

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

**Benzflavothebaone**<sup>1</sup>

K. W. BENTLEY, J. C. BALL, AND H. M. E. CARDWELL

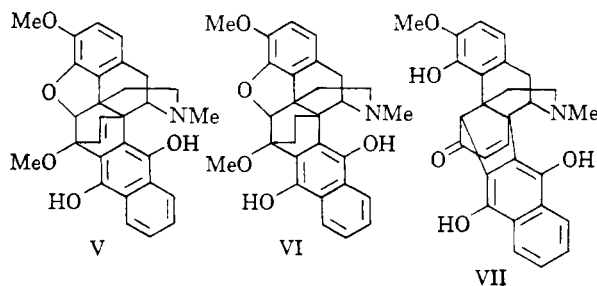
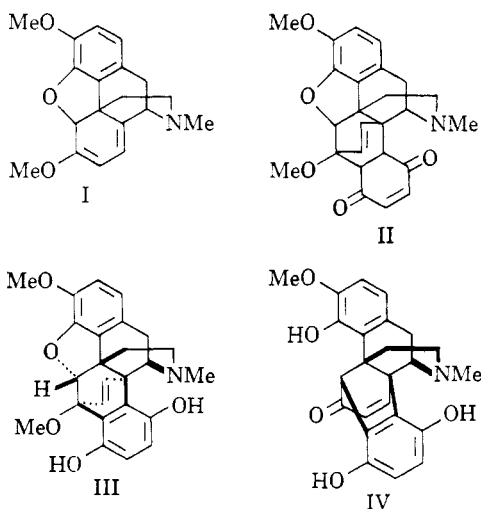
Received January 13, 1958

The Diels-Alder adduct from thebaine and 1,4-naphthaquinone has been shown to undergo most of the reactions given by thebainequinol. The acid rearrangement product, benzflavothebaone, which is analogous to flavothebaone, has been degraded to nitrogen-free products. Unlike flavothebaone it is very easily converted into a quinone.

Diels-Alder adducts between thebaine (I) and several dienophiles have been reported<sup>2-4</sup> and the stereochemistry of the *p*-benzoquinone adduct has been examined fully by Schöpf, von Gottberg, and Petri.<sup>3</sup> Sandermann, who first reported the *p*-

benzoquinone adduct (II),<sup>2</sup> observed that it underwent conversion into thebainequinol (III) on prolonged heating in ethanol, a change very easily effected in the presence of acetic acid.<sup>3</sup> The acid rearrangement of thebainequinol affords flavothebaone for which the structure (IV) has recently been established.<sup>5,6</sup> The 1,4-naphthaquinone adduct of thebaine would be expected to show similar behavior, and its reactions have in fact been found to be parallel to those of thebainequinol.

The adduct itself was sensitive to air and readily decomposed to tars, and the product m.p. 240° described by Sandermann<sup>2</sup> was very probably the isomerized base, thebaine-1,4-naphthaquinol (V) which is quite stable; a different crystalline modification m.p. 267° was obtained by us. It resembles thebainequinol in forming a monoacetyl derivative and a monomethyl ether which could not be quaternized at the *N*-atom with methyl iodide or methyl sulfate owing to the steric hindrance at the *N*-atom by one of the OH-groups. In this respect the base resembles thebainequinol; conversion of thebainequinol to flavothebaone (IV) results in the movement of the aromatic nucleus in space



(1) A preliminary report of this work has already been published; K. W. Bentley, J. C. Ball, and H. M. E. Cardwell, *Chem. and Ind. (London)*, 1483 (1956).

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

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

(4) K. W. Bentley and A. F. Thomas, *J. Chem. Soc.*, 1863 (1956).

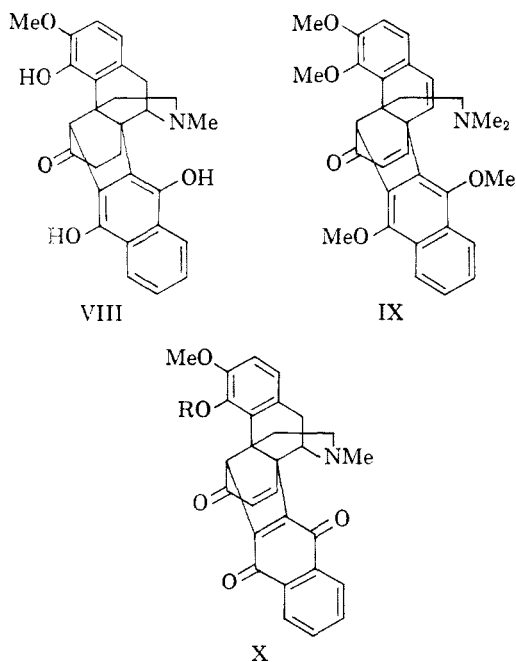
(5) K. W. Bentley, J. Dominguez, and J. P. Ringe, *Chem. and Ind. (London)*, 1353 (1956); *J. Org. Chem.*, **21**, 1348 (1956); **22**, 409, 418, 422, 424, 599 (1957).

(6) J. Meinwald and G. A. Wiley, *Chem. and Ind. (London)*, 957 (1956); *J. Am. Chem. Soc.*, **79**, 2569 (1957).

sufficiently far away from the nitrogen atom for quaternization to be possible in the rearranged series. Catalytic reduction readily afforded dihydrothebaine-1,4-naphthaquinol (VI).

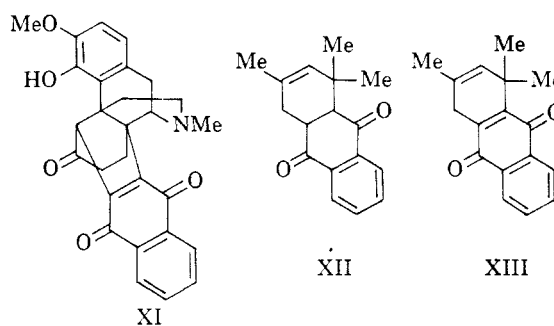
When treated with concentrated hydrochloric acid in glacial acetic acid at 100° for 6 hours, thebaine-1,4-naphthaquinol afforded the hydrated hydrochloride of benzflavothebaone (VII),  $C_{23}H_{25}O_5 \cdot N \cdot HCl \cdot 2H_2O$ . Benzflavothebaone dissolved in aqueous alkalis to give a deep purple-red solution, different in color from that of flavothebaone, and very sensitive to air oxidation, the color being discharged rapidly in air. The monomethyl ether of thebaine-1,4-naphthaquinol, obtained by treatment of the base with hot methyl sulfate or with hot methyl *p*-toluenesulfonate, was rearranged to the monomethyl ether of benzflavothebaone. The latter was soluble in alkalis to give a yellow solution which was stable in air. Dihydrobenzflavothebaone (VIII) was obtained by acid rearrangement of dihydrothebaine-1,4-naphthaquinol and also by sodium amalgam-reduction of benzflavothebaone. In alkalis, dihydrobenzflavothebaone was rapidly oxidized on shaking in air.

Triacetylbenzflavothebaone and benzflavothebaone trimethyl ether methiodide have been prepared. The latter was readily degraded in hot alkali to the methine base (IX) which was more conveniently obtained from benzflavothebaone without isolation of the intermediate quaternary salt. Under the same conditions dihydrobenzflavothebaone afforded the dihydromethine.



Oxidation of benzflavothebaone by air in dilute alkalis gave benzflavothebaone-quinone (X, R = H). This gave a monoacetyl derivative (X, R =  $CH_3CO$ ) in poor yield and could not be successfully converted into the methiodide for degradative

studies. The quinone absorbed two moles of hydrogen on catalytic reduction affording dihydrobenzflavothebaone (VIII) whereas reduction with sulfurous acid gave benzflavothebaone. Air oxidation of alkaline dihydrobenzflavothebaone afforded dihydrobenzflavothebaone-quinone (XI). In warm alcoholic alkali, benzflavothebaone-quinone gave a deep purple solution which faded on standing in air. Similar behavior has been described for the compound (XII) which Fieser and Wieghard<sup>7</sup> have prepared by Diels-Alder reaction of 1,1,3-trimethylbutadiene with 1,4-naphthaquinone; the adduct (XII) gave the quinone (XIII) on treatment with air in the presence of potassium hydroxide, and this quinone gave a blue-green solution in alcoholic potash, the color fading on shaking.



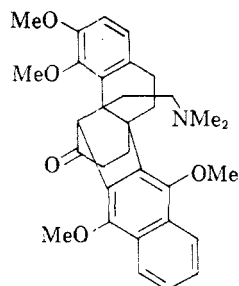
Catalytic reduction of the methine base afforded the tetrahydro compound (XIV). No success was obtained with Hofmann degradation of the methine but pyrolysis of the methine *N*-oxide<sup>8</sup> readily gave the neutral compound (XV) in quite good yield. The ultraviolet spectrum of the nitrogen-free substance was very similar to that of the methine base. Pyrolysis of the dihydromethine *N*-oxide and of the tetrahydromethine *N*-oxide afforded the neutral compounds XVI, and XVII respectively. The three nitrogen-free products XV, XVI, and XVII on hydrogenation gave the common product XVIII,  $C_{30}H_{32}O_5$ .

In the parent flavothebaone series, the methine base underwent rearrangement in hot ethanolic alkali to a non-isomeric base, the  $\psi$ -methine, in about 80% yield. This reaction has been attempted many times with benzflavothebaone methine but crystalline products have not been isolated. The neutral compound XV from the methine likewise gave non-crystalline products but the methine methiodide was converted, in very poor yield, into the  $\psi$ -methine methiodide (XIX), the ultraviolet spectrum of which closely resembled those of the crude materials from the alkali treatment of the methine base and of the nitrogen-free product (XV).

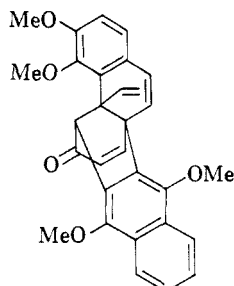
Mechanisms for the conversion of thebaine-1,4-naphthaquinol into benzflavothebaone and of

(7) L. F. Fieser and C. W. Wieghard, *J. Am. Chem. Soc.*, **62**, 153 (1940).

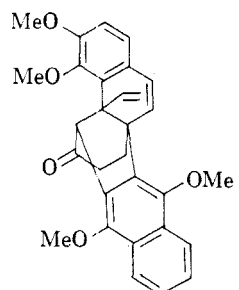
(8) K. W. Bentley, J. C. Ball, and J. P. Ringe, *J. Chem. Soc.*, 1963 (1956).



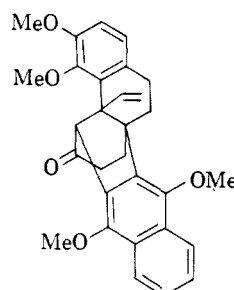
XIV



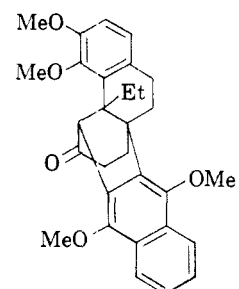
XV



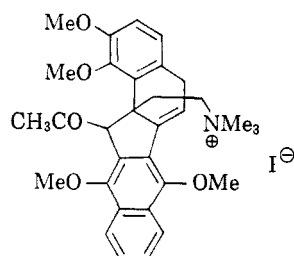
XVI



XVII



XVIII



XIX

the methine into the  $\psi$ -methine are essentially the same as those in the flavothebaone series and need no further elaboration. The structure of benzflavothebaone is assumed by analogy with that of flavothebaone; as the structure of the latter has now been established,<sup>5</sup> complete degradation of the neutral compound (XVIII) has not been attempted. Bromination afforded a tribromo derivative  $C_{30}H_{29}O_5Br_3$ , and hydroxylamine in alcoholic pyridine gave the oxime  $C_{30}H_{33}O_5N$ , which underwent Beckmann rearrangement to an isomeric compound.

#### EXPERIMENTAL

Unless otherwise stated, all ultraviolet spectra were measured in methanol solution.

**Attempted preparation of thebaine-1,4-naphthaquinone.** 1,4-Naphthaquinone (1.02 g.) dissolved in chloroform (10 ml.) was added to thebaine (2 g.) in chloroform (10 ml.); a distinct deepening in color was apparent. The solution was evaporated in a stream of air without heating and afforded a yellowish crystalline solid which, on becoming dry, turned black within a few seconds. On account of the sensitivity to air, recrystallization was never achieved. When the reaction was attempted in 2-ethoxyethanol, the only product to be isolated was thebaine-1,4-naphthaquinol, m.p. 267°. This proved to be the only clean crystalline material obtainable and was always formed after heating for some time in alcohol or more quickly in the higher-boiling 2-ethoxyethanol.

**Thebaine-1,4-naphthaquinol.** Thebaine (40 g.) was dissolved in hot 2-ethoxyethanol (200 ml.) and 1,4-naphthaquinone (20.4 g.) in hot 2-ethoxyethanol (100 ml.) was added. With pure 1,4-naphthaquinone a deepening in color was observed, but this was not noticeable with the usual samples, which contained dark impurities. On boiling for 10 min., the solution became darker in color but no solid matter separated, even on cooling. Glacial acetic acid (32 ml.) was added and the solution was heated under reflux for a further 10 min. Thebaine-1,4-naphthaquinol separated as white prisms on cooling, and these were washed with cold alcohol. The yield was 55 g., m.p. 267° (dec.), unchanged on recrystallization from 2-ethoxyethanol. (Sandermann<sup>2</sup> gave m.p. 239–240°).  $[\alpha]_D^{25} +34^\circ \pm 2^\circ$  ( $CHCl_3$ ,  $c$ , 0.79).  $\lambda_{max}$ : 215; 250; 300; 335, and 350  $m\mu$ ;  $\epsilon_{max}$ : 47,860, 28,180; 4,169, 7,079, and 7,943.

*Anal.* Calcd. for  $C_{29}H_{27}O_5N$ : C, 74.2; H, 5.8. Found: C 74.3, H, 5.6.

Rapid crystallization from 2-ethoxyethanol or from alcohol gave granular prisms; slow crystallization from the same solvents gave slender rods as well. The base was sparingly soluble in alcohol and showed no tendency to dissolve in alkalis; no coupling with diazotized sulfanilic acid could be detected. No methiodide separated when a benzene solution containing methyl iodide was allowed to stand for 3 days. Concentrated sulfuric acid gave a very intense permanganate-color with the base.

The *hydrochloride* was obtained when the base was dissolved in alcoholic HCl and diluted with water as white rods, m.p. 215° dec.

*Anal.* Calcd. for  $C_{29}H_{27}O_5N.HCl.H_2O$ : C, 66.4; H, 5.8; Cl, 6.8. Found: C, 66.4; H, 6.1; Cl, 6.1.

When an alcoholic solution of the salt was boiled for a few minutes and then allowed to cool, hydrolysis occurred and the original base, m.p. 267°, was deposited. This behavior is parallel to that of thebaine quinol.

**Monoacetylthebaine-1,4-naphthaquinol.** Thebaine-1,4-naphthaquinol (1.0 g.) was dissolved in pyridine (10 ml.), acetic anhydride (5 ml.) added, the solution was allowed to stand at room temperature for 24 hr., and then evaporated *in vacuo* on a water bath. Dilute acetic acid was added, the solution treated with sodium bicarbonate and the precipitated base was collected and crystallized from alcohol. Recrystallization from 2-ethoxyethanol gave *monoacetylthebaine-1,4-naphthaquinol* as colorless needles m.p. 267°, depressed to 240° on mixing with the starting material.

*Anal.* Calcd. for  $C_{31}H_{29}O_6N$ : C, 72.9; H, 5.7; (1)  $CH_3CO$ , 9.4. Found: C, 72.4; H, 5.6;  $CH_3CO$ , 9.3.

**Thebaine-1,4-naphthaquinol monomethyl ether.** Thebaine-1,4-naphthaquinol (2 g.) was dissolved in hot methyl sulfate (5 ml.), the solution cooled in ice and treated with ether (40 ml.) to remove excess of methyl sulfate, and the sticky precipitate collected. Trituration with a small quantity of ethanol gave a white product which was sparingly soluble in water but readily so in dilute acids. Recrystallization from 2-ethoxyethanol gave *thebaine-1,4-naphthaquinol monomethyl ether*, m.p. 252°, unchanged on further recrystallization.  $[\alpha]_D^{25} -48^\circ \pm 1^\circ$  ( $CHCl_3$ ,  $c$ , 1.25).

*Anal.* Calcd. for  $C_{30}H_{29}O_5N$ : C, 74.5; H, 6.1, active H, 0.21. Found: C, 74.3; H, 6.2; active H, 0.25.

The same product was obtained by methylation with methyl *p*-toluenesulfonate following the directions of Schöpf *et al.*<sup>3</sup> for the methylation of flavothebaone.

**Dihydrothebaine-1,4-naphthaquinol.** Thebaine-1,4-naphthaquinol (3.0 g.) dissolved in glacial acetic acid (40 ml.) was shaken under hydrogen with platinum oxide (0.1 g.). One mole of hydrogen was absorbed in 30 min. at 18°. The solution was filtered (kieselguhr), diluted with water, treated with ammonia solution, and the product collected and crystallized from alcohol when *dihydrothebaine-1,4-naphthaquinol* was obtained as orange needles, m.p. 266°.  $[\alpha]_D^{25} 0^\circ \pm 1^\circ$   $\lambda_{max}$ : 215; 253; 290; 330, and 343  $m\mu$ ;  $\epsilon_{max}$ : 79,430; 47,860; 3,981; 7,950, and 8,320.

*Anal.* Calcd. for  $C_{23}H_{23}O_5N$ : C, 74.0; H, 6.2. Found: C, 74.0; H, 6.2.

The hydrochloride was obtained as glistening plates, m.p. 210–212°, sintering at 205°, from dilute hydrochloric acid.

*Anal.* Calcd. for  $C_{23}H_{23}O_5N \cdot HCl \cdot H_2O$ : C, 66.2; H, 5.8; Cl, 6.8. Found: C, 66.7; H, 5.8; Cl, 7.0.

*Benzflavothebaone hydrochloride.* Thebaine-1,4-naphthaquinol (40 g.) was dissolved in hot glacial acetic acid (120 ml.) and concentrated hydrochloric acid (120 ml.) was added. A crystalline salt began to separate after 20 min. under reflux; heating was continued for 4 hr. on a steam bath. Hot water (250 ml.) was added and, after cooling, the product was collected and dried in air, when 36.5 g. of *benzflavothebaone hydrochloride* was obtained as yellow plates, m.p. 264° (dec.). Recrystallization in bulk was found to be inconvenient, but for analysis it was achieved by adding concentrated HCl to an alcoholic solution of the salt.  $[\alpha]_D^{25} + 434^\circ \pm 4^\circ$  (EtOH, *c*, 0.36).

*Anal.* Calcd. for  $C_{23}H_{23}O_5N \cdot HCl \cdot 2H_2O$ : C, 63.6; H, 5.7; Cl, 6.7. Found after drying at 140° *in vacuo*: C, 63.5; H, 5.8; Cl, 7.5. Loss in weight of air-dried salt on heating at 140° *in vacuo*: Calcd. for loss of HCl from  $C_{23}H_{23}O_5N \cdot 2HCl \cdot 2H_2O$ : 6.5. Found: 6.6, 7.1.

An intense red solution was obtained on dissolving the salt in concentrated sulfuric acid. In alkalis an exceedingly intense purple-red solution was obtained and, on shaking, the color was discharged. Positive diazo-coupling occurred with the alkaline solutions both before and after air oxidation. Ultraviolet spectrum:  $\lambda_{max}$ : 235; 250 (inflection); 288, and 385 m $\mu$ .  $\epsilon_{max}$ : 44,670; 26,300; 7,586, and 4,266. Spectrum in aq. 2*N* NaOH with dithionite antioxidant: 7,586, and 4,266. Spectrum in aq. 2*N* NaOH with dithionite antioxidant:  $\lambda_{max}$ : 510 m $\mu$   $\epsilon_{max}$ : 3,981.

*Benzflavothebaone monomethyl ether hydrochloride.* Thebaine-1,4-naphthaquinol monomethyl ether (178 mg.) was dissolved in glacial acetic acid (2 ml.), concentrated HCl (3 ml.) was added and the solution was heated under reflux for 1 hr. After concentration to 2 ml. the solution was treated with more concentrated HCl (3 ml.) and the precipitated salt (106 mg.) was collected and recrystallized from dilute acetic acid, m.p. 255–260° (dec.)  $[\alpha]_D^{25} + 301^\circ \pm 1^\circ$  (EtOH, *c*, 0.87).

Ultraviolet spectrum in 2*N* NaOH:  $\lambda_{max}$ : 420 m $\mu$   $\epsilon_{max}$ : 3,981.

*Anal.* Calcd. for  $C_{23}H_{27}O_5N \cdot HCl \cdot 2H_2O$ : C, 64.2; H, 5.6; Cl, 6.6; active-H, 1.1. Found after drying at 140° *in vacuo*: C, 63.7; H, 5.8; Cl, 6.3; active-H, 1.2.

In aqueous sodium hydroxide a yellow solution was obtained which was unaffected on shaking in air. Diazotized sulfanilic acid gave an intense red solution in alkalis; concentrated sulfuric acid gave a crimson color.

*Dihydrobenzflavothebaone hydrochloride.* When treated with concentrated hydrochloric acid and glacial acetic acid in the manner outlined for the rearrangement of thebaine-1,4-naphthaquinol to benzflavothebaone hydrochloride the dihydro compound behaved in a similar way, depositing the almost-white dihydrobenzflavothebaone hydrochloride as the hydrated salt in almost quantitative yield. M.p. 280–290°.  $[\alpha]_D^{25} + 152^\circ \pm 3^\circ$  (EtOH, *c*, 0.49),  $\lambda_{max}$ : 247; 286, and 335 m $\mu$ .  $\epsilon_{max}$ : 33,110; 6,026, and 5,012.

*Anal.* Calcd. for  $C_{22}H_{27}O_5N \cdot HCl \cdot 2H_2O$ : C, 63.4; H, 6.1; Cl, 6.7. Found after drying at 140° *in vacuo*: C, 63.0; H, 5.8; Cl, 6.9.

In concentrated sulfuric acid a moderately intense green color resulted. Aqueous alkali gave a bright red solution, the

(9) Flavothebaone also forms a dihydrochloride. These salts are only stable in the presence of excess of hydrochloric acid, and slowly lose hydrogen chloride on drying in the air. These salts are believed to be formed by protonation of the system  $O=C-C=C-Ar$  to  $HO=C-C=C-Ar$ . The dihydrochlorides are noticeably different in color from the monohydrochlorides, see ref. 5, paper 4.

color being discharged on shaking in air. Both the initial alkali-solution and the air-oxidized one gave deep red colors on addition of diazotized sulfanilic acid.

*Reduction of benzflavothebaone with sodium amalgam.* Benzflavothebaone hydrochloride (1.0 g.) was dissolved in hot alcohol (25 ml.) and sodium amalgam (0.5 g. Na in 30 g. Hg) added. The color remained yellow for several minutes and then on warming became red-brown, and after a short time an orange solid began to separate. When most of the amalgam had reacted, concentrated hydrochloric acid was added dropwise; the color of the solution changed sharply to green and addition of more HCl gave a precipitate which was collected and recrystallized from water (100 ml.) to which concentrated hydrochloric acid was added. Dihydrobenzflavothebaone hydrochloride was obtained as very pale yellow plates. M.p. 280–290°.  $[\alpha]_D^{25} + 148^\circ \pm 3^\circ$  (EtOH *c*, 0.45),  $\lambda_{max}$  and  $\epsilon_{max}$  the same as for dihydrobenzflavothebaone. The reduction product gave the same alkali- and concentrated sulfuric acid colors as the material from the rearrangement of dihydrothebaine-1,4-naphthaquinol.

*Triacetylbenzflavothebaone.* Benzflavothebaone hydrochloride (2 g.) was dissolved in hot acetic anhydride (10 ml.) and pyridine (3 ml.) was added to the clear solution which was then boiled for 1 hr. The mixture was then diluted with water (100 ml.) and decomposed with sodium carbonate, and the product was collected. Three recrystallizations from alcohol gave *triacetylbenzflavothebaone* as colorless needles, m.p. 258–260°.  $[\alpha]_D^{25} + 237^\circ + 2^\circ$  (CHCl<sub>3</sub>, *c*, 0.59).  $\lambda_{max}$ : 215; 230; 280, and 340 m $\mu$ .  $\epsilon_{max}$ : 60,260; 60,250; 16,980, and 2,239.

*Anal.* Calcd. for  $C_{34}H_{31}O_5N$ : C, 70.2; H, 5.4; (3) CH<sub>3</sub>CO, 22.2. Found: C, 69.9; H, 5.4; CH<sub>3</sub>CO, 20.7.

*Benzflavothebaone trimethyl ether methiodide.* The air in a flask containing a suspension of benzflavothebaone hydrochloride (20 g.) in methyl sulfate (68 ml.) was expelled with hydrogen and a solution of sodium hydroxide (25 g.) in boiled water (75 ml.) added slowly so that the reaction temperature was kept around 40° (mechanical stirring). After the addition, the temperature was raised to 60–70° to decompose the excess of methyl sulfate, and hot water (100 ml.) followed by an excess of aqueous potassium iodide was added. The solution was heated to the boiling point, treated with charcoal, filtered, and the minutely crystalline product collected from the cold filtrate. *Benzflavothebaone trimethyl ether methiodide*, m.p. 198–200° (dec.), was thus obtained, m.p. unchanged on recrystallization from water.  $[\alpha]_D^{25} + 244^\circ \pm 2^\circ$  (CHCl<sub>3</sub>, *c*, 0.72).

*Anal.* Calcd. for  $C_{22}H_{24}O_5NI \cdot 2H_2O$ : C, 56.9; H, 5.7; I, 18.8. Found after drying at 140° *in vacuo*: C, 56.7, 56.8; H, 5.6 5.8; I, 19.2.

*Benzflavothebaone trimethyl ether methine.* Treatment of benzflavothebaone trimethyl ether methiodide with hot aqueous alkali readily converted it into the methine. The alternative method below obviates the need to prepare the intermediate methiodide, and affords a higher overall yield.

Benzflavothebaone hydrochloride (40 g.) was covered with methyl sulfate (136 ml.) contained in a 1-l. flask with a sealed-in stirrer. The air was displaced by means of hydrogen and NaOH (50 g.) in boiled water (150 ml.) was added slowly so as to maintain the reaction temperature at 40°. (Strong cooling delays the reaction which subsequently gets out of control.) The reaction mixture was heated to 80–90° to decompose excess of methyl sulfate, and then poured into hot water (1 l.). Sodium hydroxide was added until the mixture was alkaline to litmus, followed by more NaOH (50 g.) dissolved in a little water (rapid stirring was desirable at this stage). Separation of the methine began at once, and after 15 min. at 95° the aqueous phase was removed by decantation and the solids washed well with water. Recrystallization from alcohol (200 ml.) (charcoal treatment) gave 36 g. of *benzflavothebaone trimethyl ether methine* as colorless prisms, m.p. 199°.  $[\alpha]_D^{25} - 21^\circ \pm 2^\circ$  (CHCl<sub>3</sub>, *c*, 0.70).  $\lambda_{max}$ : 233; 280, and 345 m $\mu$   $\epsilon_{max}$ : 63,100; 23,400, and 22,910.

*Anal.* Calcd. for  $C_{32}H_{33}O_5N$ : C, 75.2; H, 6.5. Found: C, 74.9; H, 6.5%.

The *methiodide* was obtained when a slight excess of methyl iodide was added to a solution of the methine in benzene; after a few minutes the solution became turbid and deposited a granular solid. Recrystallization from water gave yellow needles, m.p.  $244^\circ$ .  $[\alpha]_D^{24} -14^\circ \pm 1^\circ$  ( $CHCl_3$ , c. 1.78).

*Anal.* Calcd. for  $C_{33}H_{36}O_5NI \cdot H_2O$ : C, 59.1; H, 5.7; I, 18.9. Found: C, 59.1; H, 5.8; I, 19.4.

The *picrate*, prepared in and recrystallized from alcohol, was obtained as yellow prisms, m.p.  $232^\circ$ .

*Anal.* Calcd. for  $C_{33}H_{36}O_{12}N_4$ : C, 61.6; H, 4.9; N, 7.6. Found: C, 61.9; H, 4.8; N, 7.9.

*Benzflavothebaone quinone.* Air was bubbled into a solution of benzflavothebaone hydrochloride (2 g.) in water (100 ml.) containing 0.880 of ammonia solution (40 ml.) and covered with a layer of benzene (100 ml.), until the aqueous phase became colorless and the benzene phase a clear orange. The benzene phase was separated, dried with sodium sulfate (short drying, as the product tended to crystallize), and evaporated when *benzflavothebaone quinone* was obtained as a dark orange crystalline solid (1.25 g.) m.p.  $269^\circ$ , raised to  $278^\circ$  on recrystallization from 2-ethoxyethanol,  $[\alpha]_D^{20} +220^\circ \pm 40^\circ$  ( $CHCl_3$ , c. 0.67).  $\lambda_{max}$ : 215; 250 (inflection); 290 (inflection); 335; 410 (inflection)  $\mu\mu$ .  $\epsilon_{max}$ : 21,880; 15,850; 6,760; 3,310, and 310.

*Anal.* Calcd. for  $C_{28}H_{23}O_5N$ : C, 74.1; H, 5.1; N, 3.1. Found: C, 73.9; H, 5.1; N, 2.9.

The melting point was variable ( $278^\circ$  highest recorded) and mere recrystallization from alcohol or aqueous 2-ethoxyethanol gave a material paler in color and of lower melting point (down to  $265^\circ$ ). The use of sodium hydroxide in place of ammonia gave the same compound but in about one third the yield. A solution of the quinone in dilute acid was treated with excess alkali and warmed; this caused the solution to become deep purple (like benzflavothebaone in alkali), the color being discharged on shaking.

*Acetylbenzflavothebaone quinone.* A solution of benzflavothebaone quinone (650 mg.) in acetic anhydride (8 ml.) and pyridine (2 ml.) was heated under reflux for one hour and the resulting red solution diluted with water and decomposed with sodium carbonate. The acetyl compound was collected and crystallized from alcohol (20 ml.) to give 180 mg. of deep orange needles, m.p.  $234-235^\circ$ .

*Anal.* Calcd. for  $C_{30}H_{25}O_5N \cdot \frac{1}{2}H_2O$ : C, 71.4; H, 5.2. Found: C, 71.4; H, 5.3.

*Catalytic reduction of benzflavothebaone quinone.* The quinone (1.0 g.) in glacial acetic acid (20 ml.) with platinum oxide (0.05 g.) was shaken under hydrogen at  $19^\circ$ . Absorption ceased after 2 hr. when 2 moles had been absorbed. Warm concentrated hydrochloric acid was added and the solution was cooled. Brownish needles separated (0.61 g.). This product was recrystallized from alcohol with the addition of concentrated hydrochloric acid to yield pale orange-yellow plates, m.p.  $280-290^\circ$ . The ultraviolet and infrared spectra were the same as those of dihydrobenzflavothebaone; colors with concentrated sulfuric acid and with alkalis were the same as those of dihydrobenzflavothebaone.

*Reduction of benzflavothebaone quinone with sulfurous acid.* When sulfur dioxide was bubbled into an aqueous alcoholic hydrochloric acid solution of the quinone the color of the solution changed from orange to yellow-orange within about 5 min. The resulting solution was concentrated by boiling and treated with concentrated hydrochloric acid and the resulting crystalline solid was collected, m.p.  $260-270^\circ$ .  $[\alpha]_D^{25} +433^\circ \pm 2^\circ$  (EtOH, c. 0.58).  $\lambda_{max}$ : 235; 250 (inflection); 290; 370  $\mu\mu$ .  $\epsilon_{max}$ : 42,660; 25,120; 6,918; 3,981.

Acetylation of this material gave a product m.p.  $248^\circ$ , unchanged on further recrystallization, which did not depress the melting point of authentic triacetylbenzflavothebaone, and had the same ultraviolet spectrum as this compound.

*Air oxidation of dihydrobenzflavothebaone.* Under the condi-

tions already outlined for the air oxidation of benzflavothebaone to the quinone, the dihydro compound (2 g.) afforded a *dihydrobenzflavothebaone quinone* (1.4 g.) which like the quinone had a rather variable melting point. Colors in concentrated sulfuric acid and in alkalis were like those of the quinone but the ultraviolet spectrum did show a definite difference.  $\lambda_{max}$ : 253; 280 (inflection); 330.  $\mu\mu$ .  $\epsilon_{max}$ : 19,950; 8,913; 3,715.

*Anal.* Calcd. for  $C_{28}H_{25}O_5N$ : C, 73.8; H, 5.5. Found: C, 74.1; H, 5.6.

*Dihydrobenzflavothebaone trimethyl ether dihydromethine.* The methine base readily absorbed 2 moles of hydrogen on catalytic reduction over platinum oxide in acetic acid solution at  $20^\circ$ . *Dihydrobenzflavothebaone trimethyl ether dihydromethine* was obtained as needles, m.p.  $171^\circ$ , from methanol.  $[\alpha]_D^{20} +154^\circ \pm 2^\circ$  ( $CHCl_3$ , c. 0.80).  $\lambda_{max}$ : 239, 290  $\mu\mu$ .  $\epsilon_{max}$ : 69,180; 8,913.

*Anal.* Calcd. for  $C_{32}H_{37}O_5N$ : C, 74.6; H, 7.2. Found: C, 74.3; H, 7.3.

The *methiodide* was obtained after 30 min. when methyl iodide was added to a benzene solution of the base. It was obtained as colorless needles, m.p.  $262^\circ$ , on recrystallization from water.

*Anal.* Calcd. for  $C_{33}H_{40}O_5NI \cdot 2H_2O$ : C, 58.8; H, 6.3; I, 18.9. Found: C, 58.7; H, 6.3; I, 18.8.

*Benzflavothebaone trimethyl ether methine N-oxide perchlorate.* The methine (1 g.) was treated with 30% hydrogen peroxide (5 ml.) on a steam bath for 1 hr. during which time an orange oil and a watery aqueous phase were produced. The volatile materials were removed *in vacuo* and the crude *N-oxide* was dissolved in dilute hydrochloric acid. Addition of aqueous sodium perchlorate gave a white gel which crystallized on shaking. Two recrystallizations from aqueous alcohol gave the *perchlorate* as white needles, m.p.  $181^\circ$ .

*Anal.* Calcd. for  $C_{32}H_{34}O_{10}NCl \cdot H_2O$ : C, 59.4; H, 5.6. Found: C, 59.0; 59.4; H, 5.5, 5.6.

*Benzflavothebaone trimethyl ether desazamethine.* The methine (15 g.) and 30% hydrogen peroxide (45 ml.) in a 250 ml. flask were heated for 40 min. on a steam bath and evaporated to dryness at 15 mm. When heated under 15 mm. pressure, decomposition occurred around  $150-160^\circ$  (bath temperature) over about 30 min. Purification of the crude material was achieved by crystallization from acetic acid followed by chromatography of the benzene-soluble materials. In this way 6.1 g. of *benzflavothebaone trimethyl ether desazamethine* m.p.  $244^\circ$ , sintering at  $230^\circ$  was obtained.  $[\alpha]_D^{21} +49^\circ \pm 1^\circ$  ( $CHCl_3$ , c. 2.12).  $\lambda_{max}$ : 237; 283; 344  $\mu\mu$ .  $\epsilon_{max}$ : 74,130; 25,120; 3,311.

*Anal.* Calcd. for  $C_{30}H_{26}O_5$ : C, 77.2; H, 5.6. Found: C, 76.8; H, 5.6.

The compound was completely insoluble in acids and in alkalis but did dissolve in organic solvents.

*Catalytic reduction.* Reduction was rather slow in acetic acid solution in the presence of platinum oxide at  $50^\circ$ . Fresh samples of catalyst had to be added from time to time and complete absorption of 3 moles took more than 6 hr. The catalyst was removed, the mixture was evaporated, and the product was recrystallized from ethanol. *Hexahydrobenzflavothebaone trimethyl ether desazamethine* (XVIII) was obtained as colorless prisms, m.p.  $253^\circ$ ,  $[\alpha]_D^{23} +165^\circ \pm 2^\circ$  ( $CHCl_3$ , c. 0.49)  $\lambda_{max}$ : 240; 287  $\mu\mu$ .  $\epsilon_{max}$ : 74,130; 10,470.

*Anal.* Calcd. for  $C_{30}H_{32}O_6$ : C, 76.2; H, 6.8. Found: C, 76.0; H, 6.8.

*Dihydrobenzflavothebaone trimethyl ether desazamethine* (XVI). The methine (5.7 g.) was heated on the water bath for 90 min. with 30% hydrogen peroxide (17 ml.) and the mixture then evaporated to dryness *in vacuo*. The resulting *N-oxide* was decomposed at  $150-170^\circ/15$  mm., and the product crystallized from acetic acid. Three grams of *dihydrobenzflavothebaone trimethyl ether desazamethine* (XVI) was obtained as colorless prisms, m.p.  $256^\circ$ ,  $[\alpha]_D^{25} +137^\circ \pm 2^\circ$  ( $CHCl_3$ , c. 0.68).

*Anal.* Calcd. for  $C_{30}H_{28}O_6$ : C, 76.8; H, 6.0. Found: C, 76.8; H, 6.1.

**Catalytic reduction.** Under the conditions described for the catalytic reduction of benzflavothebaone trimethyl ether desazamethine, this compound absorbed 2 moles of hydrogen in 4 hr. giving *hexahydrobenzflavothebaone trimethyl ether desazamethine* (XVIII) as prisms, m.p. 253° alone or mixed with a specimen prepared as in the previous experiment.

**Dihydrobenzflavothebaone trimethyl ether desazadihydromethine** (XVII). Dihydrobenzflavothebaone trimethyl ether dihydromethine (4.1 g.) was heated on the water bath for 90 min. with 30% hydrogen peroxide (15 ml.). The mixture was evaporated *in vacuo* and the resulting *N*-oxide decomposed at 150–170°/15 mm. The product was crystallized first from methanol and finally from aqueous acetic acid as colorless prisms, m.p. 257°  $[\alpha]_D^{24} + 215^\circ \pm 2^\circ$  (CHCl<sub>3</sub>, *c*, 0.48).

*Anal.* Calcd. for C<sub>30</sub>H<sub>30</sub>O<sup>1/2</sup>H<sub>2</sub>O: C, 75.0; H, 6.5. Found: C, 75.1, 75.0; H, 6.3, 6.3.

**Catalytic reduction.** Under the conditions already described for the other two desazamethines the desazadihydromethine absorbed 1 mole of hydrogen, giving hexahydrobenzflavothebaone trimethyl ether desazamethine (XVIII) as colorless prisms, m.p. 251°, alone or mixed with material prepared by the hydrogenation of the other two desazamethines.  $[\alpha]_D^{23} + 168^\circ \pm 2^\circ$  (CHCl<sub>3</sub>, *c*, 0.49).

**Attempts to convert benzflavothebaone trimethyl ether methine into a  $\psi$ -methine.** Numerous attempts were made to bring about the conversion of benzflavothebaone trimethyl ether methine into a  $\psi$ -methine under conditions which were effective in the flavothebaone series (*i.e.* 20% alcoholic potassium hydroxide for 6 hr. under reflux). A crystalline specimen was never obtained and the starting material was never recoverable. The colored tarry products were basic and gave noncrystallizable salts with methyl iodide and with perchloric acid, and attempts at chromatographic purification were also fruitless. The crude  $\psi$ -methine gave an intensely blue solution in concentrated sulfuric acid (flavothebaone  $\psi$ -methine behaves in a similar way) and its ultraviolet spectrum differed from that of the methine.  $\lambda_{\max}$ : 243; 300 (inflection); 340 (inflection)  $\mu\mu$ .  $\epsilon_{\max}$ : 89,130; 13,180, 3,980.

**Benzflavothebaone trimethyl ether  $\psi$ -methine methiodide.** Solid potassium hydroxide was slowly added to a solution of benzflavothebaone trimethyl ether methine methiodide (2 g.) in boiling water (80 ml.) and the solution was boiled under reflux for 5 hr. When cold, the droplets of red oil that separated were extracted with chloroform to give a powdery varnish-like solid. Excess of potassium iodide was added to a solution of the crude material in hot water, and, on cooling and shaking, a sticky solid adhered to the flask and it was possible to decant the clear mother liquor, which on further cooling separately deposited colorless needles. The yield of pure benzflavothebaone trimethyl ether  $\psi$ -methine methiodide was about 0.1 g. Recrystallization from water brought

the m.p. to 253°, depressed to 224° on mixing with the original methine methiodide of m.p. 244°.

$\lambda_{\max}$ : 245; 285 (inflection); 330; 345  $\mu\mu$ .  $\epsilon_{\max}$ : 114,800; 15,140; 8,318; 3,630.

*Anal.* Calcd. for C<sub>30</sub>H<sub>30</sub>O<sub>5</sub>Ni: C, 59.7; H, 6.0; I, 19.7. Found: C, 59.4, 59.4; H, 5.9; I, 19.4.

**Bromination of hexahydrobenzflavothebaone trimethyl ether desazamethine.** This nitrogen-free product (550 mg.) in chloroform solution (10 ml.) was treated with a standard solution of bromine in chloroform. The addition of 2 molecular equivalents of bromine left only a slight orange color and much hydrogen bromide was evolved; the color of further amounts of bromine was not discharged. The excess of bromine was expelled from the reaction mixture with a current of air and the solvent evaporated to give a viscous brown oil which on trituration with methanol gave a sparingly soluble crystalline solid (490 mg.). Recrystallization from ethyl acetate-methanol and then from acetic acid gave *tribromohexahydrobenzflavothebaone trimethyl ether desazamethine* as colorless needles, m.p. 207° (dec.),  $[\alpha]_D^{25} + 168^\circ \pm 6^\circ$  (CHCl<sub>3</sub>, *c*, 0.47).

*Anal.* Calcd. for C<sub>30</sub>H<sub>25</sub>O<sub>5</sub>Br<sub>3</sub>: C, 50.6; H, 4.1; Br, 34.2. Found: C, 50.8; H, 4.1; Br, 35.9, 35.4.

**Hexahydrobenzflavothebaone trimethyl ether desazamethine oxime** was prepared from the ketone (2.0 g.) and hydroxylamine hydrochloride (1 g.) in alcohol-pyridine and was obtained as colorless rods, m.p. 247°, on recrystallization from methanol;  $[\alpha]_D^{25} + 89^\circ \pm 3^\circ$  (CHCl<sub>3</sub>, *c*, 0.45). Yield 1.78 g.

*Anal.* Calcd. for C<sub>30</sub>H<sub>33</sub>O<sub>5</sub>N: C, 73.8; H, 6.8; N, 2.9. Found: C, 73.9; H, 6.8; N, 2.8.

**Beckmann rearrangement.** The oxime (0.80 g.) in chloroform (10 ml.) was cooled in an ice-salt mixture and treated with thionyl chloride (2 ml.). After 1 hr. at room temperature, the volatile materials were evaporated in a stream of air and finally on a steam bath *in vacuo*. The greenish product crystallized from methanol when *hexahydrobenzflavothebaone trimethyl ether desazamethine isoxime* was obtained as slender colorless rods (0.33 g.) m.p. 183.  $[\alpha]_D^{25} - 14^\circ \pm 4^\circ$  (CHCl<sub>3</sub>, *c*, 0.29).

*Anal.* Calcd. for C<sub>30</sub>H<sub>33</sub>O<sub>5</sub>N: C, 73.8; H, 6.8; N, 2.9. Found: C, 73.9; H, 6.4; N, 2.9%.

The rearranged oxime was insoluble in water, dilute hydrochloric acid, warm 30% aqueous sodium hydroxide, and hot concentrated hydrochloric acid.

**Acknowledgments.** One of us (J.C.B.) wishes to thank the Kent Education Committee for a grant, and the Department of Scientific and Industrial Research for a Maintenance Allowance.

ABERDEEN, SCOTLAND