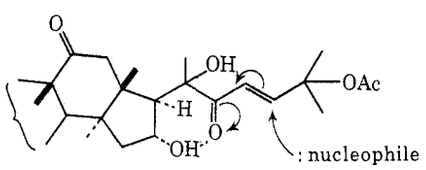
Fabacein showed relatively low cytotoxicity (ED_{50} = 1 μg/ml) toward human carcinoma of the nasopharynx in tissue culture (KB),[10] in contrast with the potent cytotoxicity shown by cucurbitacin B ($ED_{50} \cong 10^{-6}$ μg/ml).[5] Earlier studies in this laboratory have demonstrated the importance of highly electrophilic conjugated systems in relation to the cytotoxicity of several classes of terpenoids.[11] Saturation of the conjugated Δ^{23} double bond in the cucurbitacins is accompanied by a profound lessening in cytotoxicity of the resultant dihydrocucurbitacin derivatives.[5,6] Consequently, reactions of the side chain conjugated ketone with biological macromolecules may play an important role in the mechanism by which cucurbitacins exert their cytotoxic effects. The marked diminution in cytotoxicity which accompanies the acetylation of the C-16 hydroxyl group of cucurbitacin B suggests that the free hydroxyl group may be important for the reactivity of the conjugated ketone. Thus, hydrogen-bonding interaction between the C-16 hydroxyl group and the C-22 ketone could activate the α,β-unsaturated ketone toward nucleophilic attack by a biological macromolecule, as shown. The lessened cytotoxicity



of fabacein, then, may result from the diminished reactivity of the conjugated ketone in the C-16 acetate ester.

Experimental Section

Melting points were determined on a Mettler FP2 melting point apparatus. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Ultraviolet spectra were recorded on a Coleman Hitachi EPS-3T recording spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates HA-100 spectrometer using TMS as an internal standard. Mass spectra were recorded on either Hitachi Perkin-Elmer RMU-63 or AEI MS-902 spectrometers, equipped with direct insertion probes. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Acetylation of Fabacein to Triacetate 3.—A solution of fabacein[4] (1, 12 mg) in anhydrous pyridine (0.5 ml) was treated with acetic anhydride (0.5 ml). The reaction mixture was stirred overnight at room temperature under nitrogen. The solution was evaporated *in vacuo* and the residue was dissolved in ethanol and reevaporated. The oily residue (12 mg) was separated by preparative tlc on Brinkmann Silplates with 1% methanol–chloroform. The major band was eluted with ethyl acetate. Attempts to crystallize the product were unsuccessful. The amorphous product (**3**, 10 mg) showed R_f 0.68 on Brinkmann Silplates with 2% methanol–chloroform; R_f 0.80 on ChromAr plates with 1% methanol–ether; R_f 0.70 on polyamide plates with 70% methanol–water; uv ($CHCl_3$) 230 nm (ε 10,000); $[\alpha]^{25}D$ +2.5° (*c* 3.60, $CHCl_3$); ir ($CHCl_3$) 2.92, 3.36, 3.43, 5.76, 5.92, 6.15, 7.38, 8.09, and 9.70 μ; nmr ($CDCl_3$) τ 2.94 (1 H, d, J = 16 Hz), 3.66 (1 H, d, J = 16 Hz), 4.32 (1 H, m), 4.62 (1 H, d of d, J = 14, 5 Hz), 4.90 (1 H, b t, J = 8 Hz), 5.80 (1 H, s), 7.92 (3 H, s), 8.04 (3 H, s), 8.19 (3 H, s), 8.46 (6 H, s), 8.62 (3 H, s), 8.72 (3 H, s), 8.94 (3 H, s), and 9.01 (3 H, s); mass spectrum *m/e* 582, 412, 385, 325, 189, 112, 111, 96, and 43.

Acetylation of Cucurbitacin B to Triacetate 3.—Cucurbitacin B (**2**, 40 mg) was acetylated as above. The product obtained after preparative tlc (35 mg) showed the same rotation, ir, uv, nmr, mass spectrum, and R_f values as the product (**3**) of acetylation of fabacein (**1**).

Solvolysis of Triacetate 3 to Fabacein (1).—A solution of triacetate **3** (30 mg) in 10% aqueous methanol (0.5 ml) was treated with triethylamine (4 drops) and allowed to stand overnight at room temperature. The solution was evaporated *in vacuo*. The major component (21 mg), obtained by preparative tlc on Brinkmann Silplates with 2% methanol–chloroform, was crystallized from dichloromethane–absolute ethanol. The product (10 mg), mp 197–200°, was characterized as fabacein (**1**) by mixture melting point, ir, uv, nmr, mass spectrum, and tlc comparisons with an authentic sample.

Registry No.—**1**, 37710-13-7; **2**, 6199-67-3; **3**, 37710-14-8.

(10) Cytotoxicity was assayed, under the auspices of the National Cancer Institute, by the procedure described in *Cancer Chemother. Rep.*, **25**, 1 (1962).

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Benzo[*b*]thiophenes from Thiophenes. A Facile Approach

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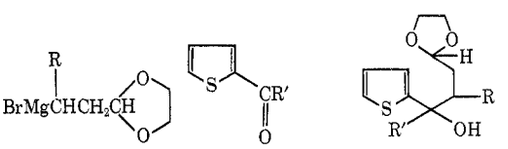
Benzo[*b*]thiophenes are generally synthesized by ultimate construction of the thiophene component onto thiophenol precursors. The alternative approach, *i.e.*, annellation of the benzene ring on preformed thiophenes, appears to have received scant attention.[1] Elaboration of such a route is herein described and is exemplified by the preparation of compounds **4a–d**, **4f–h**, and **5**.

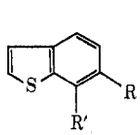
Grignard reagent **1a** has recently attracted attention



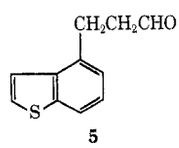
1a, R = H
b, R = CH_3

2a, R′ = H
b, R′ = CH_3
c, R′ = C_2H_5
d, R′ = *i*-C_3H_7
e, R′ = *t*-C_4H_9
f, R′ = OC_2H_5

3a, R = R′ = H
b, R = H; R′ = CH_3
c, R = H; R′ = C_2H_5
d, R = H; R′ = *i*-C_3H_7
e, R = H; R′ = *t*-C_4H_9
f, R = R′ = CH_3
g, R = CH_3; R′ = C_2H_5
h, R = H; R′ = $CH_2CH_2CHOCH_2CH_2O$



4a, R = R′ = H
b, R = H; R′ = CH_3
c, R = H; R′ = C_2H_5
d, R = H; R′ = *i*-C_3H_7
f, R = R′ = CH_3
g, R = CH_3; R′ = C_2H_5
h, R = H; R′ = CH_2CH_2CHO



5

as a synthetic tool.[2] We chose to treat it with thiophenes **2a–e**. Products **3a–d** were subsequently submitted to the action of 10% refluxing H_2SO_4; this brought about hydrolysis, cyclization, and aromatization and produced benzo[*b*]thiophenes **4a–d** in 60–70%

(1) B. Iddon and R. M. Scrowston in "Advances in Heterocyclic Chemistry," Vol. 11, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1970, pp 177–381.

(2) G. Buchi and H. Wuest, *J. Org. Chem.*, **34**, 1121 (1969).

TABLE I

BENZO[b]THIOPHENES[a]

Compd	Yield,[b] %	Bp, °C (mm)	Deriv	Mp, °C	Empirical formula
4a	68	...[c]	Picrate	148–149	C_8H_6S
4b[d]	61	79–84 (4)	Picrate	140–144	C_9H_8S
4c	70	88–91 (5)			$C_{10}H_{10}S$
4d	64	106–109 (4)			$C_{11}H_{12}S$
4f[e]	42	110–115 (4)	Picrate	118–122	$C_{10}H_{10}S$
4g	44	116–122 (4)	Picrate	102–104	$C_{11}H_{12}S$
4h	90[f]	110–115 (0.05)[g]	Semicarbazone	176–178	$C_{11}H_{10}OS$

[a] Satisfactory analytical data (0.3 for C, H, N) for benzo[b]thiophenes 4c and 4d and the indicated derivatives of 4b, 4f, 4g, and 4h are reported. [b] Isolated material, purity >95% (nmr) and based on thiophene component. [c] Steam distilled out of reaction mixture. [d] A. V. Sunthankar and B. D. Tilak, *Proc. Indian Acad. Sci., Sect. A*, **32**, 390 (1950); *Chem. Abstr.*, **47**, 12346*d* (1953). [e] M. Pailer and E. Romberger, *Monatsh. Chem.*, **91**, 1070 (1960). [f] Yield based on purified 3h. [g] Nmr δ 2.5–3.3 (m, 4, aliphatic H), 6.80–7.57 (m, 5, aromatic H), 9.50 (t, 1, CHO); ir $\nu_{C=O}$ 1720 cm^{-1}.

overall yields. Attempts to effect such a transformation on **3e** gave complex mixtures of rearranged materials. Furthermore, variation of the Grignard component made possible the preparation of disubstituted systems. For example **1b**, upon reaction with **2b** and **e**, gave products **3f** and **g**, which, in turn, furnished **4f** and **g**.

Efforts aimed at extending the method led us to prepare benzo[b]thiophenes bearing ready-made functionalized side chains at C_4 and C_7. To this end, thiophene **2f** was treated with 2 equiv of **1a**, whereupon the product (**3h**) was cleanly converted in refluxing acid into aldehyde **4h**. Similarly, the 4-substituted isomer (**5**) was obtained by cyclization of the adduct of 2 equiv of **1a** and ethyl thiophene-3-carboxylate.

Experimental Section

General.—Melting points were determined on a Mettler apparatus and are uncorrected. Nmr data (Varian A-60, TMS as internal standard) were consistent with assigned structures. The intermediate crude oils **3a–g** were characterized solely by means of nmr and were converted as is into the products offered in Table I. Microanalyses were performed in our laboratories by Messrs. P. van den Bosch and H. Eding.

Starting Materials.—The required thienyl ketones were made by $SnCl_4$-promoted acylation of thiophenes as described for **2b**:[3] ethyl 2-thienyl ketone,[4] bp 102–104° (13 mm); isopropyl 2-thienyl ketone,[5] bp 104–106° (13 mm); and *tert*-butyl 2-thienyl ketone, bp 78–81° (3 mm), yield 61% (*Anal.* Calcd for $C_9H_{12}OS$: C, 64.25; H, 7.19. Found: C, 64.23; H, 7.25.) [nmr δ 1.31 (s, 9, *tert*-butyl). 6.94, (m, 1, H_4 thienyl proton), 7.39 (d, 1, H_5 thienyl proton), 7.62, (d, 1, H_3 thienyl proton)]. Ethyl thiophene-3-carboxylate was prepared from 3-bromothiophene.[6a,b] 2-(2-Bromopropyl)-1,3-dioxolane was prepared from crotonaldehyde, ethylene glycol, and HBr[7] and was then converted into **1b** using conditions described for **1a**.[2]

The preparation of the benzo[b]thiophenes is illustrated by the synthesis of **4d**.

7-Isopropylbenzo[b]thiophene (4d).—To a solution of **1a**, prepared from 1.6 g (0.065 g-atom) of Mg and 12.3 g (0.065 mol) of 2-(2-bromoethyl)-1,3-dioxolane in 50 ml of THF,[2] was added dropwise a solution of 5.1 g (0.036 mol) of **2d** in 20 ml of Et_2O. After 2 hr the mixture was poured onto 10% NH_4Cl solution, which was extracted with Et_2O. The organic phase, upon drying (Na_2SO_4) and solvent removal left 8.3 g (90%) of oily **3d**: nmr δ 0.87 (2d, 6, *i*-C_3H_7), 2.93 (s, 1, OH), 3.80 (m, 4, dioxolane protons). It was added slowly to 150 ml of refluxing 10% H_2SO_4. After 1 hr, the product was extracted into Et_2O, which was then scrubbed ($NaHCO_3$), dried, and evaporated to leave an oily residue. Fractionation thereof afforded 3.6 g of **4d** (64% based on **2d**), bp 106–109° (4 mm).

1,5-Di(1,3-dioxolan-2-yl)-3-hydroxy-3-(2-thienyl)pentane (3h).—This compound, mp 48–49° [(*i*-Pr)$_2$O], was prepared in 80% yield by treating **2f** with 2 equiv of **1a** as described above, nmr δ 3.50 (s, 1, OH). *Anal.* Calcd for $C_{15}H_{22}O_5S$: C, 57.30; H, 7.05. Found: C, 57.32; H, 7.03.

3-(4-Benzo[b]thienyl)propionaldehyde (5).—This compound, prepared from ethyl thiophene-3-carboxylate and 2 equiv of **1a**, followed by acid treatment of the resulting oil, was obtained in 40% yield, bp 126–128° (0.01 mm): nmr δ 9.58 (t, 1, CHO); ir $\nu_{C=O}$ 1720 cm^{-1}. The semicarbazone was prepared in alcohol and melted at 186–187°. *Anal.* Calcd for $C_{12}H_{13}N_3OS$: C, 58.28; H, 5.30; N, 16.93. Found: C, 57.91; H, 5.40; N, 16.93.

Registry No.—**1a**, 37610-80-3; **1b**, 37610-86-9; **2a**, 98-03-3; **2b**, 88-15-3; **2c**, 13679-75-9; **2d**, 36448-60-9; **2e**, 20409-48-7; **2f**, 2810-04-0; **3a**, 37610-85-8; **3b**, 37610-87-0; **3c**, 37610-88-1; **3d**, 37610-89-2; **3f**, 37610-90-5; **3g**, 37610-91-6; **3h**, 37610-92-7; **4a**, 95-15-8; **4a** picrate, 4500-67-8; **4b**, 14315-15-2; **4b** picrate, 37610-95-0; **4c**, 16587-42-1; **4d**, 37610-97-2; **4f**, 37610-98-3; **4f** picrate, 37610-99-4; **4g**, 37611-00-0; **4g** picrate, 37611-01-1; **4h**, 37611-02-2; **4h** semicarbazone, 37611-03-3; **5**, 37611-04-4; **5** semicarbazone, 37614-49-6.

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Reactivity of First-Singlet Excited Xanthene Laser Dyes in Solution

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The useful lifetimes of xanthene laser dyes are limited primarily by an apparently irreversible photochemical reaction.[1] We report quantum efficiencies and photoproduct absorption spectra for this reaction.

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