Decarboxylation of a Benzo[*b*]thiophene-2-carboxylic Acid (1)

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5-Hydroxy-3-methylbenzo[*b*]thiophene-2-carboxylic acid can be decarboxylated by refluxing with 48% hydrobromic acid for 30 minutes. Yield and quality of the product are better than for the previously used copper-quinoline decarboxylation. The 5-methoxy analog of the above acid is stable to decarboxylation under these conditions; however, it demethylates readily under the reaction conditions, and the phenol thus afforded decarboxylates.

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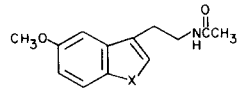
Indole messenger substances have been intensively studied for both their modes of action and the physiological responses they elicit (2). A useful tool in these studies has been the use of isosteric heterocycles and analogs (3). Application of this strategy to the pineal hormone melatonin (**1**) has led to interest in its benzothiophene isostere **2** (3,4).

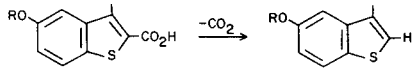
In connection with efforts to synthesize analogs of **2**, we have investigated selected aspects of the synthesis of **2** reported by Campaigne and coworkers (5). A portion of our efforts have focussed upon the decarboxylation of **3** to give 3-methyl-5-hydroxybenzo[*b*]thiophene (**4**), a key intermediate in the Campaigne scheme (5). In our hands, decarboxylation of **3** with copper and quinoline (5a) suffered only modest and poorly reproducible yields (20-40%), besides entailing a laborious workup and purification. We postulated that the poor yield was due to interaction of the phenol with the copper or cuprous ion catalyst (6) of the decarboxylation reaction, a contention which is supported by the excellent yields obtained in similar systems (7) not bearing this functional group.

Aromatic acids bearing electron-releasing substituents have been reported to undergo smooth decarboxylation in boiling 48% hydrobromic acid (8). Under these conditions, **3** reacts rapidly to give **4** as the sole product in *ca.* 60% yield. While only a modest improvement in yield is obtained, this method offers a greatly simplified extractive workup compared to the method of Campaigne, *et al.*, (5a).

Since the ultimate goal of the synthetic sequence was the methoxy derivative **2**, we examined the reaction of the methyl ether **5** in hopes that a later etherification (5c) might be obviated. While we anticipated some demethylation of the ether (9), we were surprised to find that none of the desired **6** was detectable. Instead, **4** was isolated in poor yield, together with a second, unidentified phenol. These results, together with the remarkable stability of **5** to decarboxylation under these conditions (38% recovered after 1 hour), suggest that the reaction may be highly specific for the hydroxylated benzothiophene. To elucidate this point and to establish a mechanistic rationale for these observations are the subjects of our continuing studies.



1, X = N-H
2, X = S



3, R = H
5, R = CH_3

4, R = H
6, R = CH_3

EXPERIMENTAL

General.

Melting points were determined using a Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded as mineral oil mulls using a Beckman Acculab 4 instrument; nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R24-B spectrometer, using acetone-d_6 as the solvent and tetramethylsilane as the internal standard. Spectra of previously reported substances were identical to those of authentic samples prepared in the laboratories of E. Campaigne (10). Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Reagents for syntheses were obtained from Aldrich, and were used as supplied. Hydrobromic acid (48%) was obtained from Sargent-Welch.

5-Hydroxy-3-methylbenzo[*b*]thiophene (**4**).

5-Hydroxy-3-methylbenzo[*b*]thiophene-2-carboxylic acid (5a) (**3**, 10.4 g., 5 mmoles) was suspended in 240 ml. of 48% hydrobromic acid and the vigorously stirred mixture was immersed in an oil bath which had been preheated to 150°. The mixture was heated with continuous stirring for 30 minutes, was cooled briefly, and was poured into an equal volume of water. The mixture was extracted with three 50 ml. portions of dichloromethane. The combined organic layers were washed with brine, and were extracted with two 25 ml. portions of saturated sodium bicarbonate. The organic layers were dried, were filtered through a short column of silica, and the solvent was removed to afford

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5.07 g. (60%) of **4**, a colorless solid, m.p. 91-93° [lit. (5a) m.p. 93-94°].

Acidification of the bicarbonate extracts and collection of the tan precipitate afforded 0.80 g. (7%) of the starting material.

We noted during the optimization experiments for this process two critical factors: 1) **3** is best added as a uniform, fine powder to the vigorously stirred hydrobromic acid solution. Lumps of **3** dissolve only slowly relative to the rate of reaction, and high conversions require rapid, uniform suspension of the substrate. 2) Timing of the reaction is of considerable importance. We obtained the highest yields and conversions after 30 minutes of reaction; after only 40 minutes the yield fell to *ca.* 20%, while shorter reaction times (or longer times at lower temperatures) gave poor conversion.

5-Methoxy-3-methylbenzo[*b*]thiophene-2-carboxylic acid (**5**).

This compound was prepared by the method reported for **3** (5a,11). 3-Methoxyacetophenone (0.25 mole) was condensed with rhodanine to give an adduct, m.p. 177-181°, in 56% yield; ir: 3170, 1700, 1565, 1450, 1200, 1060, 1020, 800, and 690 cm^{-1}; nmr: 2.72 (s, 3H), 3.88 (s, 3H), 6.54 (broad s, 1H), 6.94-7.19 (m, 3H), 7.39 (d, 1H, J = 7 Hz).

Anal. Calcd. for $C_{12}H_{11}NO_2S_2$: C, 54.33; H, 4.15; N, 5.28; S, 24.17. Found: C, 54.34; H, 4.25; N, 5.22; S, 24.04.

The acetophenone-rhodanine adduct (10 g., 0.38 mole) was saponified and the crude mercaptocinnamic acid (5a) was cyclized in 65% yield overall; compound **5** was obtained as a tan powder, m.p. 231-234° (ethanol) [lit. (11) 249-251° (acetic acid)]; ir: 2800 (broad), 1660, 1510, 1450, 1275, 1250, 1210, 1010, 900, 840 cm^{-1}; nmr: 2.77 (s, 3H), 3.94 (s, 3H), 7.02-7.63 (m, 2H), 7.90 (d, 1H, J = 8 Hz).

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.44; H, 4.54; S, 14.43. Found: C, 59.37; H, 4.71; S, 14.26.

Attempted Decarboxylation of **5**.

A flask charged with 50 ml. of 48% hydrobromic acid and 3.56 g. (16 mmoles) of **5** was heated to reflux for 1 hour. Workup of the mixture as described above afforded 1.09 g. of insoluble material, m.p. > 270°. There was recovered 1.35 g. (38%) of the starting material, identified by ir and mixed melting point, from the bicarbonate extracts of the dichloromethane soluble material. The residual organic solution yielded 0.27 g. (9%) of **4**, identified by m.p., ir, and mobility on tlc.

REFERENCES AND NOTES

(1) Supported by a grant (5T32-GM07651-02) from the National Institutes of Health. Funds for the purchase of the NMR spectrometer used in this study were provided by grants from the National Science Foundation and the DuPont Company.

(2) K. M. Shaw, *Adv. Drug Res.*, **11**, 75 (1977); W. W. Douglas, in "The Pharmacologic Basis of Therapeutics", 5th Ed., L. S. Goodman and A. Gilman, Eds., MacMillan Publishing Co., 1975, p. 613 ff.

(3) T. R. Bosin, E. Campaigne, A. Dinner, R. B. Rogers, and R. P. Maickel, *J. Toxicol. Environ. Health*, **1**, 515 (1976).

(4) T. R. Bosin and E. Campaigne, *Adv. Drug Res.*, **11**, 191 (1977).

(5a) E. Campaigne, T. Bosin, and E. S. Neiss, *J. Med. Chem.*, **10**, 270 (1967); (b) E. Campaigne and A. Dinner, *J. Pharm. Sci.*, **58**, 892 (1969); (c) E. Campaigne and A. Dinner, *J. Med. Chem.*, **13**, 1205 (1970).

(6) T. Cohen and R. A. Schambach, *J. Am. Chem. Soc.*, **92**, 3189 (1970).

(7) E. Campaigne and Y. Abe, *J. Heterocyclic Chem.*, **12**, 889 (1975).

(8) E. Biekert and W. Schäfer, *Chem. Ber.*, **93**, 642 (1960).

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, John Wiley and Sons, New York, N. Y., 1967, p. 451.

(10) We thank Prof. Campaigne for his sponsorship of the early portions of this study.

(11) P. M. Chakrabarti, N. B. Chapman, and K. Clarke, *J. Chem. Soc. C*, 1 (1969).