[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE UNIVERSITY, ABERDEEN]

Flavothebaone. Part III. Structure of Flavothebaone[1]

K. W. BENTLEY, J. DOMINGUEZ, AND J. P. RINGE

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Dihydro-thebainequinol has been converted into dihydroflavothebaone. A complete structure is allotted to flavothebaone, and on the basis of this the mechanisms of the production of this base from thebainequinol and of the transformation of flavothebaone trimethyl ether methine to the ψ-methine are discussed.

Schöpf, von Gottberg, and Petri[2] believed, on the basis of the orange-red color of the sodium salt of flavothebaone, that this base contained the system (I), whereas in part I of this series[3] we allotted the part structure (II) to flavothebaone, indicating our preference for the further attachment of the quinol nucleus to position 5 of the phenanthrene skeleton, leaving the α,β-unsaturated ketone system unconjugated with either phenolic nucleus. In further exploration of this problem 2,5-dimethoxybenzalacetone has been synthesized, and the ultraviolet spectrum of this substance has been found to be so significantly different from that of flavothebaone trimethyl ether (Fig. 1) both in intensity and in the

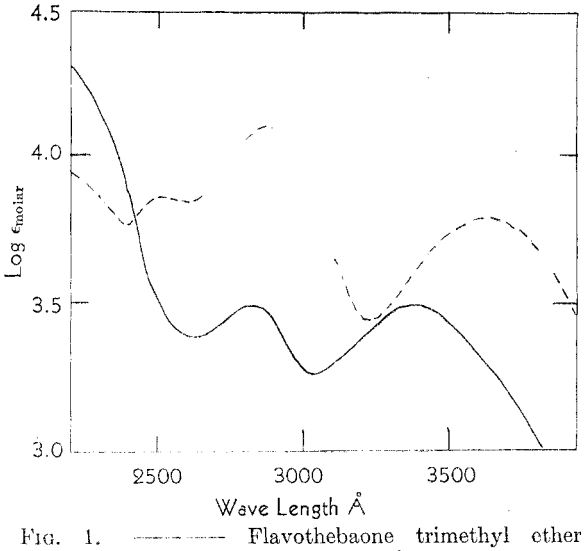


FIG. 1. ———— Flavothebaone trimethyl ether; – – – – – 2,5-Dimethoxybenzalacetone.

positions of the absorption maxima and minima that we conclude that the system (I) is *not* present in flavothebaone.

Whereas flavothebaone trimethyl ether and its methine fail to condense with piperonal, dihydroflavothebaone trimethyl ether and its methine both form piperonylidene derivatives (ultraviolet spectra, Fig. 2), indicating that flavothebaone contains

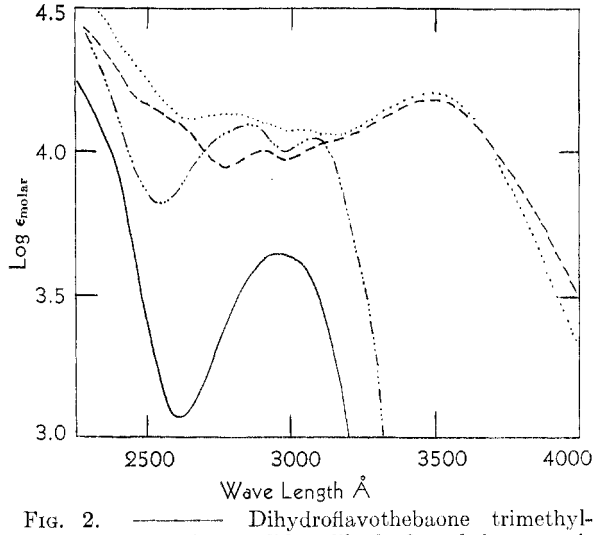


FIG. 2. ———— Dihydroflavothebaone trimethyl-ether; – – – – – Piperonylidenedihydroflavothebaone trimethyl ether; - · · · · · · · - Dihydroflavothebaone trimethyl ether methine; . . . . Piperonylidenedihydroflavothebaone trimethyl ether methine.

the system (III). The group R in (III) cannot be the ethanamine chain [which we have shown in Part II[4] to retain its original point of attachment at C_{13} of the phenanthrene skeleton as in thebainequinol (IV)] and must accordingly be the quinol nucleus; the system (I) cannot therefore be present in flavothebaone. The quinol nucleus has thus been shown to be linked at positions 5 (see above) and 14 (Part I) of the phenanthrene skeleton, and the conclusions that (V) represents the structure of flavothebaone is inescapable.

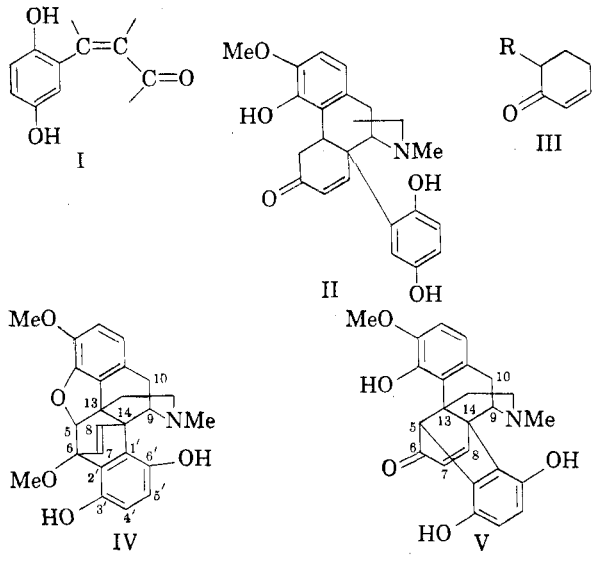
The mechanism of the process leading to the migration of the quinol nucleus from its original position at C_6 in thebainequinol (IV) to C_5 in flavothebaone leads to the requirements that dihydro-thebainequinol should suffer a similar rearrangement to dihydroflavothebaone. Schöpf, von Gottberg, and Petri[2] reported that the heating of dihydro-thebainequinol with 48% hydrobromic

(1) Work taken from the theses of J. Dominguez (D. Phil., Oxford, 1953) and J. P. Ringe (Ph.D., Aberdeen, August 1956). Since this paper was written some of the material therein, and the correct structure for flavothebaone, has been reported by J. Meinwald and G. A. Wiley, *Chemistry & Industry*, 957 (1956).

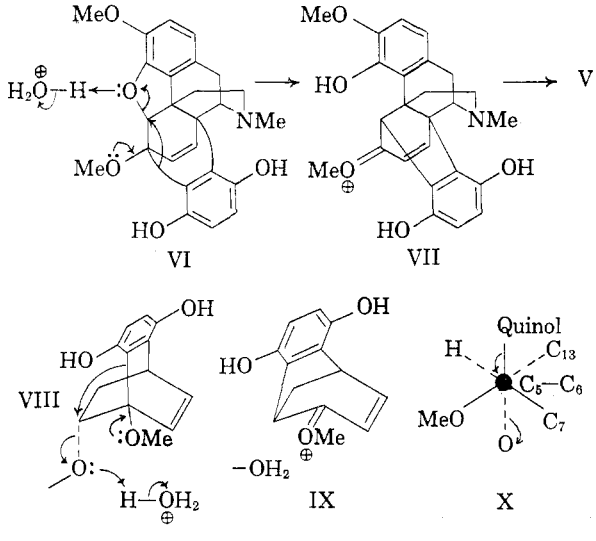
(2) C. Schöpf, von Gottberg, and Petri, *Ann.*, **536**, 216 (1938).

(3) K. W. Bentley and J. Dominguez, *J. Org. Chem.*, **21**, 1348 (1956).

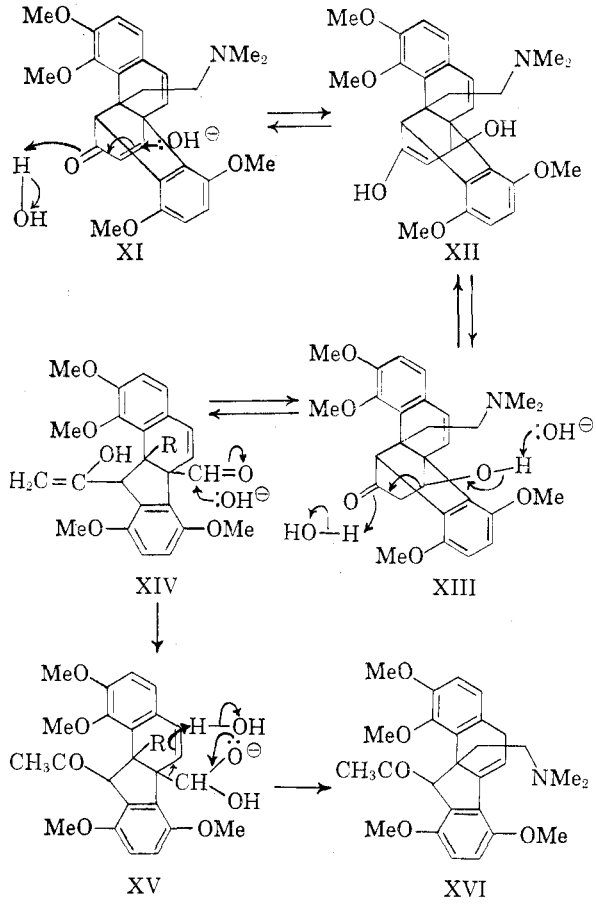
(4) Bentley, Dominguez, and Ringe, *J. Org. Chem.*, **22**, 409 (1957).



acid causes only demethylation. We have found, however, that this base can be rearranged to dihydroflavothebaone under the same conditions as are required for the conversion of thebainequinol into flavothebaone. This result, also observed by Meinwald and Wiley, ref. 1, has been rigorously confirmed by the preparation by this route of dihydroflavothebaone, its hydrochloride and dihydroflavothebaone trimethyl ether methine, with comparison of each of these with authentic material prepared from flavothebaone, by melting point, mixed melting point, optical rotation, ultraviolet and infrared spectra. Flavothebaone may thus with confidence be allotted the complete structure (V).



Representation of the mechanism of the transformation of thebainequinol (IV) into flavothebaone (V) as a concerted opening of the oxide ring and migration of the quinol nucleus followed by hydrolysis, (VI) → (VII) → (V), is mechanistically and stereochemically acceptable. The addition of *p*-benzoquinone to thebaine takes place on the same side of the cyclohexadiene ring as the nitrogen-containing side chain (approach from the other side of this ring is impossible owing to the steric arrangement) and thus the quinol nucleus of thebainequinol (IV) is *trans* to the oxygen of the 4,5-oxide bridge; both the C_6-quinol and the C_5-O bonds will be axial, the conformation of ring C in (IV) and (VI) will be as shown in (VIII), and the migration of the quinol nucleus to C_5, represented by (VIII) = (IX) [projection along C_6—C_5 bond, (X)], is seen to be perfectly acceptable. The double bond of (IV) does not enter into the reaction at all. This rearrangement is of interest because the electron deficiency at C_5 resulting from the addition of a proton to the cyclic ether oxygen atom is made up by the migration of the quinol nucleus, whereas in all previously reported rearrangements in the morphine-thebaine group it has to be met by the migration of the ethanamine chain.[5]



The transformation of flavothebaone trimethyl ether methine into the ψ-methine (XVI)[4] presents no particular difficulties. The skeleton of the ψ-methine is already present in the methine (XI), and the rearrangement may be represented as involving the hydration of the $\alpha\beta$-unsaturated ketone system, (XI) ⟶ (XIII), followed by dealdolisation, (XIII) ⟶ (XIV), and base-catalysed elimination of formic acid from the resulting β,γ-unsaturated aldehyde,

(5) K. W. Bentley, "The Chemistry of the Morphine Alkaloids," The Clarendon Press, Oxford, 1954.

(XIV) ⟶ (XVI), this step being irreversible. On the basis of this mechanism the 7,8 and 9,10 double bonds and the carbonyl group are all essential to the reaction, and in accord with this we have found that flavothebaone trimethyl ether, dihydroflavothebaone trimethyl ether methine and flavothebaone trimethyl ether methine oxime are all unaffected by prolonged boiling with 30% alcoholic potassium hydroxide.

The ultraviolet spectrum of flavothebaone and the color of the sodium salt of the phenol are, however, difficult to explain at first sight on the basis of the structure (V). The ultraviolet spectrum of flavothebaone shows two absorption bands with λ_{max} 2800 and 3350 Å, ϵ_{max} 2250 and 2200. The first of these is normal [*cf.* Δ^7-thebainone (XVII), λ_{max} 2850 Å, ϵ_{max} 2150], and we believe that the other is the long wave length α,β-unsaturated ketone absorption band greatly intensified by perturbation by the aromatic quinol nucleus, which at its closest point of approach is only 3 Å from the double bond. In support of this may be cited the following facts.

(a) Transformation of C=C—C=O into C=C—C=N—OH results in a marked change in the spectrum (Fig. 3)

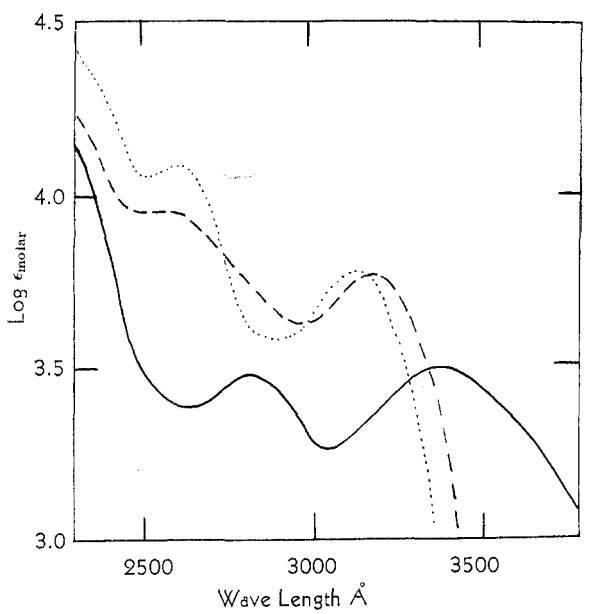


FIG. 3. ——— Flavothebaone trimethyl ether; - - - - - Flavothebaone trimethyl ether oxime; . . . . . Flavothebaone trimethyl ether ψ-methine oxime.

(b) The spectrum of benzoflavothebaone, the naphthalene analog of (V), prepared from 1,4-naphthoquinone,[6] apart from the normal naphthalene bands is identical with that of flavothebaone (Fig. 4).

(c) The spectrum of the base (XVIII), prepared

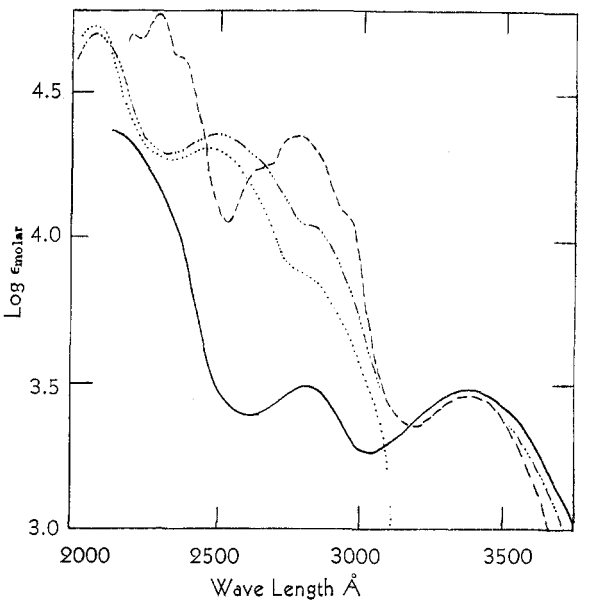
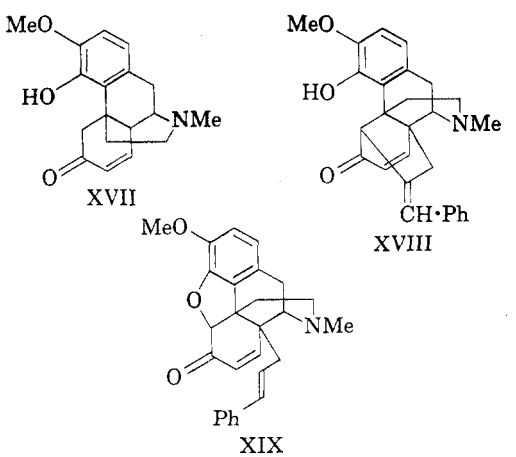


FIG. 4. ——— Flavothebaone trimethyl ether; - - - - - Triacetylbenzoflavothebaone; · · · · · · · · The base (XVIII); . . . . . The styrenoid base (XIX).

by the rearrangement of (XIX),[7] is a very close summation of the spectra of styrene and flavothebaone (Fig. 4).



The enhanced color (orange) of the acid hydrochloride of flavothebaone (F·2HCl) is doubtless due to a modification of the C=C—C=O band resulting from protonation to $C{=}C{-}\overset{+}{C}{=}OH$.

The sodium salt of quinol absorbs very near the visible region of the spectrum, and perturbation of the anion of (V) by the α,β-unsaturated ketone system could well cause a shift of the absorption band to longer wave lengths so that the violet and blue would be absorbed, in which case an alkaline solution of (V) would be orange-red, as is indeed found with flavothebaone. An alkaline solution of benzoflavothebaone, in which a different ion is involved is quite different in color, being a deep violet-red.

(6) K. W. Bentley, J. C. Ball, and H. M. E. Cardwell, *Chemistry & Industry* (1956).

(7) K. W. Bentley and J. C. Ball, *Chemistry and Industry*, 1428 (1956).

Methylation of thebainequinol with methyl sulfate and alkali affords a monomethyl ether (probably the 3′-methyl ether) isomeric with that obtained by Schöpf,[2] but methylation with hot methyl sulfate alone affords Schöpf's monomethyl ether, thebainequinol monomethyl ether A, believed to be the 6′-methyl ether resulting from methylation of the betaine. These two ethers afford isomeric flavothebaone monomethyl ethers on rearrangement.

EXPERIMENTAL

2,5-Dimethoxybenzalacetone. (a) Ten per cent aqueous sodium hydroxide (1.5 ml.) was added to a solution of 2,5-dimethoxybenzaldehyde (1.25 g.) in acetone (8 ml.) and water (4 ml.), and the mixture allowed to stand for 15 min. Water (75 ml.) was then added and the oily product kept in the refrigerator overnight, when it solidified. On recrystallization from 40% ethanol *2,5-dimethoxybenzalacetone* was obtained as light yellow plates, m.p. 50–51°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8. Found: C, 69.6; H, 6.8.

(b) 2,5-Dimethoxybenzaldehyde (1.25 g.) in acetone (4 ml.) was added to water (75 ml.) with vigorous stirring, and 10% aqueous sodium hydroxide (1.5 ml.) added to the resulting emulsion. The mixture was shaken for 10 hr., the solid product collected and recrystallized from 40% ethanol, when it was obtained as light yellow plates, m.p. 50–51°, alone and mixed with material prepared as in (a) above.

Piperonylidenedihydroflavothebaone trimethyl ether. Dihydroflavothebaone trimethyl ether (0.6 g.), alcohol (60 ml.), piperonal (0.3 g.) and a solution of sodium (0.1 g.) in ethanol (5 ml.) were heated together on the water bath for 2 hr. The resulting green solution was concentrated *in vacuo*, diluted with water, acidified with hydrochloric acid and excess of piperonal extracted with ether. The aqueous solution was made alkaline with ammonia and the piperonylidene derivative extracted with ether. Evaporation of the dry ethereal extract afforded 0.7 g. of *piperonylidenedihydroflavothebaone trimethyl ether* as an amorphous yellow solid, m.p. 140–145°. This base could not be crystallized.

Anal. Calcd. for $C_{35}H_{35}O_7N$: C, 72.3; H, 6.1. Found: C, 72.0; H, 6.4.

The *picrate* crystallized on long standing in ethanol, and was obtained as canary yellow prisms, m.p. 166–167° on recrystallization from 2-ethoxyethanol.

Anal. Calcd. for $C_{35}H_{35}O_7N.C_6H_3O_7N_3$: C, 60.8; H, 4.7. Found: C, 61.2; H, 5.0.

Rearrangement of dihydro-thebainequinol. Concentrated hydrochloric acid (420 ml.) was added to a hot solution of dihydro-thebainequinol (25 g.) in glacial acetic acid (120 ml.), and the mixture heated on the steam bath for 2 hr., and boiled under reflux for a further 2 hr. A white precipitate separated during the period of heating. The mixture was cooled in ice and the product collected; yield 24 g. of dihydroflavothebaone hydrochloride, m.p. >350°, $[\alpha]_D^{20}$ +239° (MeOH, c. 2.82). (Schöpf, von Gottberg, and Petri[2] give $[\alpha]_D^{14}$ +242°).

Dihydroflavothebaone was obtained from a hot aqueous solution of the hydrochloride by neutralization with aqueous potassium bicarbonate in the presence of a small amount of sodium dithionite. On recrystallization from methanol it was obtained as very pale fawn needles m.p. 175–180°, undepressed on mixing with a specimen prepared by the reduction of flavothebaone. The base dissolved in sodium hydroxide solution to give a pale yellow solution that rapidly turned orange-red on exposure to air, as did an authentic sample of dihydroflavothebaone prepared by the reduction of flavothebaone. We were, however, unable to prepare flavothebaone by the autoxidation of the dihydro-compound as reported by Schöpf, von Gottberg, and Petri.[2]

Dihydroflavothebaone trimethyl ether methine. Dihydroflavothebaone trimethyl ether (12 g.) and methyl iodide (12 g.) were allowed to stand in benzene (500 ml.) for 2 days, the product was collected and recrystallized from water when *dihydroflavothebaone trimethyl ether methiodide* was obtained as colorless prisms, m.p. 239–240°.

Anal. Calcd. for $C_{27}H_{31}O_5N.CH_3I$: C, 56.8; H, 5.8; I, 21.4. Found: C, 56.5; H, 5.9; I, 21.0.

Fifty per cent aqueous sodium hydroxide (50 ml.) was added to a boiling solution of the methiodide (12 g.) in water (700 ml.), when the methine at once began to separate as oily droplets. The mixture was boiled for 15 min., cooled in ice, when the methine solidified, and the solid matter was collected. On recrystallization from 45% ethanol or from light petroleum (b.p. 100–120°) *dihydroflavothebaone trimethyl ether methine* was obtained as colorless prims, m.p. 125–126°, $[\alpha]_D^{20}$ +139° ($CHCl_3$, c. 2.26).

Anal. Calcd. for $C_{28}H_{33}O_5N$: C, 72.5; H, 7.2. Found: C, 72.8; H, 7.3.

The *perchlorate*, prepared in and recrystallized from ethanol, was obtained as colorless irregular plates, m.p. 252°.

Anal. Calcd. for $C_{28}H_{33}O_5N{\cdot}HClO_4{\cdot}{}^1/_2H_2O$: C, 58.6; H, 6.1. Found: C, 58.5; H, 6.3.

The *picrate*, prepared in and recrystallized from ethanol, was obtained as yellow plates, m.p. 183°.

Anal. Calcd. for $C_{28}H_{33}O_5N{\cdot}C_6H_3O_7N_3$: C, 58.9; H, 5.2; N, 8.1. Found: C, 59.0; H, 5.0; N, 7.9.

The *methiodide*, prepared in benzene and recrystallized from a 4:1 ether/alcohol mixture, was obtained as pale yellow prisms, m.p. 226–227°, $[\alpha]_D^{20}$ +74° (H_2O, c. 2.53).

Anal. Calcd. for $C_{28}H_{33}O_5N.CH_3I$: C, 57.5; H, 6.0; I, 21.0. Found: C, 57.2; H, 5.9; I, 20.8.

The *piperonylidene derivative*, prepared in the same way as the piperonylidene derivative of dihydroflavothebaone trimethyl ether, was obtained as an amorphous solid, m.p. 138–148°.

Anal. Calcd. for $C_{36}H_{37}O_7N$: C, 72.5; H, 6.2. Found: C, 72.0; H, 6.5.

Dihydroflavothebaone trimethyl ether methine from dihydroflavothebaone. Twenty-five per cent aqueous sodium hydroxide (550 ml.) was slowly added to a mixture of dihydroflavothebaone hydrochloride (80 g.) and methyl sulfate (400 ml.) during 1 hr., at 40–45°, under an atmosphere of hydrogen, with mercury sealed stirring. The temperature was then raised to 60–70°, and maintained there for 15 min., after which a homogeneous solution was obtained. The temperature was raised to 95°, sodium hydroxide (200 g.) in water (300 ml.) was slowly added, and the mixture stirred at 95–100° for 15 min. and cooled in ice water. The crystalline product was collected, washed well with water and recrystallized from 45% ethanol, when dihydroflavothebaone trimethyl ether was obtained as colorless prisms, m.p. 125–126°, undepressed on mixing with a specimen prepared as above from dihydroflavothebaone trimethyl ether methiodide; yield 60 g.

Thebainequinol monomethyl ether A. Thebainequinol (10 g.) was heated with methyl sulfate (20 ml.) at 150° until a homogeneous solution was obtained. The solution was cooled and poured into ether (100 ml.), when a sticky solid was obtained; this became crystalline on rubbing. The solid was collected, dissolved in water and aqueous sodium carbonate added, when a voluminous white precipitate was formed. This was collected and recrystallized from 2-ethoxyethanol, when *thebainequinol monomethyl ether A* was obtained as colorless prisms, m.p. 221–222°.

Anal. Calcd. for $C_{26}H_{27}O_5N$: C, 72.0; H, 6.2, (3)OMe, 21.5. Found: C, 71.7; H, 6.3; OMe, 22.0.

Rearrangement of thebainequinol monomethyl ether A. Thebainequinol monomethyl ether A (5 g.), glacial acetic acid (25 ml.) and concentrated hydrochloric acid (250 ml.) were heated together on the water bath for 4 hr. *Flavothe-*

baone monomethyl ether hydrochloride separated and was collected and recrystallized from water, when it was obtained as yellow prisms, m.p. 310° (dec.), (lit.[2] 308°).

Anal. Calcd. for $C_{25}H_{25}O_5N \cdot HCl \cdot {}^1/_2H_2O$: C, 64.5; H, 5.8; Cl, 7.6. Found: C, 64.1, H, 6.0; Cl, 7.3.

Flavothebaone monomethyl ether, prepared from the hydrochloride, was obtained as stout yellow prisms, m.p. 272° (lit.[2] 272°) on recrystallization from 90% methanol (the base was very sparingly soluble in anhydrous methanol).

Anal. Calcd. for $C_{25}H_{25}O_5N \cdot 1{}^1/_2H_2O$: C, 67.1; H, 6.3. Found: C, 67.1; H, 6.0.

Thebainequinol monomethyl ether B. Methyl sulfate (25 ml.) was slowly added with stirring to a boiling solution of thebainequinol (5 g.) and potassium hydroxide (35 g.) in 50% 2-ethoxyethanol (150 ml.) over a period of 40 min. The mixture was cooled and diluted with water (150 ml.) and the solid product was collected. Thebainequinol monomethyl ether B was obtained as colorless needles, m.p. 258° on recrystallization from 2-ethoxyethanol. (Schöpf, von Gottberg, and Petri[2] give m.p. 238° for a thebainequinol monomethyl ether prepared from thebainequinol and methyl *p*-toluenesulfonate.)

Anal. Calcd. for $C_{26}H_{27}O_5N$: C, 72.0; H, 6.2. Found: C, 72.0; H, 6.3.

Rearrangement of thebainequinol monomethyl ether B. The rearrangement of thebainequinol monomethyl ether B in a mixture of acetic and hydrochloric acids afforded a flavothebaone monomethyl ether hydrochloride, m.p. 320°.

Anal. Calcd. for $C_{25}H_{25}O_5N.HCl.1{}^1/_2H_2O$: C, 62.1; H, 6.0. Found: C, 62.3; H, 5.8.

The free base was obtained as yellow prisms, m.p. 248–249°.

Anal. Calcd. for $C_{25}H_{25}O_5N.H_2O$: C, 68.6; H, 6.1. Found: C, 68.9; H, 5.8.

Acknowledgments. We wish to thank Sir Robert Robinson for his constant interest and advice and Dr. H. M. E. Cardwell for much helpful discussion.

ABERDEEN, SCOTLAND

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, THE UNIVERSITY, ABERDEEN]

Flavothebaone. Part IV.[1] Degradation of *N*-Oxides and Exhaustive Methylation of Reduced Methines

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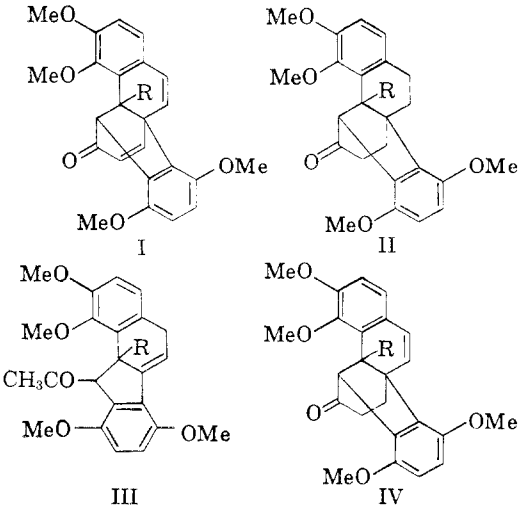
Flavothebaone trimethyl ether methine *N*-oxide has been degraded to a desaza-compound, alkaline rearrangement of which affords the desaza-ψ-methine also obtainable from the ψ-methine *N*-oxide. The trimethyl ether methine has been hydrogenated to a tetrahydro-compound also obtained from dihydroflavothebaone trimethyl ether methine. The *N*-oxides of these bases have been degraded to desaza-compounds which are not identical with the products of Hofmann degradation of the metho-hydroxides. The Hofmann products are believed to be of the thebenone type. The various desaza-methines have been related by hydrogenation.

It has previously been shown[2] that the degradation of *N*-oxides of methine bases in the morphine-thebaine group proceeds with the elimination of dimethylhydroxylamine and formation of vinyl compounds, in cases where there is no free hydroxyl group at position 4. Application of this reaction to flavothebaone trimethyl ether methine (I, R = $CH_2CH_2NMe_2$) affords the desaza-methine (I, R = CH = CH_2) which is shown by the ultraviolet spectrum to be a genuine derivative of the methine. Hydrogenation of the desazamethine (I, R = CH = CH_2) affords the hexahydrodesazamethine (II, R = Et). When the desazamethine is heated with alcoholic potassium hydroxide it undergoes the ψ-methine rearrangement[2] giving flavothebaone trimethyl ether desaza-ψ-methine (III, R = CH = CH_2) also obtainable by the thermal decomposition of the ψ-methine *N*-oxide. Hydrogenation of the desaza-ψ-methine affords the dihydroderivative (III, R = Et).

Catalytic hydrogenation of flavothebaone trimethyl ether methine affords dihydroflavothebaone trimethyl ether dihydromethine (II, R = $CH_2CH_2NMe_2$) also obtainable by the catalytic reduction of dihydroflavothebaone trimethyl ether methine (IV, R = $CH_2CH_2NMe_2$) (Part III). Degradation of the *N*-oxide of dihydroflavothebaone trimethyl ether dihydromethine affords the desaza-compound (II, R = CH = CH_2) which yields (II, R = Et) on hydrogenation; (II, R = Et) is also obtained by the



(1) Part III: K. W. Bentley, J. Dominguez, and J. P. Ringe, *J. Org. Chem.*, 22, 418 (1957).

(2) K. W. Bentley, J. C. Ball, and J. P. Ringe, *J. Chem. Soc.*, 1963 (1956).