The Structure of Thebainehydroquinone

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A reexamination of thebainehydroquinone and several of its derivatives indicates that structure IVa is to be preferred to the previously accepted "phenolbetaine" structure (V). This conclusion is based largely on ultraviolet and infrared absorption studies. In connection with this investigation, thebainehydroquinone-10-acetate (IX), thebainehydroquinone diacetate (X) and dehydrothebainequinone (XI) were prepared and characterized for the first time.

The reaction of p-benzoquinone (I) with the alkaloid thebaine (II) results in the formation of a yellow, crystalline, Diels-Alder adduct, thebaine-quinone (III).[2,3] When III is heated with acids or bases, or simply refluxed with high-boiling solvents, it is converted into a colorless, crystalline isomer, thebainehydroquinone. It would be natural to assume that this colorless product is simply the aromatized tautomer (IV) of III, and this was the first structure suggested for it by Schöpf.[3] However, some peculiarities in the chemistry of thebainehydroquinone led Schöpf to a subtle but significant modification of this proposal which resulted in the conclusion that the true structure of this substance is that of a "phenolbetaine" (which might be better termed a zwitterion), shown below as V.[4] Prior to our work on the structure of flavo-

II → III

IV   V

thebaone,[5] a simple rearrangement product of the-bainehydroquinone, it was important to us to clarify the nature of its precursor. This was particularly necessary since the zwitterion formulation seemed intrinsically improbable. It was felt that if the properties of thebainehydroquinone could not be reconciled with expectations based on structure IV, there existed the serious possibility that some gross error had been made in assuming that the formation of thebainehydroquinone involved only aromatization. The results of our investigation of this problem are now presented.

The difference between IV and V is, of course, rather small, and not of the type one could hope to establish unequivocally by chemical means. The chief evidence sought was, therefore, physical. Our evaluation of the appropriate data has led us to the adoption of the internally hydrogen-bonded formula IVa as the most plausible representation for thebainehydroquinone. This conclusion serves to place subsequent speculation on the structure of flavothebaone[5] on firm ground.

To begin with, some key derivatives of thebaine-hydroquinone were required. Preparations of its monoacetate, monomethyl ether, and monomethyl ether monoacetate (presumably VI, VII, and VIII respectively) were carried out as described previously.[3] In addition, a new monoacetate (IX) and a diacetate (X) were prepared for the first time. The success in obtaining IX and X was of some preliminary importance, since one of the striking properties of thebainehydroquinone motivating the assignment of structure V was the presumed inability of the C_{10}-hydroxyl group to form a normal acetate ester.[3]

A summary of the functional group reactions and some of the salient properties of the thebaine-hydroquinone derivatives studied is given in Chart 1. It is interesting to note that acetylation of the C_7-hydroxyl group (of either IVa, VII, or IX) can be brought about in the usual way with acetic anhydride in pyridine, but not with acetyl chloride in dioxane. In sharp contrast, while the C_{10}-hydroxyl group (of IVa or VI) withstands acetylation by acetic anhydride in pyridine, it reacts readily with acetyl chloride (or in the case of IVa, acetic anhydride as well) in dioxane. It thus appears that one position is attacked only in the presence of an
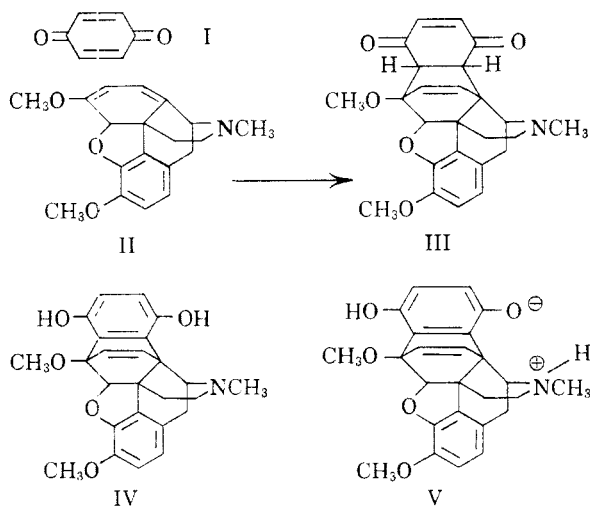
(1) Opportunity Fellow, John Hay Whitney Foundation, 1955–1956; Allied Chemical and Dye Corp. Fellow, 1956–1957.

(2) W. Sandermann, Ber., 71, 648 (1938).

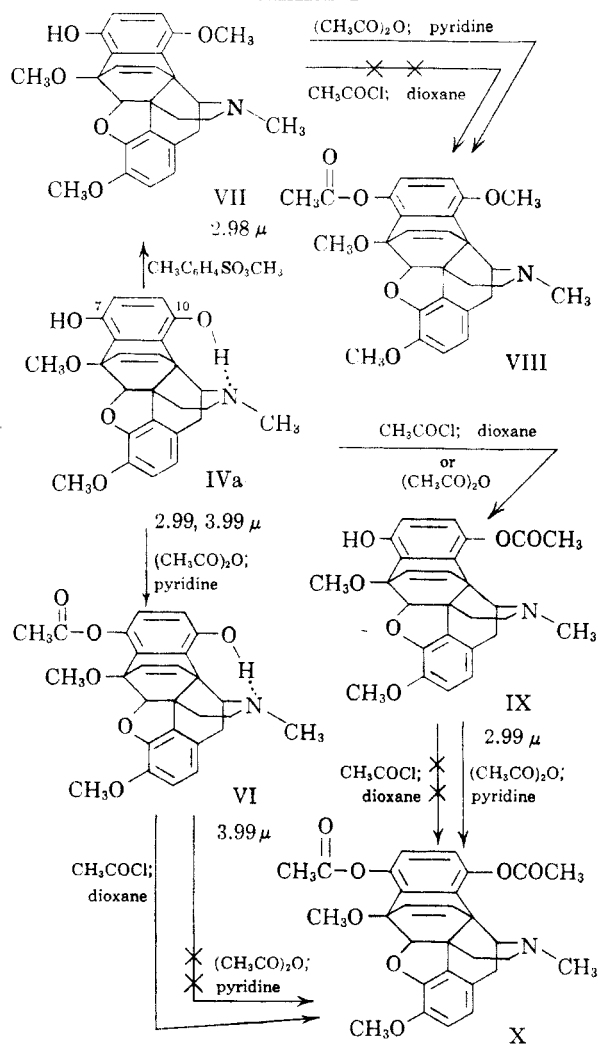(3) C. Schöpf, K. von Gottberg, and W. Petri, Ann., 536, 216 (1938).

(4) A review of these arguments would be unnecessary and cumbersome at this point. They can be found in reference 3. The "phenolbetaine" formulation was accepted without further comment by K. W. Bentley, The Chemistry of the Morphine Alkaloids, Clarendon Press, Oxford, 1954.

(5) J. Meinwald and G. A. Wiley, J. Am. Chem. Soc., 79, 2569 (1957).

external base, while the other is attacked only in its absence.[6]

The ultraviolet spectra of thebainehydroquinone in both neutral [$\lambda_{max.}^{EtOH}$ 310 mμ (3.78), shoulder ca. 290 mμ] and acidic media [$\lambda_{max.}^{EtOH}$, 0.1N H$^+$, 311 mμ (3.83), shoulder 290 mμ] are strikingly similar. Furthermore, they are essentially the same as that of the monomethyl ether (VII) [$\lambda_{max.}^{EtOH}$, 0.1N H$^+$, 310 mμ (3.83), shoulder ca. 290 mμ], which from its mode of formation seems clearly to be the 10-methyl derivative. This would not be expected if the ionic structure V were correct, since

CHART I

then the neutral spectrum would represent the phenoxide species, which should differ significantly from both thebainehydroquinone in acid and from VII.

Further support for the assignment of the proton to the C_{10} oxygen rather than to the tertiary nitrogen is obtained from an examination of spectral shifts in alkali. IVa and VII suffer bathochromic shifts of 5 and 10 mμ respectively, when dissolved in tenth normal sodium hydroxide solution. Under similar conditions, hydroquinone monomethyl ether undergoes a bathochromic shift of 17 mμ, whereas hydroquinone itself shows a hypsochromic shift of 13 mμ. The fact that IVa undergoes a spectral shift toward *longer* wave lengths in base, and that it has a spectrum similar to that of VII under these conditions, indicates that a single hydroxyl group is ionizing, and that it is the first rather than the second ionization. In addition, the failure of IVa to ionize doubly under conditions where hydroquinone apparently does, suggests that one of the protons must be strongly hydrogen-bonded. Inspection of molecular models reveals that the tertiary nitrogen atom is very favorably situated for participation in a hydrogen bond with the C_{10}-hydroxyl group.[7] The zwitterion formula (V) would have predicted that any shift in alkali should have been to *shorter* wave lengths, in analogy with the behavior of hydroquinone.

The infrared spectra of IVa and its derivatives can be interpreted in a fashion consistent with the above conclusions. In IVa itself, the 2.99 μ band could be ascribed to the weakly hydrogen-bonded C_7-hydroxyl group, and the 3.99 μ band to the strongly hydrogen-bonded C_{10}-hydroxyl group. On the basis of these bands, structures could be allotted independently to the various derivatives of IVa discussed above. The results are in full accord with the earlier deductions. The pertinent data are included in Chart 1, and need no detailed discussion.

In the course of these studies, two new reactions of IVa which are, however, of no special structural significance were carried out, and it seems appropriate to append these findings at this point. IVa was found to react with potassium t-butoxide in t-butyl alcohol, to yield a small amount of an indicator (the chief reaction being simply the reversible ionization of IVa), which was not further investigated. Finally, silver oxide was found to transform IVa smoothly into a beautifully crystalline, ruby-red dehydro compound (XI), which

(6) Although hypotheses can be constructed to rationalize this behavior, they will not be elaborated at this point in the interest of brevity.

Several unsuccessful efforts were made to prepare thebainehydroquinone dimethylether as described by Schöpf. The product seemed to be a flavothebaone derivative, on the basis of ultraviolet spectra, but no definite conclusions could be reached.
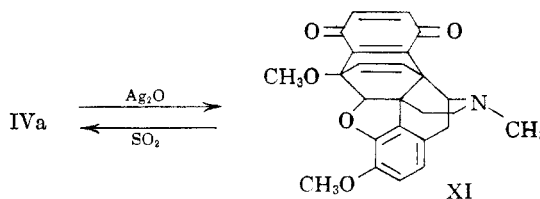
Attempts to prepare thebainehydroquinone-7-methylether using diazomethane were also fruitless (cf. ref. 4). Since the completion of this work, this ether has been prepared and characterized in a thorough study of the flavothebaone problem by K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, **22**, 418 (1957).

(7) Schöpf and co-workers (ref. 3) have already called attention to the proximity of these centers.

could be reconverted to IVa by means of sulfur dioxide.

EXPERIMENTAL[8]

Thebainehydroquinone (IVa). The enolization of thebaine-quinone (II) was carried out using the Schöpf procedure calling for glacial acetic acid in xylene.[3] Quantitative yields of IVa were obtained. Recrystallization from absolute methanol, as suggested by Schöpf, was found to be superior to any other purification procedure, in spite of the remarkable insolubility of the compound (*ca.* 2.2 g./l. at reflux and *ca.* 0.7 g./l. at 7°). Colorless needles were obtained, m.p. 264–265.0° (lit. 270°).[3] Infrared spectrum (KBr): 2.99, 3.99, 6.13, 6.24 μ; (CHCl$_3$): 2.99, 3.94, 6.11 μ. Ultraviolet spectra: $\lambda_{max.}^{EtOH}$, 0.1N H$^+$, 311 mμ (3.83), shoulder *ca.* 290 mμ; $\lambda_{max.}^{EtOH}$, 310 mμ (3.78), shoulder *ca.* 290 mμ; $\lambda_{max.}^{EtOH-H_2O}$, 6$N$ H$^+$, 306 mμ (3.83); $\lambda_{max.}^{EtOH}$, 0.1N OH$^-$, 315 mμ (3.23), shoulder 298 mμ (3.14).

Anal. Calcd. for C$_{25}$H$_{25}$O$_5$N: C, 71.57; H, 6.01; N, 3.32. Found: C, 71.46; H, 6.06; N, 3.58.

Thebainehydroquinone-7-acetate (VI). This derivative was prepared by treatment of IVa with acetic anhydride and pyridine as previously described.[3] Partial hydrolysis of the ester appeared to occur during work-up if the reaction mixture was poured into water instead of using the prescribed method. The product crystallized from absolute benzene or methanol-water as colorless prisms, m.p. 256–257° (lit. 259° dec.).[3] Infrared spectrum (CHCl$_3$): 3.99, 5.69 μ.

Thebainehydroquinone-10-methyl ether (VII). VII was prepared as described previously.[3] Recrystallization from methanol yielded rectangular plates, m.p. 238–240° (lit. 238°).[3] Infrared spectrum (KBr): 3.01 μ. Ultraviolet spectra: $\lambda_{max.}^{EtOH}$, 0.1N H$^+$, 310 mμ (3.83), shoulder *ca.* 290 mμ; $\lambda_{max.}^{EtOH}$, 0.1N OH$^-$, 320 mμ (3.63), shoulder *ca.* 294 mμ (3.45).

Thebainehydroquinone-7-acetate-10-methyl ether (VIII). VIII was prepared from VII using acetic anhydride and pyridine.[3] It crystallized from absolute methanol as colorless needles, m.p. 249–251° (lit. sinters 250°, m.p. 259°).[3] Infrared spectrum (KBr): 3.67, 5.73 μ.

Thebainehydroquinone-10-acetate (IX). A. A sample of 0.5 g. of IVa was mixed with 1 ml. of acetyl chloride in 5 ml. of purified dioxane. A visible reaction occurred which converted the needles into a white paste. After standing for 24 hr. the paste had transformed into a colorless glass. The solvent was stripped off, and the residue treated with 5% sodium bicarbonate solution and ethyl acetate. The organic layer was separated, a few drops of acetic anhydride were added, and the solution was concentrated until crystallization occurred.

IX, obtained in this way, crystallized from ethyl acetate containing a small amount of acetic anhydride as colorless prisms, m.p. 222.0–222.5°. Infrared spectrum (CHCl$_3$): 2.99, 5.70 μ.

Anal. Calcd. for C$_{27}$H$_{27}$O$_6$N: C, 70.25; H, 5.95; N, 3.04; acetyl, 9.33. Found: C, 70.33; H, 6.00; N, 3.08; acetyl, 9.98.

B. A 0.5 g. sample of finely ground IVa was dissolved in 5 ml. of acetic anhydride. After 2 hr. most of the thebaine-hydroquinone had dissolved and large, white crystals began to appear. After 48 hr. had elapsed, the reaction mixture was poured into dilute acetic acid. The free base (IX) was precipitated by addition of saturated sodium bicarbonate solution. After filtering, washing and drying, the precipitated IX recrystallized from ethyl acetate containing acetic anhydride as colorless prisms with melting point and infrared spectrum identical with those of the product obtained by procedure A.

Thebainehydroquinonediacetate (X). A. From thebaine-

hydroquinone-7-acetate (VII). A 0.8 g. sample of VII was dissolved in 10 ml. of purified dioxane, and 2 ml. of acetyl chloride was added. After standing overnight at room temperature, a white precipitate had appeared. The solvent was evaporated to dryness in vacuum and the residue shaken with a mixture of saturated sodium bicarbonate solution and ethyl acetate. After separating layers, the ethyl acetate solution was dried over magnesium sulfate and evaporated. The infrared spectrum of the crude product contained neither the 2.99 μ nor the 3.99 μ hydroxyl bands. However, it could not be crystallized from dry benzene, and two recrystallizations from absolute ethanol-benzene yielded a crystalline material whose infrared spectrum showed a 3.94 μ band, indicating that the C$_{10}$-acetyl group was being cleaved.

B. From *thebainehydroquinone-10-acetate* (IX). A 0.5 g. sample of IX was dissolved in 5 ml. of pyridine containing 2 ml. of acetic anhydride. After standing for 24 hr. at room temperature, the solvent was evaporated under reduced pressure. A tan solid remained whose infrared spectrum was the same as that of the crude product obtained in procedure A. It crystallized as colorless rods, m.p. 187.0–187.7° from ethyl acetate containing a little acetic anhydride. Infrared spectrum (CHCl$_3$): 3.57, 5.69, 6.11, 6.12 μ.

Anal. Calcd. for C$_{29}$H$_{29}$O$_7$N: C, 69.00; H, 5.76; N, 2.79. Found: C, 69.01; H, 6.10; N, 2.68.

Ultraviolet spectra of hydroquinone and hydroquinone monomethylether. Hydroquinones $\lambda_{max.}^{EtOH}$, 0.1N H$^+$, 294 mμ (3.47); $\lambda_{max.}^{EtOH}$, 0.1N OH$^-$, 281 mμ (3.68). Hydroquinone monomethylether: $\lambda_{max.}^{EtOH}$, 0.1N H$^+$, 292 mμ (3.46); $\lambda_{max.}^{EtOH}$, 0.1N OH$^-$, 309 mμ (3.49).

Attempted preparation of methyl ethers using diazomethane. Unchanged starting material was recovered in all instances of attempts to cause IVa to react with diazomethane in ether, xylene, or methanol. Using trimethyl borate as a catalyst, the reaction also failed. Finally, attempts to replace the acetyl groups in VI and IX by methyl groups using diazomethane plus pyridine were abortive.

Action of potassium t-butoxide on thebainehydroquinone. A sample of IVa was dissolved in *t*-butyl alcohol containing potassium *t*-butoxide. The solution was deep red. Acidification with 6N hydrochloric acid gave an orange solution plus a white precipitate. The precipitate was readily identified as recovered IVa by its melting point, mixture melting point with an authentic sample, and infrared spectrum.

The orange mother-liquors were found to contain an indicator which was red-violet in base and orange in solutions more acidic than dilute acetic acid. On passing sulfur dioxide through the acidic solution, the color was changed to bright yellow. None of these species was isolated or characterized.

Dehydrothebainequinone (XI). A 0.25 g. sample of IVa was added to a stirred suspension of 1 g. of dry silver oxide and 1 g. of anhydrous sodium sulfate in absolute benzene. After 0.5 hr., the mixture was filtered, and the red-orange solution separated into two portions. One portion was saturated with sulfur dioxide. A white precipitate of recovered IVa (identified by m.p., mixture m.p., and infrared spectrum) was obtained.

The other portion of the filtrate was evaporated to dryness, and the solid recrystallized from ethyl acetate. XI formed ruby-red plates, m.p. 113–115°. Infrared spectrum (CHCl$_3$): 2.99, 6.01, 6.12, 6.22, 6.30 μ. Ultraviolet spectrum: $\lambda_{max.}^{EtOH}$, 2.94 mμ (3.73) plateau; 312 mμ (3.77). An equimolar mixture of XI and IVa shows a $\lambda_{max.}^{EtOH}$ at 312 mμ, with an intensity expected from a summation of the spectra of the two components.

Anal. Calcd. for C$_{25}$H$_{23}$O$_5$N: C, 71.93; H, 5.55; N, 3.36. Found: C, 72.02; H, 5.44; N, 3.30.

A suspension of IVa in water reduced periodic acid solution and was converted into a ruby-red solid, which appeared identical with that described above.

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(8) All melting points were taken on a calibrated Fisher-Johns hot-stage. Ultraviolet spectra were recorded using a Beckman ultraviolet spectrophotometer, model DK. Infrared spectra were recorded using a Perkin-Elmer double-beam instrument, model 21.