[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF ROCHESTER]

The Conversion of *trans* to *cis* Fusions of Rings II and III in the Morphine Series

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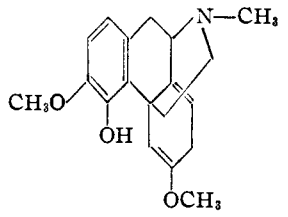
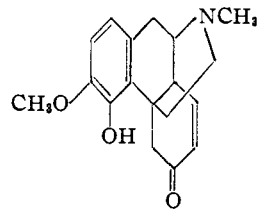
The conversion of β-thebainone (rings II/III *trans*) to thebainone (rings II/III *cis*) by three methods is described.

The observations of Small and Browning[2] on the hydrolysis of phenolic dihydrothebaine (I)[3] have made available derivatives of the morphine series possessing a *trans*[4] fusion of rings II and III, and certain substances of this configuration at C_{14} are available by synthesis.[5] No direct interconversions of *trans* to *cis* compounds or the reverse have yet been reported, however.

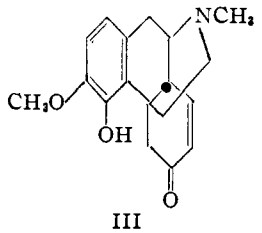
We have been able to convert β-thebainone (rings II/III *trans*) (II) into thebainone (rings II/III *cis*) (III) by three different methods.



I



II



III

Thus β-thebainone, $[\alpha]D$ +114°, mutarotates in the presence of sodium ethoxide and from the resulting mixture, $[\alpha]^{27}D$ −23°, thebainone can readily be isolated. The rotation of the crude mixture corresponds, on the assumption that only these two C_{14} epimers are present, to a conversion of 84%, although we have been unable to isolate more than 59% of pure thebainone from the mixture. Thebainone on treatment with sodium ethoxide gives a mixture of similar specific rotation.

β-Thebainone is also unstable to acids and warming in acetic acid solution is sufficient to produce a change in rotation from +114 to approximately 0°. Thebainone can be isolated from the resulting mixture in 57% yield either as its hydriodide or as free base.

Finally, we have observed that the 2,4-dinitrophenylhydrazone of β-thebainone is readily isomerized to that of thebainone by warming in acetic acid. This epimerization at C_{14} is so facile, in fact, that for preparative purposes it is necessary to make use of the very low solubility of the perchlorate of β-thebainone-2,4-dinitrophenylhydrazone in order to remove it from the acidic medium as it is formed. The change is readily followed polarimetrically, as with the free base, and the observations are facilitated by the unusually high rotation exhibited by thebainone-2,4-dinitrophenylhydrazone ($[\alpha]^{27}D$ −1013° in glacial acetic, $[\alpha]^{27}D$ −1375° in chloroform). The isomerization is essentially complete in five to six hours at steam-bath temperatures, and although undoubtedly an equilibrium is established, the position of this equilibrium lies so far toward the *cis* series that unchanged *trans* dinitrophenylhydrazone cannot be detected, nor does it appear as a result of heating the pure *cis* compound in acetic acid for the same period. Thus pure β-thebainone-2,4-dinitrophenylhydrazone mutarotates under these conditions from a small positive value to −655° and the rotation of pure thebainone-2,4-dinitrophenylhydrazone drops from −1013 to −728° under the same conditions, but in both cases a certain amount of decomposition takes place, and if the decomposition products are removed by chromatography on alumina, upon which they remain strongly adsorbed while the dinitrophenylhydrazones are readily eluted, the crude dinitrophenylhydrazone fraction before crystallization has in each case a rotation closely approximating that of pure thebainone-2,4-dinitrophenylhydrazone and yields only this substance on crystallization.

The isomerizations of β-thebainone base are clearly merely additional examples of acid- and base-catalyzed equilibrations involving the C_{14} hydrogen as a proton and do not require further comment, although why the *cis* configuration is of comparable or even greater stability than the *trans* is not immediately obvious. Presumably the isomerization of β-thebainone-2,4-dinitrophenylhydrazone is analogous to the acid-catalyzed isomerization of the base, and can be formulated as the loss of hydrogen at C_{14} as a proton from the conjugate acid of the dinitrophenylhydrazone followed by the inverse addition of a proton at C_{14}, although here again, the reason for the preponderance of *cis* isomer in the product is not clear.

In ignorance of the work of Bentley and Wain,[6] who were able to prepare the β,γ-unsaturated ketone

(1) Merck and Co., Inc., Post-Doctorate Fellow, 1951.

(2) L. F. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939).

(3) Called "dihydrothebaine-φ" by K. W. Bentley, R. Robinson and A. E. Wain, *J. Chem. Soc.*, 958 (1952). Its structure has recently been clarified in exemplary fashion by G. Stork, THIS JOURNAL, **74**, 768 (1952).

(4) Morphine and related substances having the same configuration at C_{14} are considered to have *cis* fusions of rings II and III (*cf.* C. Schöpf and F. Borkowsky, *Ann.*, **452**, 211 (1927)). Stork's ingenious argument ("The Alkaloids," Vol. II, Academic Press, Inc., New York, N. Y., 1952, p. 175) that the catalytic hydrogenation of thebaine to dihydrocodeine methyl ether (taken in conjunction with the demonstration (p. 172) that the hydrogen atoms on C_5 and C_6 of codeine are *cis*, and with other evidence) is sufficient to assign unambiguously the *cis* configuration to the fusion of rings II and III greatly strengthens Schöpf's contention, but both arguments are presumptive, and a rigorous proof of this point is lacking.

(5) M. Gates and G. Tschudi, THIS JOURNAL, **72**, 4839 (1950); (b) **74**, 1109 (1952).

(6) K. W. Bentley and A. E. Wain, *J. Chem. Soc.*, 967 (1952).

of this series, we attempted to prepare this substance by acidifying under irreversible conditions[7] the enolate anions, prepared in liquid ammonia by the action of potassium amide, of these ketones (II and III), but in each case recovered the starting ketones. Presumably these results indicate that under the conditions used, complete conversion to the anion had not occurred, possibly because of poor solubility relationships.

By making use of the facile isomerization of β-thebainone to thebainone in acetic acid, the latter substance can be prepared directly from phenolic dihydrothebaine in 47% yield, and this fact coupled with the availability of phenolic dihydrothebaine simply and in high yield from thebaine by the elegant method of Bentley, Robinson and Wain[2] makes this route to thebainone attractive as a preparative procedure.[8]

We are grateful to Merck and Company, Inc., for generous financial support and for supplies of thebaine.

Experimental[9]

β-Thebainone was prepared and purified as described by Small and Browning,[2] using phenolic dihydrothebaine prepared by the excellent method of Bentley, Robinson and Wain.[3,10] We have observed both the low-melting form of β-thebainone perchlorate recently described by Bentley and Wain,[6] and the higher-melting form (m.p. 150–155°) described by Small and Browning.

β - Thebainone - 2,4 - dinitrophenylhydrazone. — β-Thebainone perchlorate (435 mg.), m.p. 150–155°, was dissolved in 3 cc. of glacial acetic acid and treated with 210 mg. of 2,4-dinitrophenylhydrazine. On warming on the steam-bath, the dinitrophenylhydrazine went into solution and within a few minutes a copious crystalline precipitate of β-thebainone-2,4-dinitrophenylhydrazone perchlorate separated. Heating was continued for 20 minutes and the mixture was then cooled and the precipitate collected and washed with acetic acid, 514 mg. (89%). The free base was recovered from this perchlorate by suspension in dilute ammonia and extraction with chloroform. The washed, dried, filtered and concentrated chloroform extracts yielded 431 mg. of orange-red glass which crystallized on scratching under ethyl acetate–alcohol, m.p. 207–211°. Several crystallizations from ethyl acetate gave 304 mg., m.p. 224–225°, $[\alpha]^{20}D$ +13.5° (*c* 1.85, chf).

Anal. Calcd. for $C_{24}H_{25}N_5O_6$: C, 60.12; H, 5.26. Found: C, 60.08; H, 5.14.

This substance is occasionally obtained as a solvate, m.p. 150–160° with foaming.

The Base-catalyzed Isomerization of β-Thebainone.—β-Thebainone hydrate, 317 mg., purified through its perchlorate and finally crystallized from dilute acetone, $[\alpha]^{27}D$ +110°, was dissolved in 5 cc. of absolute alcohol and treated with 13 cc. of a freshly prepared solution of 8.0 g. of sodium in 200 cc. of absolute alcohol. The mixture was allowed to stand for 35 minutes, then diluted further with alcohol and carbonated. The solid carbonate salts were removed by filtration, dissolved in water, extracted three times with chloroform and the chloroform extracts were combined with the original alcoholic filtrate. Removal of solvents yielded 297 mg. of crude base as a brown glass which was dissolved in acetone. An aliquot was removed, the acetone replaced by alcohol and its specific rotation determined, $[\alpha]^{27}D$ −23°. This corresponds to 84% thebainone, 16% β-thebainone, on the assumption that only these bases are present. The remaining acetone solution was passed through a short column of alumina for decolorization, the column was further eluted with acetone and the colorless acetone eluates concentrated. The residue was crystallized from ethyl acetate to give 175 mg. (59.5%, corrected for aliquot removed) of colorless prisms, m.p. 125–152°, gas evolution,[11] $[\alpha]^{27}D$ −45° (*c* 2.68, alc). Its infrared spectrum was indistinguishable from that of an authentic sample of thebainone half-hydrate. Its hydriodide, m.p. 267–269° dec., showed no depression in m.p. when mixed with an authentic sample of thebainone hydriodide of m.p. 271–272° dec. (reported 258–259°,[12] 258–261°[13]). Its methiodide, m.p. 251–252° dec.,[14] showed no depression in m.p. when mixed with authentic thebainone methiodide, m.p. 252–254° dec. (reported[13] 250–251°).

Thebainone half-hydrate (308 mg.) treated with sodium ethoxide and processed as above, gave a mixture of $[\alpha]^{27}D$ −27° (*c* 2.85, alc.) which on decolorization and crystallization as above yielded 163 mg. (53%) of thebainone, m.p. 125–149°, gas evol. at latter temperature, $[\alpha]^{28}D$ −48.5° (*c* 2.04, alc.).

Isomerization of β-Thebainone in Acetic Acid.—A solution of 180 mg. of β-thebainone hydrate ($[\alpha]^{27}D$ +118°) in 1.8 cc. of glacial acetic acid was heated for 35–40 minutes on the steam-bath under nitrogen. The cooled red-violet solution was made basic with ammonia, extracted several times with chloroform and the extracts concentrated under diminished pressure. The colorless residue had $[\alpha]^{27}D$ −1° (*c* 0.64, alc.) corresponding to a content of thebainone of about 71% on the assumption that only this base and β-thebainone were present. The base was converted to its hydriodide (m.p. crude 255–260° dec.) and then reconverted to the free base and crystallized from ethyl acetate to give 99 mg. (56.5%) of thebainone half-hydrate as colorless prisms, m.p. 130–146°, gas evolution at 152°, $[\alpha]^{28}D$ −46° (*c* 2.61, alc.). Its methiodide had m.p. 251.5–252.5° and did not depress the m.p. of an authentic sample of thebainone methiodide.

Isomerization of β-Thebainone-2,4-dinitrophenylhydrazone in Acetic Acid.—β-Thebainone-2,4-dinitrophenylhydrazone (51 mg., m.p. 223–227°, $[\alpha]^{26}D$ +12.9°) in 12 cc. of glacial acetic acid was heated for six hours on the steam-bath. At the end of this period, which appears to be optimum for this transformation, since both shorter and longer periods give lower rotations, the specific rotation of the mixture was $[\alpha]^{26}D$ −655° ($[\alpha]^{26}D$ of pure thebainone-2,4-dinitrophenylhydrazone in acetic acid, −1013°). The mixture was diluted with water, made basic with ice-cold ammonia and extracted several times with chloroform. The washed and dried chloroform extracts were chromatographed on alumina. Development with alcohol-free chloroform caused a clearly defined DNP band to pass into the filtrate leaving a dark, strongly adsorbed band of decomposition products at the top of the column. Removal of solvent from the eluate gave 40 mg. (78%) of orange-red glass, $[\alpha]^{28}D$ −1250° (*c* 0.338, chf.) ($[\alpha]^{26}D$ of pure thebainone-2,4-dinitrophenylhydrazone in chloroform, −1375°) which crystallized immediately on scratching under ethyl acetate and which after crystallization from this solvent had m.p. 201–201.5° and did not depress the m.p. of thebainone-2,4-dinitrophenylhydrazone.

(7) A. J. Birch, *Quart. Rev.*, **4**, 69 (1950); *J. Chem. Soc.*, 1551 (1950); see also M. J. S. Dewar, "Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, p. 103.

(8) Although we have not carried out extensive development of this preparation, it appears to compare favorably with earlier methods. *Cf.* C. Schöpf and H. Hirsch, *Ann.*, **489**, 224 (1931); L. F. Small and co-workers, THIS JOURNAL, **54**, 2122 (1932); **56**, 2159 (1934); *J. Org. Chem.*, **3**, 618 (1939); U. Weiss and N. Weiner, *ibid.*, **14**, 194 (1949).

(9) All melting points are corrected. Analyses were carried out by Miss Claire King of these laboratories.

(10) We are indebted to Sir Robert Robinson for supplying the details of this method to us before publication.

(11) Although thebainone half-hydrate has been reported by several authors as melting sharply in the neighborhood of 148 to 150°, in our hands this substance, even though very rigorously purified by many crystallizations of both base and hydriodide, has always melted unsharply from about 130–152°, with softening as low as 120° and with copious gas evolution, but no darkening, at 150–152°. We have attempted many times to obtain this substance in anhydrous crystalline form, but if solutions in benzene or in ethyl acetate are strongly concentrated so as to remove the water present, no crystallization takes place until water is either added deliberately or is absorbed from the atmosphere. We do not consider the m.p. of this substance to be a good criterion of either purity or identity. A similar behavior is shown by dihydrothebainone (*cf.* citation 5b and also T. D. Perrine and L. F. Small, *J. Org. Chem.*, **17**, 1543 (1952)).

(12) C. Schöpf and H. Hirsch, *Ann.*, **489**, 224 (1931).

(13) D. E. Morris and L. Small, THIS JOURNAL, **56**, 2159 (1934). We are indebted to Dr. Small for a sample of thebainone.

(14) These m.ps. were taken on finely ground material. The same material, but as coarse crystals, shows a capillary m.p. of 255–257° dec.

Thebainone-2,4-dinitrophenylhydrazone.—A mixture of 924 mg. of thebainone and 660 mg. of 2,4-dinitrophenylhydrazine in 6 cc. of glacial acetic acid was heated on the steam-bath for 30 minutes, cooled, diluted with water, made basic with ammonia and extracted several times with chloroform. The chloroform extracts were washed, dried, concentrated and chromatographed on alumina. Development with alcohol-free chloroform gave a DNP fraction, passing into the filtrate, of 1.32 g. after removal of solvent. This residue crystallized directly from the chloroform during concentration and after several crystallizations from ethyl acetate orange prisms of m.p. 201.5–202.5°, $[\alpha]^{26}D$ −1375° (*c* 1.31, chf.), $[\alpha]^{26}D$ −1013° (*c* 0.460, acetic acid), were obtained.

Anal. Calcd. for $C_{24}H_{25}N_5O_6$: C, 60.13; H, 5.26. Found: C, 60.34; H, 5.49.

We have also sometimes obtained this substance as a solvate with alcohol of m.p. 120–145° with foaming, partial resolidification and remelting at 195–206°. Cleavage of this dinitrophenylhydrazone (187 mg.) to thebainone was achieved by refluxing in 8 cc. of acetone containing 1 cc. concentrated hydrochloric acid and a little mesityl oxide for two hours and 15 minutes. The mixture was diluted with water and extracted with chloroform to remove non-basic dinitrophenylhydrazones, and then made basic with ammonia. The precipitated thebainone (96 mg.) was removed by extraction with chloroform and purified through its hydriodide, m.p. 271–272°. On recovery from this salt, it melted at 130–150°, gas evolution at 152–154°, $[\alpha]^{25}D$ −48.1° (*c* 1.87, alc.) and gave a methiodide of m.p. 251–253°.

The Action of Acetic Acid on Thebainone-2,4-dinitrophenylhydrazone.—A solution of 54 mg. of thebainone-2,4-dinitrophenylhydrazone in glacial acetic acid was heated on the steam-bath for six hours, after which its specific rotation in this solvent had dropped to −728° (*c* 0.227). Processing as described above for the isomerization of β-thebainone-2,4-dinitrophenylhydrazone yielded a crude DNP fraction directly from the chromatographic column whose specific rotation was −1200° (*c* 0.423, chf.) and which gave only unchanged thebainone-2,4-dinitrophenylhydrazone on crystallization.

Thebainone from Phenolic Dihydrothebaine.—A solution of 549 mg. of phenolic dihydrothebaine in 4 cc. of 50% acetic acid was heated under nitrogen on the steam-bath for 45 minutes. The cooled solution was made basic with ammonia and extracted several times with chloroform. The chloroform extracts were washed, dried and concentrated and the residue therefrom was converted to its hydriodide, crystallized as such, reconverted to the free base and decolorized by chromatography on alumina using acetone as an elution solvent. The residue from the acetone solution on crystallization from wet benzene yielded a total of 248 mg. (47%) of thebainone half-hydrate m.p. 122–152°, gas evolution at the latter temperature, $[\alpha]^{30}D$ −45.5°.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE UNIVERSITY COLLEGE OF SCIENCE AND TECHNOLOGY]

Studies on the Degradation of Kopsine, the Alkaloid of *Kopsia fruticosa*. II

BY ANIL BHATTACHARYA

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Kopsine, $C_{22}H_{26}O_4N_2$, the alkaloid of *Kopsia fruticosa*, on mild degradation with aqueous and alcoholic alkali produces two new bases—kopsidine, $C_{20}H_{24}O_3N_2$, m.p. 142° (dec.) and kopsidinine, $C_{19}H_{22}O_2N_2$, m.p. 248° (dec.), which is free from methoxy. Their isolation, analyses, properties and ultraviolet absorption curves have been described. Kopsine produces 2-methylindole, C_9H_9N, m.p. 57°; indole-2-carboxylic acid, $C_9H_7O_2N$, m.p. 199°; and an uncharacterized base (in traces) on fusion with potassium hydroxide.

In a previous communication[1] the preliminary studies on the isolation and properties of kopsine, $C_{22}H_{26}O_4N_2$, m.p. 220° (dec.), the new alkaloid of *Kopsia fruticosa*, have been reported. It was also recorded that with ethanolic ammonia, Kopsine suffers mild hydrolysis and produces a new base, kopsidine, $C_{20}H_{24}O_3N_2$, m.p. 142° (dec.), containing a methoxy group. The same base, kopsidine, has been obtained by hydrolysis of the original base, kopsine, with a dilute aqueous sodium hydroxide solution (0.4%). It forms a crystalline hydrochloride, $C_{20}H_{24}O_3N_2 \cdot HCl$, m.p. 340° (dec. at 290°), produces a rose-red coloration with perchloric acid and responds to all the tests for alkaloidal reagents. A comparative study of the molecular formula of kopsine and kopsidine suggested that kopsidine might be a deacetylation product of kopsine, but on acetylation under various conditions kopsidine failed to produce kopsine or its acetylation product.

On hydrolysis with a strong ethanolic solution of potassium hydroxide (20%) kopsine yields a methoxyl free base, kopsidinine, $C_{19}H_{22}O_2N_2$, m.p. 248° (dec.) (yield 10%). It forms light brown needles which are highly soluble in methanol, ethanol, acetone, ethyl acetate and chloroform, moderately soluble in ether and benzene but insoluble in petroleum ether. Kopsidinine forms a crystalline hydrochloride, $C_{19}H_{22}O_2N_2 \cdot HCl$, which does not melt but decomposes at 295°. It produces an orange-red precipitate with potassium–bismuth iodide, a yellow precipitate with picric acid and a white precipitate with potassium mercuric iodide. Kopsidinine gives characteristic color reactions with alkaloidal reagents, as shown in Table I.

TABLE I

	Reagents	Color reactions
1	Concd. H_2SO_4	Colorless in cold, but gradually changes to pink
2	Erdmann reagent	Color changes from purple to red
3	Fröhde reagent	Color gradually changes to light pink

The same base, kopsidinine, has been isolated though in poor yield (1.0%), by the hydrolysis of the base, kopsine, with strong ethanolic or amyl alcoholic potassium hydroxide (60%) solution.

A comparative study of the absorption curves (Fig. 1) of both kopsine and kopsidinine shows that the curves are very similar to that of indole,[2,3] thus indicating the presence of an indole nucleus in both kopsine and kopsidinine. The physical evidence of the presence of the indole nucleus in kopsine has been established by chemical evidences which are put forward in the present communication.

(1) A. Bhattacharya, A. Chatterjee and P. K. Bose, THIS JOURNAL, **71**, 3370 (1949).

(2) M. S. Kharasch, D. W. Stanger, M. A. Bloodgood and R. R. Legault, *Science*, **83**, 36 (1936).

(3) W. A. Jacobs, L. C. Craig and A. Rothen, *ibid.*, **83**, 166 (1936).