# A Synthesis of the C-10,11 Sulfur Isosteres of Cholanthrene and 3-Methylcholanthrene (1)

*E. Campaigne, John Ashby, and G. F. Bulbenko (2)*

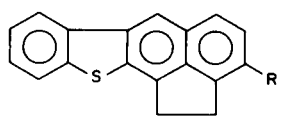
The Chemistry Laboratories, Indiana University

Interest in the synthesis and biological evaluation of the isosteres of carcinogenic natural products (3) has led to a recent synthesis of the C-10,11 sulfur isosteres (Ia and Ib) of cholanthrene and 3-methylcholanthrene by Faller (4). We had previously synthesized these compounds by an alternate route as outlined below (2).

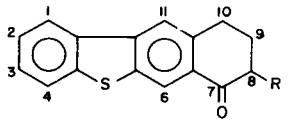
7-Keto-7,8,9,10-tetrahydrobenzo[*b*]naphtho[2,3-*d*]-thiophene (IIa) (5) and 7-keto-8-methyl-7,8,9,10-tetrahydrobenzo[*b*]naphtho[2,3-*d*]thiophene (IIb) (6) have been reported, however the position of the methyl group in IIb (8 or 9) was not rigorously proven. Comparison of the 100 MHz nmr spectra of two derived benzonaphthothiophenes (III and IV) (6) confirms the original structure assignment of IIb. In the spectrum (6) of 8-methylbenzo[*b*]naphtho[2,3-*d*]thiophene (III) a doublet for H-10 was observed along with a broadened doublet for H-9 and a broadened singlet (J = 1 Hz) for H-7. In the spectrum (6) of 7,8-dimethylbenzo[*b*]naphtho[2,3-*d*]thiophene (IV) the broadened singlet associated with H-7 in III is absent and sharp doublets for H-9 and H-10 are observed. Had the methyl group in IIb been positioned at C-9, methylation of the ketone function and subsequent aromatization would have produced broadened singlets for H-8 and H-10 in IV.

The synthetic approach was to produce a carboxymethyl side chain at the 7-position of II in order to proceed with ring closure to the acenaphthene type structure of Ia and Ib, the required isosteres. Both IIa and IIb condensed readily with methyl bromoacetate under Reformatsky conditions. The intermediate hydroxy esters were dehydrated with formic acid yielding the esters Va and Vb, respectively. The double bonds are shown to be *endo*-cyclic on the basis of evidence discussed below. Basic hydrolysis of Va gave a single acid in high yield formulated as VIa. In contrast hydrolysis of Vb gave two acids separated by fractional crystallization in approximately equal amounts. The lower melting acid was assigned structure VIb and the other structure VII. Comparison of the ultraviolet spectra of compounds VIa and VIb (Figure 1) revealed a close similarity with the model compound VIII (6). The spectrum of VII was markedly different from the others showing in particular a strong band at 278 mμ associated with conjugation of the carbonyl function with the aromatic nucleus. A similar absorption is observed with both *cis* and *trans*-cinnamic acid (268 and 272 mμ, respectively), and addition of 5 mμ for a β-alkyl substituent (7) gives a calculated value of about 277 mμ for VII.

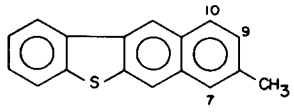
The esters Va and Vb were aromatized with palladium on charcoal and the ester functions subsequently hydrolysed with methanolic potassium hydroxide yielding 7-carboxymethylbenzo[*b*]naphtho[2,3-*d*]thiophene (IXa) and its 8-methyl homolog (IXb). The acids (IX) were converted to their respective acid chlorides with phosphorus pentachloride and cyclized under Friedel-Crafts



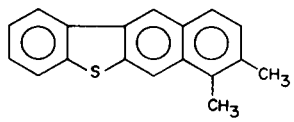
Ia, R = H
Ib, R = $CH_3$



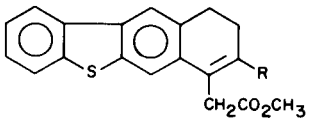
IIa, R = H
IIb, R = $CH_3$



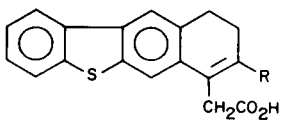
III



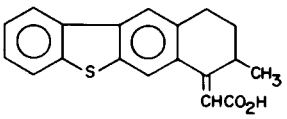
IV



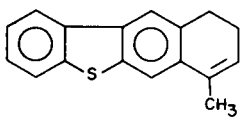
Va, R = H
Vb, R = $CH_3$



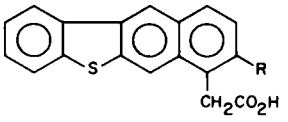
VIa, R = H
VIb, R = $CH_3$



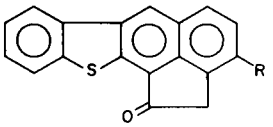
VII



VIII



IXa, R = H
IXb, R = $CH_3$



Xa, R = H
Xb, R = $CH_3$

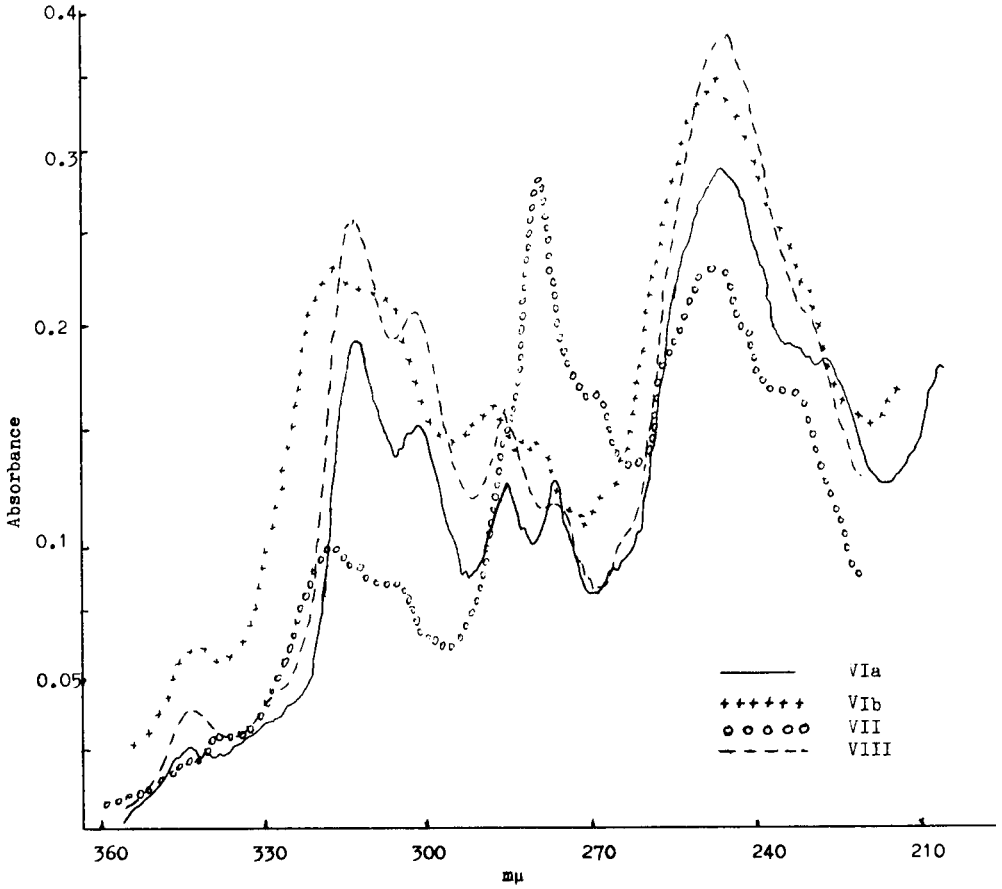



Figure 1. Ultraviolet spectra of compounds VIa, VIb, VII, and VIII taken in 95% ethanol at uniform concentration of 0.0025 g./l.

conditions using aluminum chloride yielding 1-ketobenzo[*b*]acenaphtho[4,3-*d*]thiophene (Xa) and its 3-methyl homolog (Xb). Reduction of the ketone moiety of X gave benzo[*b*]acenaphtho[4,3-*d*]thiophene (Ia) and its 3-methyl homolog (Ib) the desired isosteres.

## EXPERIMENTAL

Melting points were determined in a stirred oil bath and are uncorrected. Ultraviolet spectra were determined in 95% ethanol on a Beckman DK-1 Spectrometer. Magnesium sulfate was used as a drying agent throughout.

7-Carbomethoxymethyl-9,10-dihydrobenzo[*b*]naphtho[2,3-*d*]-thiophene (Va).

A solution of the ketone IIa (2 g., 0,008 mole) in dry benzene (20 ml.) was added with stirring to a mixture of zinc dust (4 g.), iodine (0.1 g.) and methyl bromoacetate (2 ml.) suspended in dry ether (20 ml.). The mixture was refluxed for 6 hours and filtered hot. The filtrate was hydrolysed with dilute sulfuric acid and the organic layer separated, washed with sodium carbonate (5%) and with water and dried. Removal of the solvent gave the intermediate hydroxy compound as a pale yellow oil. The oil was stirred with 98% formic acid (5 ml.) at 100° for 5 minutes and excess formic acid removed in an air stream. The resulting green oil solidified upon cooling and crystallization from aqueous methanol gave the product Va as needles (1.73 g., 71%) m.p. 82-84°; U.V. λ max (ethanol) 313 (log ε = 4.36), 302 (4.24), 285 (4.09) and 245 mμ (4.48).

*Anal.* Calcd. for $C_{19}H_{16}O_2S$: C, 74.0; H, 5.2. Found: C, 74.2; H, 5.6.

7-Carbomethoxymethyl-8-methyl-9,10-dihydrobenzo[*b*]naphtho-[2,3-*d*]thiophene (Vb).

This was prepared from the ketone IIb as described above. The product Vb crystallized from methanol (55%) m.p. 91-91.5°; U.V. λ max (ethanol) 314 (log ε = 4.37), 304 (4.31), 285 (4.20), 278 (4.20) and 245 (4.58).

*Anal.* Calcd. for $C_{20}H_{18}O_2S$: C, 74.5; H, 5.6. Found: C, 74.3; H, 5.5.

7-Carboxymethyl-8,9-dihydrobenzo[*b*]naphtho[2,3-*d*]thiophene (VIa).

The ester Va (1 g., 0.00325 mole) was refluxed in 10% potassium hydroxide for 1 hour. The resulting solution was diluted with water and acidified with diluted sulfuric acid yielding 0.8 g., (84%) of VIa. Recrystallization from benzene gave needles, m.p. 180-181°.

*Anal.* Calcd. for $C_{18}H_{14}O_2S$: C, 73.5; H, 4.8. Found: C, 73.4; H, 4.8.

7-Carboxymethylidene-8-methyl-9,10-dihydrobenzo[*b*]naphtho-[2,3-*d*]thiophene (VII).

The ester Vb (1 g., 0.0031 mole) was refluxed for 1 hour in 10% potassium hydroxide. The resulting solution was evaporated to dryness, extracted with water and acidified with dilute sulfuric acid. The precipitated mixture of acids (0.88 g., 92%) had m.p. 210-220°. The mixture was crystallized 3 times from benzene and once from aqueous methanol yielding VII (0.39 g., 41%) m.p. 232-233°.

*Anal.* Calcd. for $C_{19}H_{16}O_2S$: C, 74.0; H, 5.2. Found: C, 74.3; H, 5.2.

The combined filtrates from the above recrystallizations were evaporated and the residue crystallized from aqueous ethanol yielding 7-carboxymethyl-8-methyl-9,10-dihydrobenzo[*b*]naphtho-[2,3-*d*]thiophene (VIb) (0.316 g., 33%) m.p. 188°.

*Anal.* Calcd. for $C_{19}H_{16}O_2S$: C, 74.0; H, 5.2. Found: C, 74.1; H, 5.1.

7-Carbomethoxymethylbenzo[*b*]naphtho[2,3-*d*]thiophene.

A solution of the ester Va (1 g., 0.00325 mole) in xylene (60 ml.) was refluxed with palladium on charcoal (5%) (1 g.) for 8 hours. The catalyst was removed by filtration and the filtrate refluxed with a further portion of catalyst (1 g.) for 3 hours. Removal of the solvent gave an oil which crystallized from methanol yielding the product as plates (0.8 g., 80%) m.p. 98-99°.

*Anal.* Calcd. for $C_{19}H_{14}O_2S$: C, 74.5; H, 4.6. Found: C, 74.2; H, 4.9.

7-Carbomethoxymethyl-8-methylbenzo[*b*]naphtho[2,3-*d*]thiophene.

This was prepared from the ester Vb as described above with the exception that the second reflux period was extended to 11 hours. The product crystallized from acetone-methanol (80%) m.p. 181-182°.

*Anal.* Calcd. for $C_{20}H_{16}O_2S$: C, 75.0; H, 5.0. Found: C, 74.8; H, 5.1.

7-Carboxymethylbenzo[*b*]naphtho[2,3-*d*]thiophene (IXa).

A solution of 7-carbomethoxymethylbenzo[*b*]naphtho[2,3-*d*]-thiophene (2.27 g., 0.0074 mole) in methanol (25 ml.) was refluxed with aqueous potassium hydroxide (45%, 15 ml.) for 2 hours. The methanol was distilled and the remaining solutions diluted with water (80 ml.) and acidified with dilute sulfuric acid. The resultant precipitate was filtered and crystallized from benzene (1.8 g., 83%) m.p. 214-216°.

*Anal.* Calcd. for $C_{18}H_{12}O_2S$: C, 74.0; H, 4.1. Found: C, 73.8; H, 4.2.

7-Carboxymethyl-8-methylbenzo[*b*]naphtho[2,3-*d*]thiophene (IXb).

This acid was prepared from its ester as described above, and crystallized from benzene (81%) m.p. 263-265°.

*Anal.* Calcd. for $C_{19}H_{14}O_2S$: C, 74.5; H, 4.6. Found: C, 74.6; H, 4.3.

1-Ketobenzo[*b*]acenaphtho[4,3-*d*]thiophene (Xa).

A mixture of the acid IXa (2.3 g., 0.0078 mole) and phosphorus pentachloride (1.7 g.) in dry benzene (30 ml.) was refluxed for 0.5 hour and the solvent removed under reduced pressure. The residue was dissolved in carbon disulfide (40 ml.) and aluminum chloride (3.7 g.) added in one portion with stirring. The mixture was gently refluxed for 2 hours and poured over ice. The carbon disulfide was allowed to evaporate and the aqueous suspension extracted with hot benzene (3 x 25 ml.). Reduction in volume gave the product (1.4 g., 63%) m.p. 220-230°. A further recrystallization from benzene gave needles m.p. 235-236°.

*Anal.* Calcd. for $C_{18}H_{10}SO$: C, 78.9; H, 3.7. Found: C, 78.6; H, 3.9.

1-Keto-3-methylbenzo[*b*]acenaphtho[4,3-*d*]thiophene (Xb).

This was prepared from the acid IXb as described above. The crude product (66%) was eluted with benzene through a short alumina column and crystallized from ethanol as orange needles m.p. 260-261°.

*Anal.* Calcd. for $C_{19}H_{12}OS$: C, 79.1; H, 4.2. Found: C, 79.0; H, 4.0.

Benzo[*b*]acenaphtho[4,3-*d*]thiophene (Ia).

A solution of the ketone Xa (0.4 g., 0.00146 mole) in diethylene glycol (85 ml.) and acetic acid (2 ml.) was refluxed with hydrazine hydrate (85%, 12 ml.) at 150° for 2 hours. The temperature was then raised to 200° and the mixture refluxed for a further 2 hours. After cooling the mixture was added to a solution of sodium methoxide (13 g.) in diethylene glycol (100 ml.) and the mixture maintained at 200° for 2 hours. Upon cooling the mixture was diluted with water and the resultant precipitate collected (0.35 g.) m.p. 155-159°. A benzene solution of the product was passed down a short alumina column and crystallized from ethanol as orange needles (0.23 g., 62%) m.p. 165-166°, (Ref. (4) m.p. 161-162°).

*Anal.* Calcd. for $C_{18}H_{12}S$: C, 83.1; H, 4.65. Found: C, 82.9; H, 4.7.

3-Methylbenzo[*b*]acenaphtho[4,3-*d*]thiophene (Ib).

This was prepared from the ketone Xb by the method described above. The product crystallized from alcohol (62%) m.p. 188°, (Ref. (4) m.p. 189°).

*Anal.* Calcd. for $C_{19}H_{14}S$: C, 83.2; H, 5.1. Found: C, 83.3; H, 5.3.

The picrate had m.p. 182-185° (Ref. (4) m.p. 178-179°).

## REFERENCES

(1) Contribution No. 1862 from the Chemistry Laboratories of Indiana University, supported in part by Research Grant C-1948C from the National Cancer Institute, and in part by Grant GM-10366 of the National Institute of Health. Presented in part before the Division of Medicinal Chemistry, 133 National Meeting of the American Chemical Society, April 13, 1958, in San Francisco (abstracts, p 6 M).

(2) Taken in part from a thesis submitted by G.F.B. for the degree of Doctor of Philosophy at Indiana University, 1958.

(3) E. Campaigne and J. Ashby, *J. Heterocyclic Chem.*, 6, 875 (1969) and references cited therein.

(4) P. Faller, *Compt. Rend.*, 252, 1034 (1961) and *Bull. Soc. Chim. France*, 11, 3618 (1966).

(5) N. P. Buu-Hoi and P. Cagnaiant, *Chem. Rev.*, B76, 1269 (1943) and E.G.G. Werner, *Rec. Trav. Chim.*, 68, 520 (1949).

(6) E. Campaigne, J. Ashby and S. W. Osborn, *J. Heterocyclic Chem.*, 6, 885 (1969).

(7) R. B. Woodward, *J. Am. Chem. Soc.*, **64**, 72 (1942).

Received June 10, 1970 Bloomington, Indiana 47401