Nuclear Hydroxylated Metabolite of Fluradoline (2-Fluoro-11-[(β-methylamino)ethylthio]dibenz[b,f]oxepin Hydrochloride). Identification and Synthesis

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Fluradoline (2-fluoro-11-[β-(methylamino)ethylthio]dibenz[b,f]oxepin), a novel analgesic with an unique profile, was found to be extensively metabolized in man as well as in other species. One of the major metabolites of this drug appeared to be a nuclear hydroxylated derivative of the parent compound, and the site of enzymatic hydroxylation was established to be C(7) by using high-field proton nuclear magnetic spectroscopy. This structural assignment was subsequently confirmed by the synthesis of an authentic sample of 2-fluoro-7-hydroxy-11-[β-(methylamino)ethylthio]dibenz[b,f]oxepin (**2a**).

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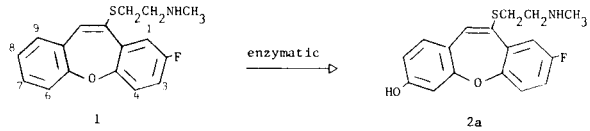
Introduction.

A major task in the study of potentially useful drugs is the detection and identification of the metabolites generated in the respective species and especially in man. Such is the case of fluradoline (HP 494), 2-fluoro-11-[(β-methylamino)ethylthio]dibenz[b,f]oxepin hydrochloride, **1**, a novel analgesic with an interesting antidepressant profile presently in clinical trials in several countries [1].

The metabolism of fluradoline is extensive in man as it is in other species [2]. One of the major metabolites found

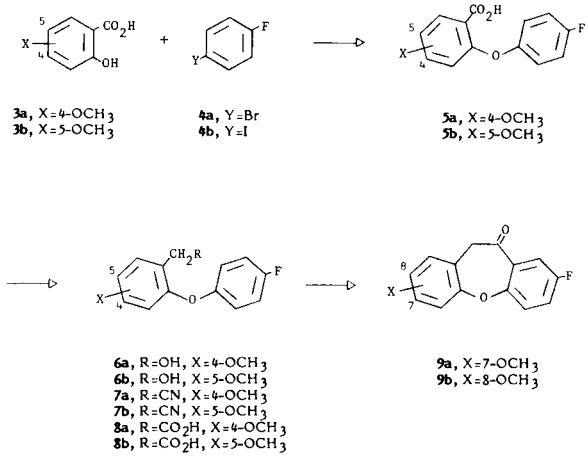


1 fluradoline 2a

in man gave a mass spectrum (m/e 317) corresponding to a hydroxylated analog of fluradoline (molecular formula $C_{17}H_{16}FNO_2S$). The 70 electron volt electron impact mass spectra of fluradoline and the isolated metabolite both gave small molecular ions (<5%) and base peaks for the loss of 43 amu [CH_3NCH_2]. The most diagnostic piece of mass spectral evidence, however, was from the mutual loss of 89 amu from the molecular ion. This loss corresponded to the loss of the entire methylaminoethylthio side chain, leaving the bare tricyclic ring system. The 212 amu peak of fluradoline (3.4%) and the 228 amu peak of the metabolite (2.3%) showed unequivocally that the additional hydroxyl group is on the tricyclic aromatic ring system. The rest of the fragmentation for the two compounds was also consistent, but the exact position of hydroxylation was still unclear.

High field ^1H nmr was employed to accurately determine the position of hydroxylation. The 200 MHz ^1H nmr spectrum of fluradoline, taken as a dilute solution in deuteriochloroform, showed a complex aromatic region from 6.95 to 7.35 ppm and a doublet of doublets centered at 7.48 ppm corresponding to the 1-H (J_{meta} = 3 Hz, $J_{F\text{-}C\text{-}C\text{-}H}$ = 10 Hz). The isolated hydroxylated metabolite gave a 200 MHz ^1H nmr spectrum with much greater definition due to the shielding effects of the hydroxy group. There was still a complex aromatic region from 6.90 to 7.30 ppm, but of much lower integrated intensity than in fluradoline. The doublet of doublets at 7.48 ppm remained unchanged while three protons were clearly shifted to higher field. These three high field protons gave the distinct pattern of a 1,2,4-trisubstituted aromatic ring [6.71 ppm (1H) J = 6.3 Hz, 6.58 ppm (1H) J = 1.5 Hz, 6.48 ppm (1H) J = 6.3 Hz and J = 1.5 Hz], placing the hydroxy group in the nonfluorinated ring at either the 7 or 8 position. By comparison to model 1,2,4-trisubstituted benzenes [3], the struc-

Scheme I



3a, X=4-OCH_3
3b, X=5-OCH_3

4a, Y=Br
4b, Y=I

5a, X=4-OCH_3
5b, X=5-OCH_3

6a, R=OH, X=4-OCH_3
6b, R=OH, X=5-OCH_3
7a, R=CN, X=4-OCH_3
7b, R=CN, X=5-OCH_3
8a, R=CO_2H, X=4-OCH_3
8b, R=CO_2H, X=5-OCH_3

9a, X=7-OCH_3
9b, X=8-OCH_3

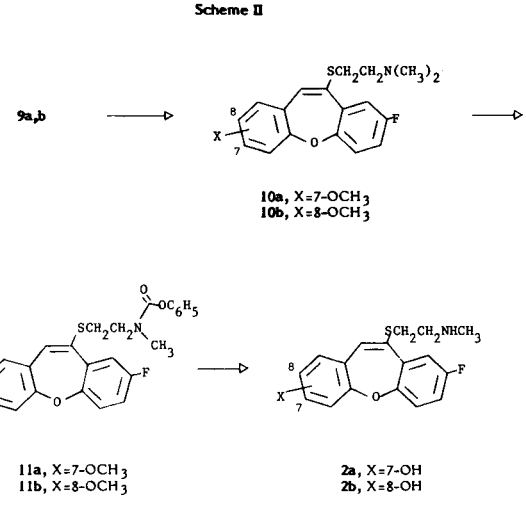
ture was determined to be 2-fluoro-7-hydroxy-11-[β-(methylamino)ethylthio]dibenz[*b,f*]oxepin, **2a**.

In order to confirm the identification of the metabolite in question, the synthesis of both the 7-hydroxy **2a** and 8-hydroxy **2b** analogs of fluradoline was carried out. The remainder of this paper covers in detail the methods used to achieve the final products.

Synthesis.

As depicted in Scheme I, phenoxybenzoic acids **5a,b** were prepared by the Ullmann reaction using an appropriately substituted salicylic acid (**3a** or **3b**) with either 4-bromofluorobenzene (**4a**) or 4-fluoroiodobenzene (**4b**). While **3b** reacted readily with **4b** in the presence of catalytic amounts of copper powder and cuprous iodide to give moderate yields of **5b** [4], the preparation of **5a** from **3a** required a large excess of **4a**, stoichiometric amount of cuprous chloride and a much longer reaction time in order to achieve comparable results. Substitution of **4a** for **4b** in the latter case only led to the extensive formation of a biphenyl derivative.

Scheme II



Reduction of **5a,b** with borane proceeded smoothly to give alcohols **6a,b**, which were converted to the corresponding nitriles, **7a,b**, by first reacting with thionyl chloride, followed by displacement with sodium cyanide. It was worth noting that the two phenylacetic acid derivatives, **8a,b**, obtainable from **7a,b** by alkaline hydrolysis displayed markedly different stability under the standard Friedel-Crafts conditions. Compound **8b** could be readily converted to the corresponding acyl chloride, which cyclized with aluminum chloride to give **9b** in high yield. In contrast, **8a** under identical conditions afforded only a complex mixture of products which appeared to be largely devoid of a carbonyl function. The difference in results could perhaps be rationalized by postulating the formation of a quinoidal intermediate [5], possible only with **8a**, which then rearranged or polymerized to give rise to other products. A

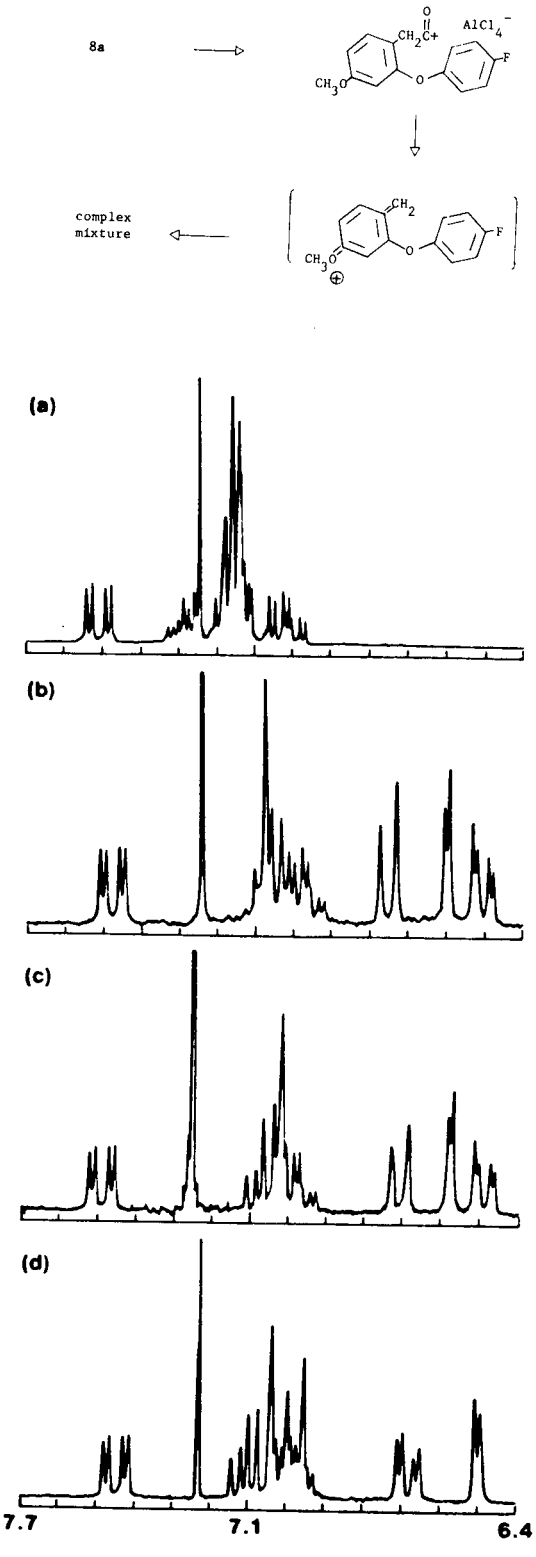


Figure 1. 200 MHz ^{1}H nmr spectra of (a) fluradoline, (b) nuclear hydroxylated metabolite of fluradoline, (c) 2-fluoro-7-hydroxy-11-[β-(methylamino)ethylthio]dibenz[*b,f*]oxepin, and (d) 2-fluoro-8-hydroxy-11-[β-(methylamino)ethylthio]dibenz[*b,f*]oxepin.

more viable approach to **9a** was by refluxing **8a** with polyphosphoric acid in an inert solvent such as 1,2-dichloroethane; the ketone **9a** so obtained was virtually of analytical purity.

The elaboration of 11-(β-methylaminoethylthio) side chain is depicted in Scheme II. Dehydrative coupling of ketones **9a,b** with β-(dimethylamino)ethanethiol in the presence of boron trifluoride etherate and glacial acetic acid afforded vinyl sulfides **10a,b** in good yields [1,6]. Reaction of these tertiary amines with phenyl chloroformate gave carbamates **11a,b**, which were converted to the phenolic amines **2a,b** by *O*-demethylation with boron tribromide, followed by alkaline hydrolysis of the carbamate moiety.

Comparison of mass spectral and ^{1}H nmr data (as shown in Figure 1) unequivocally established **2a** to be the nuclear hydroxylated metabolite of fluradoline isolated from human urine samples.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727 or a Pye Unicam SP3-200 spectrophotometer; nuclear magnetic resonance spectra were taken at 200 MHz on a Varian XL-200 NMR spectrometer, and chemical shifts were given relative to internal tetramethylsilane. Mass spectra were obtained from a Finnigan Model 4000 spectrometer interfaced to a Finnigan 9610 gas chromatograph and equipped with an INCOS data system. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Thin layer chromatograms were run on silica gel PF-254 plates, and column chromatography was perfrormed using silica gel 60 (E. Merck, AG) or adsorption alumina (Fisher Scientific).

2-(4'-Fluorophenoxyl)-4-methoxybenzoic Acid (**5a**).

A mixture of 4-methoxysalicylic acid (**3a**) (16.8 g, 0.1 mole), 4-bromofluorobenzene (**4a**) (92 g, 0.5 mole), 10 g of cuprous chloride, 3.0 g of copper powder and 34.5 g of anhydrous potassium carbonate (0.25 mole) in 150 ml of dimethylformamide was refluxed for 5 days. The cooled mixture was diluted with 1200 ml of water, filtered with the aid of celite and extracted twice with ether. The aqueous solution was acidified cautiously with 12*N* hydrochloric acid and the oily precipitate slowly solidified upon standing. The crude product was extracted into ether, washed with water, and dried over magnesium sulfate. Removal of ether under reduced pressure left a semi-crystalline solid which was chromatographed over silica gel packed in dichloromethane. Elution with the same solvent afforded a main fraction (R_f = 0.4) which was crystallized from ether/hexane to give 10.0 g (38%) of **5a**, mp 150-151.5°; ir (chloroform): 3370, 1730 cm^{-1}; ms: (M^+) m/e 262; nmr (deuteriochloroform): δ 3.80 (s, 3, CH_3), 6.30 (d, 1, aromatic H), 6.67 (q, 1, aromatic H), 7.03-7.30 (m, 5, aromatic H).

Anal. Calcd. for $C_{14}H_{11}FO_4$: C, 64.12; H, 4.23. Found: C, 63.90; H, 4.23.

2-(4'-Fluorophenoxy)-5-methoxybenzoic Acid (**5b**).

A mixture of 5-methoxysalicylic acid (**3b**) (15.6 g, 93 mmoles), 4-fluoroiodobenzene (**4b**) (22.3 g, 100 mmoles), 0.45 g of copper powder, 0.25 g of cuprous iodide and 23.9 g of anhydrous potassium carbonate in 190 ml of sieve-dried dimethylformamide was stirred at reflux for 72 hours. The cooled mixture was diluted with ice water (800 g), filtered through Celite and extracted twice with ether to remove neutral substances. Acidification of the aqueous solution with 12*N* hydrochloric acid precipitated an oil which was again taken up in ether (3 × 300 ml). The combined organic solution was washed with water, dried and evaporated to give a brownish oil. The crude product, which was slightly contaminated with unreacted **3b**, was purified by column chromatography over silica gel, using 10% methanol/dichloromethane as eluant. Evaporation of the combined fractions containing the product (R_f = 0.5) afforded 11.3 g (46%) of **5b** as a white crystalline solid. Recrystallization from ether/hexane gave colorless prisms, mp 127-129°; ir (chloroform): 3340, 1730 cm^{-1}; ms: (M^+) m/e 262; nmr (deuteriochloroform): δ 3.86 (s, 3, CH_3), 6.83 (d, 1, aromatic H), 6.97-7.13 (m, 5, aromatic H), 7.68 (d, 1, aromatic H).

Anal. Calcd. for $C_{14}H_{11}FO_4$: C, 64.12; H, 4.23. Found: C, 64.11; H, 4.25.

2-(4'-Fluorophenoxy)-4-methoxyphenylacetonitrile (**7a**).

A solution of **6a** (8.5 g, 34.2 mmoles) in 100 ml of dichloromethane was treated dropwise with 5 ml of freshly distilled thionyl chloride, and the mixture was heated at reflux for 2 hours. The cooled solution was shaken with ice (20 g) and quickly dried over magnesium sulfate to avoid hydrolysis. Evaporation of solvent under reduced pressure left a viscous oil which was dissolved in 40 ml of dimethylsulfoxide and added dropwise to a slurry of 3.5 g of sodium cyanide in 30 ml of the same solvent. After stirring at room temperature for 17 hours the mixture was quenched with 500 ml of ice-water, the organics were extracted into ether, washed with water and dried over magnesium sulfate. Evaporation of ether left an oily residue which was over 95% in purity. Further purification by column chromatography over alumina packed ether afforded 6.0 g (68%) of pure **7a**; ir (chloroform): 2275 cm^{-1}; ms: (M^+) m/e 257; nmr (deuteriochloroform): δ 3.74 (s, 5, CH_2 and CH_3), 6.36 (d, 1, aromatic H), 6.68 (q, 1, aromatic H), 6.90-7.20 (m, 4, aromatic H), 7.40 (d, 1, aromatic H).

Anal. Calcd. for $C_{15}H_{12}FNO_2$: C, 70.02; H, 4.70. Found: C, 70.16; H, 4.87.

2-(4'-Fluorophenoxy)-5-methoxyphenylacetonitrile (**7b**).

In a similar manner **6b** (7.0 g, 28.2 mmoles) was converted to 6.1 g of **7b** (84%) as a viscous oil; ir (chloroform): 2275 cm^{-1}; ms: (MH^+) m/e 258; nmr (deuteriochloroform): δ 3.74 (s, 2, CH_2), 3.84 (s, 3, CH_3), 6.84-7.12 (m, 7, aromatic H).

Anal. Calcd. for $C_{15}H_{12}FNO_2$: C, 70.02; H, 4.70; N, 5.45. Found: C, 69.93; H, 4.90; N, 5.11.

2-(4'-Fluorophenoxy)-4-methoxyphenylacetic Acid (**8a**).

A mixture of **7a** (5.3 g, 20.6 mmoles), 2.0 g of 85% potassium hydroxide pellets in 20 ml of ethanol (95%) and 5 ml of water was heated under reflux for 16 hours. The solvents were evaporated with 200 ml of water and 150 of ether. The aqueous solution was acidified with 12*N* hydrochloric acid. The precipitated oil slowly solidified upon standing and was filtered, redissolved in ether and dried (magnesium suflate). Removal of ether afforded 3.8 g (67%) of **8a** as prisms from hexane, mp 94-95°; ir (chloroform): 3500, 2950, 1710 cm^{-1}; ms: (M^+) m/e 276; nmr (deuteriochloroform): δ 3.64 (s, 2, CH_2), 3.66 (s, 3, CH_3), 6.34 (d, 1, aromatic H), 6.64 (q, 1, aromatic H), 6.92-7.20 (m, 5, aromatic H), 7.24 (d, 2, aromatic H).

Anal. Calcd. for $C_{15}H_{13}FO_4$: C, 65.21; H, 4.74. Found: C, 65.18; H, 4.78.

2-(4'-Fluorophenoxy)-5-methoxyphenylacetic Acid (**8b**).

In a similar manner **7b** (5.8 g, 22 mmoles) was converted to 5.65 g (93%) of **8b** as prisms from ether/hexane, mp 89-90.5°; ir (chloroform): 3500, 3950, 1710 cm^{-1}; ms: (M^+) m/e 276; nmr (deuteriochloroform): δ 3.66 (s, 2, CH_2), 3.84 (s, 3, CH_3), 6.80-7.04 (m, 7, aromatic H).

Anal. Calcd. for $C_{15}H_{13}FO_4$: C, 65.21; H, 4.74. Found: C, 64.72; H, 4.72.

2-Fluoro-10,11-dihydro-7-methoxy-11-oxodibenz[*b,f*]oxepin (**9a**).

A mixture of **8a** (2.0 g, 7.2 mmoles) 30 ml of polyphosphoric acid and 100 ml of dichloroethane was stirred at reflux for 24 hours. The organic solution was decanted from the cooled mixture, diluted with ether (200 ml) and washed with 5% sodium bicarbonate. After drying (magnesium sulfate) and evaporation of solvents, there was obtained 1.6 g (86%) of **9a** which was recrystallized from hexane, mp 65-68°; ir (chloroform): 1680 cm^{-1}; ms: (M^+) m/e 258; nmr (deuteriochloroform): δ 3.80 (s, 3, CH_3), 4.00 (s, 2, CH_2), 6.72-6.88 (m, 2, aromatic H), 7.16-7.40 (m, 3, aromatic H) 7.72 (q, 1, aromatic H).

Anal. Calcd. for $C_{15}H_{11}FO_3$: C, 69.76; H, 4.30. Found: C, 69.45; H, 4.26.

2-Fluoro-10,11-dihydro-8-methoxy-11-oxodibenz[*b,f*]oxepin (**9b**).

A mixture of **8b** (5.5 g, 20 mmoles) in 50 ml of dichloromethane containing 2 ml of thionyl chloride was refluxed gently for 2 hours. The excess solvent and reagent were removed under reduced pressure at 50°, leaving a glassy residue. This was triturated with 100 ml of anhydrous hexane and the solution was again concentrated to dryness. The final residue was dissolved in 100 ml of sieve-dried dichloromethane and to it was added, in small portions, 3.0 g of aluminum chloride. The mixture was vigorously stirred and gas evolution was immediate.

After stirring at room temperature for 16 hours, the mixture was quenched with water and diluted with 30 ml of ether. The biphasic solution was filtered to remove a small amount of suspension and the layers were separated. The organic phase was washed twice with water. Drying over magnesium sulfate followed by concentration *in vacuo*, afforded a thick oil which was purified by passing through a short column of alumina packed in ether. Elution with an excess of ether gave, as the main product, 412 g (81%) of **9b** as a pale yellowish solid, mp 93.5-95°; ir (chloroform): 1680 cm^{-1}; ms: (M^+) m/e 258; nmr (deuteriochloroform): 3.80 (s, 3, CH_3), 4.08 (s, 2, CH_2), 6.62-6.88 (m, 2, aromatic H), 7.16-7.40 (m, 3, aromatic H), 7.72 (q, 1, aromatic H).

Anal. Calcd. for $C_{15}H_{11}FO_3$: C, 69.76; H, 4.30. Found: C, 69.71; H, 4.32.

2-Fluoro-7-methoxy-11-[β-(dimethylamino)ethylthio]diben[*b,f*]oxepin Maleate (**10a**).

A mixture of **9a** (1.2 g, 4.65 mmoles), 2.2 g of β-dimethylaminoethanethiol hydrochloride in 19 ml of glacial acid containing 6 ml of boron trifluoride etherate was stirred at 85° for 34 hours. The cooled mixture was diluted with 200 g of ice-water and treated cautiously with 20 ml of concentrated hydrochloric acid. The small amount of neutral material was removed by ether extraction, and basification of the aqueous solution with 20% sodium hydroxide afforded a viscous oil. The crude amine was taken up in ether (3 × 250 ml), washed with water and dried over magnesium sulfate. Removal of solvent left a yellowish oil which was essentially homogeneous by tlc. Further purification was affected by passing the material through a column of silica gel packed in dichloromethane, elution with 10% methanol/dichloromethane afforded analytically pure **10** (1.2 g, 60%) as a clear oil. This was converted to a crystalline maleate in ether, mp 106-107°; ms: (MH^+) m/e 346; nmr (deuteriochloroform): 2.74 (s, 6, NCH_3), 2.88-3.32 (m, 4, CH_2CH_2), 3.84 (s, 3, OCH_3), 6.28 (s, 2, =CH), 6.72-7.36 (m, 6, aromatic and pseudoaromatic H), 7.50 (q, 1, aromatic H).

Anal. Calcd. for $C_{23}H_{28}FNO_{10}$: C, 59.86; H, 5.24; N, 3.04. Found: C, 59.64; H, 5.19; N, 2.99.

2-Fluoro-8-methoxy-11-[β-(dimethylamino)ethylthio]dibenz[*b,f*]oxepin (**10b**).

In a similar manner **9b** (3.9 g, 15 mmoles) was converted to 3.0 g (58%) of **10b**. The free base was recrystallized from ether/hexane as colorless prisms, mp 105-106°; ms: (M^+) m/e 345; nmr (deuteriochloroform): 2.26 (s, 6, NCH_3), 2.52-2.82 (m, 4, CH_2CH_2), 3.78 (s, 3, OCH_3), 6.66 (d, 1, aromatic H), 6.82 (q, 1, aromatic H), 6.96-7.24 (m, 4, aromatic and pseudoaromatic H).

Anal. Calcd. for $C_{19}H_{20}FNO_2S$: C, 66.05; H, 5.84; N, 4.06. Found: C, 66.25; H, 5.90; N, 3.99.

2-Fluoro-7-methoxy-11-[β-(*N*-methyl-*N*-phenoxycarbonyl)ethylthio]diben-[*b,f*]oxepin (**11a**).

A solution of freshly distilled phenyl chloroformate (0.78 g) in 5 ml of dichloromethane was added to a stirred mixture of **10a** (1.0 g, 3.9 mmoles), 1.4 g of potassium carbonate in 5 ml of the same solvent. Stirring was continued at room temperature for 16 hours. The cooled mixture was equilibrated with ether and water, and the organic solution was washed and dried over magnesium sulfate. Evaporation of solvent under reduced pressure left a thick oil which was purified by column chromatography over silica. Elution with dichloromethane gave, as a clear oil, 1.2 g (92%) of **11a**; ir (chloroform); 1710 cm^{-1}; ms: (M^+) m/e 452; nmr (deuteriochloroform): 3.00 (s, 3, NCH_3), 2.88-3.12 (m, 2, SCH_2), 3.52-3.78 (m, 2, NCH_2), 3.8 (s, 3, OCH_3), 6.64-7.60 (m, 12, aromatic and pseudoaromatic H).

Anal. Calcd. for $C_{25}H_{22}FNO_4S$: C, 66.50; H, 4.91; N, 3.10. Found: C, 66.67; H, 5.10; N, 2.84.

2-Fluoro-8-methoxy-11-[β-(*N*-methyl-*N*-phenoxycarbonyl)ethylthio]dibenz[*b,f*]oxepin (**11b**).

In a similar manner **10b** (2.2 g, 6.4 mmoles) was converted to 1.65 g (58%) of **11b** as prisms from hexane, mp 109°; ir (chloroform): 1710 cm^{-1} ms: (M^+) m/e 345.

Anal. Calcd. for $C_{25}H_{22}FN_4S$: C, 66.50; H, 4.91; N, 3.10. Found: C, 66.29; H, 4.81; N, 2.99.

2-Fluoro-7-hydroxy-11-[β-(methylamino)ethylthio]dibenz[*b,f*]oxepin (**2a**).

To a solution of **11a** (1.0 g, 2.2 mmoles) in 5 ml of dichloromethane was added dropwise 4 ml of 1*M* boron tribromide in the same solvent (Aldrich Chemical Co.). After stirring at room temperature for 16 hours, the mixture was equilibrated with 20 ml of ether and 10 ml of 2*N* hydrochloric acid and stirring was continued for one additional hour. The layers were separated and the organic phase was washed with water, dried (magnesium sulfate) and concentrated to a brownish oil. This material was shown to be homogeneous by thin layer chromatography (silica gel, 50:50 ether/dichloromethane, R_f = 0.82), its mass spectrum gave a molecular ion peak at m/e 435.

The phenolic carbamate so obtained (0.5 g) was dissolved in 3 ml of ethylene glycol and heated at 150° with 1.0 g of potassium hydroxide (85%) in 2 ml of water with vigorous stirring. The cooled mixture was diluted with 100 ml of water and acidified to *p*H = 2 with concentrated hydrochloric acid. The neutral and acidic components were removed by ether extraction, this was followed by saturation of the aqueous solution with solid potassium carbonate. The separated amine was taken up in a large excess of chloroform, washed and dried over magnesium sulfate. Evaporation of solvent under reduced pressure gave a crystalline solid which was recrystallized from acetone/hexane to give 185 mg (27%) of **2a** as rhombic crystals, mp 181-182° dec; ir (potassium bromide): 3440, 3300 cm^{-1}; ms: (M^+) m/e 317; nmr (deuteriochloroform): δ 2.52 (s, 3, CH_3), 2.90 (broad s, 4, CH_2CH_2), 6.48 (q, 1, aromatic H), 6.58 (d, 1, aromatic H), 6.71 (d, 1, aromatic H), 6.96-7.30 (m, 3, aromatic and pseudoaromatic H), 7.48 (q, 1, aromatic H).

Anal. Calcd. for $C_{17}H_{16}FNO_2S$: C, 64.33; H, 5.08; N, 4.41. Found: C, 64.22; H, 5.40; N, 4.25.

2-Fluoro-8-hydroxy-11-[β-(methylamino)ethylthio]dibenz[*b,f*]oxepin (**2b**).

In a similar manner **11b** (2.1 g, 4.8 mmoles) was converted to 750 mg (49%) of **2b** as rhombic crystals, mp 159-160°; ir (potassium bromide): 3430, 3280 cm^{-1}; ms (M^+) m/e 317; nmr (deuteriochloroform): δ 2.44 (s, 3, CH_3), 2.88 (s, 4, CH_2CH_2), 6.58 (d, 1, aromatic H), 6.76 (q, 1, aromatic H), 7.00-7.30 (m, 3, aromatic and pseudoaromatic H), 7.48 (q, 1, aromatic H).

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REFERENCES AND NOTES

[1] H. H. Ong, J. A. Profitt, V. B. Anderson, T. C. Spaulding, J. C. Wilker and H. M. Geyer, III, *J. Med. Chem.*, **23**, 494 (1980).

[2] After proper preparation of human urine or plasma samples, high performance liquid chromatography was used to separate and quantitate the metabolites. Repetitive injection of these samples on an analytical hplc column permitted isolation of the major metabolites in sufficient quantities to obtain mass spectral information and in many cases elucidate the structure. J. K. Wichmann, L. Godell, R. S. Hsu, J. Vogel, M. N. Agnew, H. H. Ong and D. B. Ellis, *Prog. and Abstr. Acad. Pharm. Sci. 37th National Meeting*, **14** (2), 247 (1984).

[3] C. J. Pouchart, "The Aldrich Library of NMR Spectra", Ed II, Vol 1, Adrich Chemical Company, Inc, Milwaukee, Wisconsin, 1983, pp

881-884.

[4] S. Archer, A. Zayed, R. Rej and T. A. Rugino, *J. Med. Chem.*, **26**, 1240 (1983).

[5] In a somewhat analogous manner, attempts to cyclize 4-(2-carboxy-4-methoxybenzyloxy)phenylacetic acid by the intramolecular Friedel-Crafts reaction ($SOCl_2$, $AlCl_3$) resulted in the formation of 3-methoxyphthalide, possibly through a similar quinoid intermediate; private communications, R. C. Allen and G. M. Shutske.

[6] H. H. Ong, J. A. Profitt, V. B. Anderson, T. C. Spaulding, J. C. Wilker and H. M. Geyer, III, *J. Med. Chem.*, **25**, 1150 (1982).