° without shaking, and the reaction mixture was shaken at this temperature, in nitrogen atmosphere, for seventeen hours. At the end of the shaking period the mixture was allowed to cool to room temperature. The solution was freed of catalyst and the catalyst washed with water. The combined filtrate and washings were transferred to a separatory funnel with 380 cc. of chloroform. While the two immiscible layers were being agitated by a rapid stream of nitrogen bubbles, 105 cc. of 2 *N* ammonium hydroxide was added dropwise to the mixture. A heavy precipitate, which created a nearly inseparable interphase layer, formed. The mixture was filtered by suction, the precipitate was washed thoroughly on the funnel with chloroform, and the aqueous phase of the filtrate was extracted further with chloroform. From the combined chloroform extracts, dihydromorphinone was isolated by concentration, yield 5.3 g., 14%.

The filtered *O*-desmethylthebainone (III) was dried *in vacuo*, and was thus obtained as a gray-to-brown amorphous-appearing powder. The product was purified by several recrystallizations from pyridine at steam-bath temperature in a nitrogen atmosphere. At this temperature the compound requires approximately 30 volumes of the solvent; m.p. 220–221° (dec.) in a sealed capillary, bath preheated to 200°. The analytical sample was dried over boiling acetone at 2 mm.

*Anal.*⁵ Calc'd for $C_{17}H_{19}NO_3$: C, 71.55; H, 6.71; N, 4.93.

Found: C, 71.17; H, 6.74; N, 4.92, 5.03.

The compound is moderately soluble in ethanol, slightly soluble in benzyl alcohol, and

⁴ Obtained from Baker Platinum Works, Newark, N. J.

⁵ Microanalyses by Mr. W. Saschek, Columbia University, and Oakwold Labs., Fairfax, Va.

very slightly soluble in benzene, chloroform, heptane, acetone, ethyl acetate, or dioxane. Samples obtained from several of the above solvents exhibited the same melting point and color reactions (listed below) as that obtained from pyridine.

O-desmethylthebainone (III), in alcoholic suspension, gives a purple color with a small amount of ferric chloride solution (approx. 10%), which becomes blue-green to green with more of the reagent. We observed that dihydrothebainone (V) behaves in a similar way. With Marquis' reagent the substance produces a blue-green color of low intensity. The color reaction with alkali has already been described; optical rotation: $[\alpha]_D^{25} -34.3^\circ$ (10% acetic acid, *c*, 3.62).

Isolation via the hydrochloride. The aqueous filtrate from a reaction, similar to the one leading to the above product, which started with 36 g. of morphine hydrochloride trihydrate and 1.8 g. of 10% palladium-charcoal catalyst, was evaporated to dryness under reduced pressure in a stream of nitrogen. The residue was converted to a crystalline mass by suspending in 3 successive 20-cc. portions of ethanol which were evaporated, *in vacuo*, in turn. The resulting powder was extracted with four successive 100-cc. portions of boiling ethanol, leaving dihydromorphinone hydrochloride undissolved. The alcoholic filtrates, on partial evaporation, yielded 16.4 g. of hydrochloride, from which O-desmethylthebainone, m.p. 216° (dec.) was isolated. Fractional recrystallization of the hydrochloride from ethanol and conversion to the free base gave material of identical melting point from the least soluble, intermediate, and most soluble fractions.

Oxime. The free base III (10 g.), treated with 10 g. of hydroxylamine hydrochloride in 100 cc. of water on the steam-bath for 30 minutes, yielded, on cooling, 7.0 g. of well-crystallized oxime hydrochloride. This salt exhibited a variety of melting points (243° , 265° , 274°) for the various fractions isolated from recrystallizations in methanol. These all yielded identical bases upon treatment with sodium bicarbonate, m.p. 274-279. The free base isolated, by sodium bicarbonate treatment, from the mother liquor of the oximation reaction mixture also had the same m.p. No suitable solvent for recrystallization of the oxime base was found. A crude sample was submitted to analysis.

Anal. Calc'd for $C_{17}H_{20}N_2O_3$: N, 9.33. Found (Kjeldahl): N, 8.97.

Thiosemicarbazone hydrochloride. O-desmethylthebainone (III) (2.85 g.) was brought into solution in 15 cc. of water by addition of the calculated quantity of 2 *N* hydrochloric acid, and then treated on the steam-bath with 0.91 g. of thiosemicarbazide. The thiosemicarbazide dissolved rapidly, but the solution was allowed to remain at steam-bath temperature for two hours. Some crystallization occasionally took place during this period, and was completed by cooling the mixture in an ice-bath. The filtered solid was washed with ice water, yield 2.85 g., m.p. 217° . The yellow platelets, obtained by recrystallization from water or methanol, melted at $219-220^\circ$. The color could not be removed by the use of charcoal or sodium hydrosulfite.

Anal. Calc'd for $C_{18}H_{23}ClN_4O_2S$: N, 14.19; S, 8.10.

Found: N, 14.03, 13.95; S, 8.04, 7.80.

The thiosemicarbazone base, obtained by treatment of a warm aqueous solution of the hydrochloride with sodium bicarbonate, was a yellowish, apparently amorphous powder; m.p. 210° (dec.). It could not be recrystallized from a variety of solvents and was not further investigated.

Diacetyl derivative. Ten grams of O-desmethylthebainone (III) was suspended in 80 cc. of acetic anhydride at room temperature. The solid dissolved in about ten minutes, and the brown solution was allowed to remain at room temperature for two hours. It was then poured into 160 cc. of water and shaken until the mixture became homogeneous. The subsequent work-up was carried out within an hour, since a similar reaction mixture, allowed to stand overnight, yielded only recovered III. The solution was transferred to a separatory funnel containing 100 cc. of chloroform, and was made alkaline to phenolphthalein with 28% ammonia while the two layers were thoroughly mixed with a rapid stream of nitrogen bubbles. The aqueous layer was extracted with four additional 100 cc. portions of chloroform, the combined chloroform extracts were dried with sodium sulfate, and treated

simultaneously with Darco G-60. The filtered solution was evaporated to dryness *in vacuo*, leaving an amorphous residue. Upon standing at room temperature, under nitrogen, for two days it became crystalline. This product was recrystallized from chloroform-ether mixture and obtained as needles, m.p. 181–184°; yield 5.1 g. (40%). For analysis it was recrystallized from five volumes of ethanol, but in spite of the use of additional charcoal, was obtained as light tan crystals, m.p. 183–184°.

Anal. Calc'd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79.

Found: C, 68.43; H, 6.52; N, 3.85.

M.W. Calc'd, 369.4. Found: (a) Rast, (camphor): 318 (0.0398 gm. in 0.4780 gm. camphor: $-\Delta T = 10.5^\circ$). (b) Cryoscopic in benzene: 0.2531 gm. in 36.15 gms. benzene: $-\Delta T$ (avg.) = 0.104° . M.W. = 348.

This diacetyl derivative produces no color with ferric chloride in ethanol solution. It sublimes readily at 110–115° and 3×10^{-4} mm.

O-desmethylidihydrothebainone. A solution of 25.4 g. of III in 200 cc. of water plus a slight excess over the stoichiometric quantity of 2 *N* hydrochloric acid was shaken with hydrogen and 1.5 g. of 10% palladium-charcoal until hydrogen uptake stopped. The reaction consumed 0.95 equivalent of hydrogen.

The solution was filtered and concentrated *in vacuo* to incipient crystallization. Chilling, at this point, produced a crystalline magma, which was filtered, washed twice with ice-water, and dried *in vacuo* over phosphorus pentoxide; yield 21 g., m.p. very unsharp at 165–170°.

The base was obtained by solution of the above hydrochloride in 160 cc. of lukewarm water, containing a small amount of sodium hydrosulfite, and neutralization to phenolphthalein with ammonia, 1:1. *O-desmethylidihydrothebainone* precipitated as a heavy white powder, which was readily soluble in excess ammonia. The mixture was chilled and filtered. The filter-cake was washed with cold water and then dried *in vacuo* over phosphorus pentoxide; yield 16.6 g., m.p. 274°.

An additional quantity of the base was obtained from the above aqueous mother liquors upon standing for several days after addition of sodium bicarbonate solution.

Difficulty was encountered in the recrystallization of this material for analysis, but samples that gave consistent and concordant results were finally obtained by recrystallizing first from pyridine (10–12 volumes) and then from anisole (30 volumes) and drying over boiling Methyl Cellosolve at 2 mm.

Anal. Calc'd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87.

Found: C, 71.16, 71.53; H, 6.74, 6.95; N, 5.22, 4.91.

$[\alpha]_D^{25} -68^\circ$ (*c*, 1.264 in 10% acetic acid)

The compound is readily soluble in benzyl alcohol at room temperature, and moderately soluble in boiling acetone. An aqueous suspension of the dihydro compound becomes brown with great rapidity, and addition of alkali produces a light red solution. If the addition of alkali is done in the presence of sodium hydrosulfite a colorless solution results, which, however, becomes brown in a short time.

Addition of a few drops of 10% ferric chloride solution to an aqueous or alcoholic suspension of the dihydro compound yields a purple color which can be changed to green by addition of more reagent.

With Marquis' (7) reagent an intense blue-to-green color is produced.

O-desmethylidihydrothebainone oxime hydrochloride. Purified IV (1 g.) was heated on the steam-bath with a solution of one gram of hydroxylamine hydrochloride in 25 cc. of water for 30 minutes. The solution was chilled in an ice-bath and the flask scratched with a glass rod, thereby inducing crystallization. This oxime hydrochloride was so sparingly soluble in boiling methanol that a true recrystallization could not be achieved, but since the material which was obtained upon crystallization from the mother liquors of digestion with boiling methanol had the same m.p. as the digested residue, m.p. 318–320° (dec.), the latter was considered sufficiently pure for analysis. The analytical data check best for a compound with $1.5H_2O$, without excluding those with either $1H_2O$ or $2H_2O$.

The N/HCl ratio is sufficiently close to two to leave no doubt as to the identity of this compound.

Found: N (Kjeldahl) 7.57, 7.58; HCl, 10.02. Ratio N/HCl=1.97.

Calculated for

	$C_{17}H_{23}ClN_2O_2$	$1H_2O$	$1.5H_2O$	$2H_2O$
N	8.28	7.85	7.66	7.47
HCl	10.77	10.22	9.97	9.74.

O-desmethyldihydrothebainone thiosemicarbazone hydrochloride. *O*-desmethyldihydrothebainone (2.45 g.) was added to a mixture of 0.8 g. of thiosemicarbazide in 15 cc. of water and 8.5 cc. of *N* hydrochloric acid. This was heated on the steam-bath for two hours. The resulting brown solution was cooled in an ice-bath, and seeded. The crystalline magma was refrigerated overnight, filtered, washed with ice-water, and dried *in vacuo* over phosphorus pentoxide. It was thus obtained as a colorless, microcrystalline powder, yield 2.7 g. (79%). This salt was recrystallized from four volumes of boiling water with a recovery of about 75%. The product thus obtained showed no sharp melting point, starting to sinter and discolor at about 210° and decomposing at about 250°, this latter temperature depending upon the rate of heating. The salt is also soluble in ethanol.

Anal. Calc'd for $C_{13}H_{25}ClN_4O_2S$: N, 14.11. Found: N, 14.06, 14.27.

Sulfur determinations were made but came out inexplicably high, calc'd 8.08%; found, 9.55, 9.42%. However, the excellent agreement of the nitrogen values, and the concordance of the absorption spectrum with that expected can leave little doubt as to the identity of the compound.

The corresponding base was isolated by treatment of the mother liquors of the original reaction mixture with sodium bicarbonate solution. In this manner, 0.3 g. of base was obtained as globular aggregates of very short needles, m.p. unsharp at 260–280° (dec.). It was very soluble in pyridine, boiling ethanol, and anisole, but none of these, nor any of several other solvents tried, proved to be appropriate for recrystallization, and the base was not further investigated.

Methylation of O-desmethyldihydrothebainone; dihydrothebainone. To a solution of 8.61 gms. (0.03 mole) of IV in 180 cc. of dry benzyl alcohol an ethereal solution of diazomethane⁶ (12) in slight excess of one equivalent, was added, portion-wise, in about twenty minutes. Nitrogen was evolved, but the usual end-point, disappearance of the yellow color, could not be noted due to the formation of a light red color. After standing at room temperature for about 30 minutes, the solution was shaken with 100 cc. of 1:10 hydrochloric acid. The separated benzyl alcohol layer was then washed three times with small portions of acidified water, which were combined with the original aqueous extracts. The aqueous solution was then washed five times with ether to remove the dissolved benzyl alcohol.

The aqueous solution was adjusted to approximately pH 9 with ammonia and the resulting milky dispersion was extracted with four portions of chloroform. After drying over sodium sulfate, the chloroform was evaporated to dryness *in vacuo* to yield a glassy brown residue. This could be induced to crystallize by treatment with a small volume of cold acetone. However, it was dissolved in hot acetone and the solution treated with charcoal; the cooled filtrate, upon seeding with authentic dihydrothebainone, deposited a heavy crop of crystals. After filtration, washing with ice-cold acetone, and drying, the yield was 1.3 g.; m.p. 132–133°.

The literature lists a variety of melting points, ranging from 133° to 150°, for dihydrothebainone. In our hands, authentic samples of dihydrothebainone, recrystallized from acetone, melt around 145°. Two additional recrystallizations, from acetone, of the material isolated in this experiment gave a sample that melted at 144–146° after sintering at 138°. Mixed melting point of an authentic sample (m.p. 142–145°) with this material was undepressed, sintering at 142° and melting at 144–146°.

⁶ Dry benzyl alcohol was substituted for the recommended cyclohexanol.

Confirmation of this identification was obtained by comparison of the oxime base and oxime hydrochloride with the same derivatives prepared from authentic dihydrothebainone.

	MELTING POINTS		
	This Expt.	Authentic Deriv.	Mixture
Oxime Base.....	245°	244.5-245°	244.5-245°
Oxime HCl.....	311°	319°	314°

The product of this experiment gave, in alcoholic solution, with ferric chloride, a characteristic green color, indistinguishable from that similarly produced by authentic dihydrothebainone.

An additional quantity (2.7 g.) of this same product was isolated from the original mother liquors by conversion to the alcohol-insoluble hydrochloride, using alcoholic hydrogen chloride.

Hydrogenolysis of O-desmethylthebainone oxime. Two and one-half g. of O-desmethylthebainone oxime was dissolved in a mixture of 10 cc. of glacial acetic acid and 40 cc. of water. The solution was shaken with hydrogen in the presence of 0.15 g. of 10% palladium-charcoal catalyst until absorption stopped. This corresponded to 2.18 moles of hydrogen.

After completion of the absorption and removal of the catalyst, a small portion of the filtrate was treated with excess sodium hydroxide solution and ammonia was demonstrated by odor and blueing of red litmus paper by the evolved vapors.

The remainder of the filtrate was evaporated *in vacuo* to a syrup, which was dissolved in warm ethanol. Cooling this solution resulted in the crystallization of a presumed acetate. This was filtered, washed with ice-cold alcohol, and dried *in vacuo* over phosphorus pentoxide. It melted unsharply at 187-189° when immersed in a bath at 160°; yield 0.7 g. More of this same material was obtained by concentration of the alcoholic mother liquors and precipitation with ether. This product was converted to an amorphous base, unsharp m.p. about 180°, by treatment of its aqueous solution with excess sodium bicarbonate solution.

Since this material was very soluble in chloroform and ethyl acetate, due possibly to excessive contamination with by-products, it was treated with hydroxylamine hydrochloride in water. Upon working up as described for O-desmethyldihydrothebainone oxime hydrochloride (above), material of m.p. 320° (unsharp) with preliminary sintering at 310° was obtained. By digestion with hot ethanol a crystalline sample of m.p. 315°, undepressed by admixture with an authentic sample, was obtained.

SUMMARY

The isomerization of morphine to O-desmethylthebainone is described.

Chemical and spectroscopic evidence for the structure of this compound is presented.

A mechanism for this isomerization under the influence of a palladium catalyst, based on intramolecular dehydrogenation, is suggested.

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