to 200 ml of water containing 5.8 ml of acetic acid. After standing for 1 hr, the precipitate was collected and washed with cold water. The crude product (mp 319°, 62–74% yield) was crystallized from hot water (25–50% yield): mp 347°; ir (KBr) 3350 (broad), 3180 (broad), 2880 (broad), 1720, 1680, 1650 (broad), 1600 cm^{-1}; nmr δ 1.29 (d, 3 H, J = 6 Hz, 2-CH_3), 4.42 (q, 2 H, J = 6 Hz, C_2H), 5.71 (s, 1 H, C_4H), 6.23 (s, 2 H, amido NH_2), 8.72 (s, 1 H, NH), and 10.63 (broad s, 1 H, 5-OH); uv max (MeOH) 211 mμ (ϵ 12,000), 240 (9750), and 370 (7360).

Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.03; N, 23.46. Found: C, 53.75; H, 5.14; N, 23.58.

It was observed that fairly pure **6b** could be prepared simply by warming **4b** in 30% KOH for 20 min at 80°, followed by acidification with 6 N HCl (mp 342°, 36% yield).

Registry No.—**3a**, 31926-73-5; **3b**, 31926-74-6; **4a**, 31926-75-7; **4b**, 31926-76-8; **6a** (keto), 31926-77-9; **6a** (enol), 31926-78-0; **6b** (keto), 31926-79-1; **6b** (enol), 31926-80-4; **7**, 31926-81-5; **8**, 31926-82-6; **9**, 31926-83-7; 2,6-dimethyl-4-oxonicotenonitrile, 31926-84-8.

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A Simple Synthetic Route to Benzo[c]thiophene and the Naphtho[c]thiophenes

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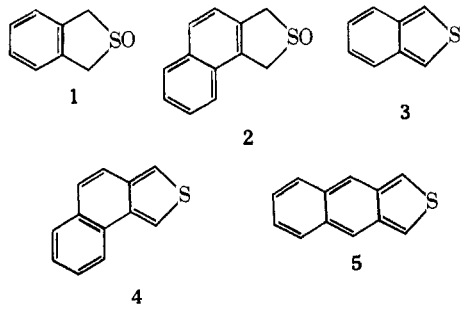
Benzo[c]thiophene (isothianaphthene, **3**) was obtained when 1,3-dihydrobenzo[c]thiophene 2-oxide (**1**) was heated with neutral alumina to 120–130°. Thiophene **3** was generated *in situ* when sulfoxide **1** was heated with acetic anhydride, as shown by the isolation of the exo and endo Diels–Alder adducts **8** and **9**, when *N*-phenylmaleimide was present in the reaction mixture. Similarly, the stable new heterocycle naphtho[1,2-c]-thiophene (**4**) was formed by heating the corresponding sulfoxide **2** with neutral alumina; thiophene **4** formed the exo and endo adducts **16** and **17** by the addition of *N*-phenylmaleimide to the thiophene ring. In contrast, naphtho[2,3-c]thiophene (**5**) could not be prepared by the alumina pyrolysis of sulfoxide **19**, which yielded only trace amounts of the disproportionation products 1,3-dihydronaphtho[2,3-c]thiophene (**20**) and 1,3-dihydronaphtho[2,3-c]thiophen-1-one (**24**). Although it was too unstable to be isolated, thiophene **5** was generated by the dehydration of sulfoxide **19**, as evidenced by trapping experiments using *N*-phenylmaleimide; three adducts (**21**, **22**, and **23**) were isolated, the major two resulting from dienophile addition to the thiophene ring of **5** and the minor product resulting from dienophile addition to the central ring of **5**.

Some time ago we reported, in a preliminary communication, that the thermolysis of 1,3-dihydrobenzo-[c]thiophene 2-oxide (**1**) and 1,3-dihydronaphtho-[1,2-c]thiophene 2-oxide (**2**) led to dehydration with the formation of benzo[c]thiophene (isothianaphthene, **3**) and the previously unreported naphtho[1,2-c]thiophene (**4**).[2] In this paper further details of this work are described, as well as attempts to extend the sulfoxide dehydration method to the synthesis of the unknown *o*-quinonoid heterocycle naphtho[2,3-c]thiophene (**5**).



1 2 3 4 5

Benzo[c]thiophene.—The pyrolysis of 1,3-dihydrobenzo[c]thiophene 2,2-dioxide (**6**) leads to the extrusion of sulfur dioxide and the generation of the unstable *o*-quinodimethane (**7**), which can be trapped *in situ* by dienophiles or which under proper conditions cyclizes intramolecularly to give benzocyclobutene.[3–5] It seemed likely that the related sulfoxide 1,3-dihydrobenzo[c]thiophene 2-oxide (**1**)[6] might undergo a similar extrusion of sulfur monoxide to give the same transformation products of **7**.[7] Indeed, when a mixture of sulfoxide **1** and *N*-phenylmaleimide (NPM) was heated to 220° in the absence of a solvent, a vigorous reaction took place. The product was not the known NPM adduct[3] of hydrocarbon **7**, however, but a mixture of two sulfur-containing isomers $C_{18}H_{13}NO_2S$, which were subsequently shown to be the endo and exo adducts (**8** and **9**) of NPM with benzo[c]thiophene. The same adduct mixture was obtained more conveniently and in excellent yield (86%) by refluxing a mixture of NPM and sulfoxide **1** in acetic anhydride. The intermediacy of benzo[c]thiophene (**3**) in these reactions was confirmed by preparing adducts **8** and **9** by the direct addition of NPM to pure thiophene **3** in benzene solution.

The isomeric adducts **8** and **9** were assigned the exo and endo structures, respectively, on the basis of their nmr spectra. In the nmr spectrum of exo adduct **8**, the two protons α to the imide carbonyls appear at δ 3.30, a position similar to that (3.43) of the corresponding protons of the NPM–anthracene adduct **10**;[8] molecular models indicate similar environments for the protons in both compounds, with no shielding in either case. The two bridgehead protons of **8** appear at δ 4.93 and the

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(2) M. P. Cava and N. M. Pollack, *J. Amer. Chem. Soc.*, **88**, 4112 (1966).

(3) M. P. Cava and A. A. Deana, *ibid.*, **81**, 4266 (1959).

(4) J. A. Oliver and P. A. Ongley, *Chem. Ind. (London)*, 1024 (1965).

(5) For a general review of the chemistry of benzo[c]thiophenes, see B. Iddon, *Advan. Heterocycl. Chem.*, in press.

(6) An nmr study of sulfoxide **1** has appeared in the literature [R. F. Watson and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 664 (1965)], but the preparation and properties of the compound were not reported.

(7) A related decomposition of some episulfoxides to sulfur monoxide and olefins has been reported: G. E. Hartzell and J. N. Paige, *ibid.*, **88**, 2616 (1966).

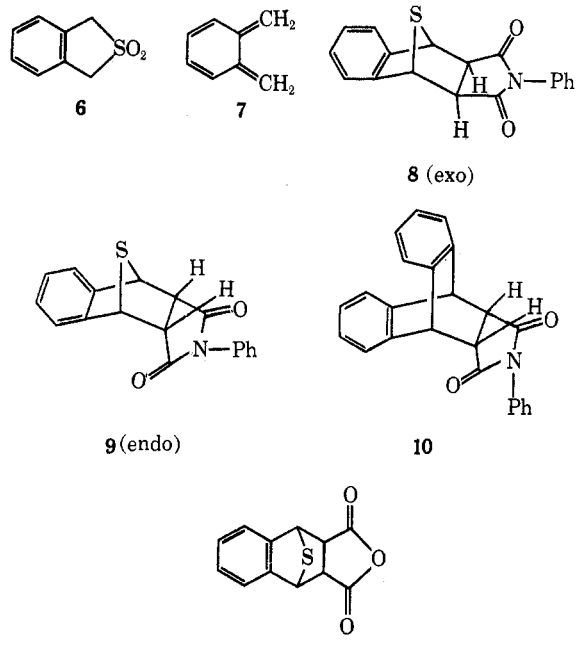
(8) M. P. Cava and R. H. Schlessinger, *Tetrahedron*, **21**, 3073 (1965).

nine aromatic protons are seen as a broad band in the δ 7.0–7.5 region.

In endo adduct **9**, the protons α to the imide carbonyls appear at δ 4.10, as a result of a strong deshielding effect of the sulfur bridge. The bridgehead protons, in an environment similar to those in exo isomer **8**, appear at δ 4.90. Finally, only seven of the nine aromatic protons are seen in the expected δ 7.0–7.5 region; the remaining two appear far upfield as a broad band centered at δ 6.43. Molecular models explain this observation by showing that rotation of the phenyl substituent of **9** brings the two protons ortho to the nitrogen within the shielding zone of the opposite aromatic ring.[9] It is also of interest to note that the two sets of nonaromatic protons of exo isomer **8**, with a dihedral angle of about 90° (J = 0 Hz), appear as sharp singlets, while the corresponding protons of endo isomer **9**, with a smaller dihedral angle (and consequently appreciable value for J), are broadened.

Benzo[c]thiophene (**3**) has been synthesized previously only by the high-temperature catalytic dehydrogenation of its 1,3-dihydro derivative.[10] We have found that the dehydration of sulfoxide **1** is useful not only for the synthesis of adducts of **3** but is easily utilized as a practical new synthetic preparation of **3** itself. Thus, when a mixture of sulfoxide **1** and neutral alumina was heated under reduced pressure at 100–125° in a sublimer, almost pure benzo[c]thiophene (**3**) condensed on the cold finger in high yield (94%) as a white crystalline crust. Completely pure **3** could be obtained by resublimation, but the recovery was poor, apparently due to polymerization of this highly reactive heterocycle.[10]

It has been reported earlier that benzo[c]thiophene reacts with maleic anhydride to give an adduct, mp 153–154°, the stereochemistry of which was not determined.[10] In a brief reexamination of this reaction, we obtained a product, mp 148–152°, which was shown by nmr to be a mixture of the exo and endo isomers **11** and **12** in a ratio of 1:1.25. The protons α to the carbonyls in **11** and **12** appear at δ 3.55 and 4.29, respectively.



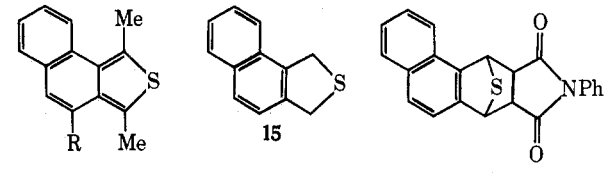
6 **7** **8** (exo) **9** (endo) **10** **11** (exo) **12** (endo)

Naphtho[1,2-c]thiophene.—Prior to our study, the only known derivatives of naphtho[1,2-c]thiophene (**4**) were the 1,3-dimethyl derivative **13** and the corresponding 7-carboxylic acid (**14**); the preparation of these compounds required a multistep synthesis from 2,5-dimethylthiophene.[11] We found that dehydration of 1,3-dihydronaphtho[1,2-c]thiophene 2-oxide (**2**), prepared by the periodate oxidation[12] of the corresponding known sulfide **15**,[13] affords a simple route to the parent heterocycle **4**. Thus, pyrolysis of sulfoxide **2** in the presence of neutral alumina at 160–180° gave, after resublimation, pure naphtho[1,2-c]thiophene (**4**), mp 110–112°, in 47% yield. In contrast to benzo[c]thiophene, the naphtho analog **4** was quite stable to storage at room temperature. Its ultraviolet spectrum showed a complex series of bands (see Experimental Section) which were very similar to those reported[11] for its 1,3-dimethyl derivative **13**.

In contrast also to the more reactive thiophene **3**, **4** did not add to NPM at room temperature, but addition did take place at 100° to give a mixture of the exo adduct **16** and the endo adduct **17**. The mixture of adducts **16** and **17** was also conveniently obtained, and in high yield, by refluxing a mixture of acetic anhydride, NPM, and sulfoxide **2**.

The stereochemistry of adducts **16** and **17** was assigned on the basis of their nmr spectra, which were qualitatively similar to those of adducts **8** and **9**. The spectra of **16** and **17** were, however, more complex because of the asymmetric environment in the vicinity of the naphthalene ring. Thus, in the spectrum of exo adduct **16**, the two protons α to the imide carbonyls appear as a sharp singlet at δ 3.43. The bridgehead protons, however, experience deshielding to different degrees by the naphthalene ring and appear as singlets at δ 5.13 and 5.55. The aromatic protons form a complex band in the δ 7.2–8.1 region.

In the endo isomer **17**, the two protons α to the imide carbonyls appear as a multiplet at δ 4.24. Complex splitting results from coupling with the two non-equivalent bridgehead protons, which appear as multiplets centered at δ 5.07 and 5.57. In addition to nine aromatic protons in the δ 6.8–8.1 region, the two protons of the phenyl substituent ortho to the nitrogen atom experience strong shielding by the naphthalene nucleus and appear as a multiplet centered at δ 5.93.



13, R = H
14, R = CO_2H
15
16 (exo)
17 (endo)

(9) In a preliminary communication (ref 1), the absorption at δ 6.43 was assigned incorrectly to the two aromatic protons ortho to the bicyclic ring. The correct assignment became clear upon inspection of the nmr spectra of the corresponding NPM adducts of 1,3-dimethylthieno[3,4-c]thiophene: M. P. Cava and N. M. Pollack, *J. Amer. Chem. Soc.*, **89**, 3639 (1967), and N. M. Pollack, Ph.D. dissertation, Wayne State University, 1968.

(10) R. Meyer, H. Kleinert, S. Richter, and K. Gewald, *J. Prakt. Chem.*, **20**, 244 (1963).

(11) O. Dann and H. Distler, *Chem. Ber.*, **87**, 365 (1954).

(12) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(13) M. P. Cava, R. L. Shirley, and B. W. Erickson, *ibid.*, **27**, 755 (1962).

Naphtho[2,3-*c*]thiophene.—Some time ago we reported the synthesis of the deep red 1,3-diphenylnaphtho[2,3-*c*]thiophene (**18**), a remarkably stable substance despite its 2,3-naphthoquinonoid structure.[14] In order to gain some insight into the extent to which the phenyl substituents stabilize this compound, we investigated the synthesis of the parent heterocycle **5** by the sulfoxide dehydration route. Sulfoxide **19**, prepared by the periodate oxidation of the known sulfide **20**,[15] did indeed undergo dehydration to naptho[2,3-*c*]-thiophene (**5**) when heated in acetic anhydride in the presence of NPM, as evidenced by the formation of a mixture of adducts in fairly good yield. This mixture was resolved by crystallization and chromatography into a major isomer (A) and two minor isomers (B and C); infrared and tlc examination of the mother liquors failed to reveal the presence of a fourth adduct.

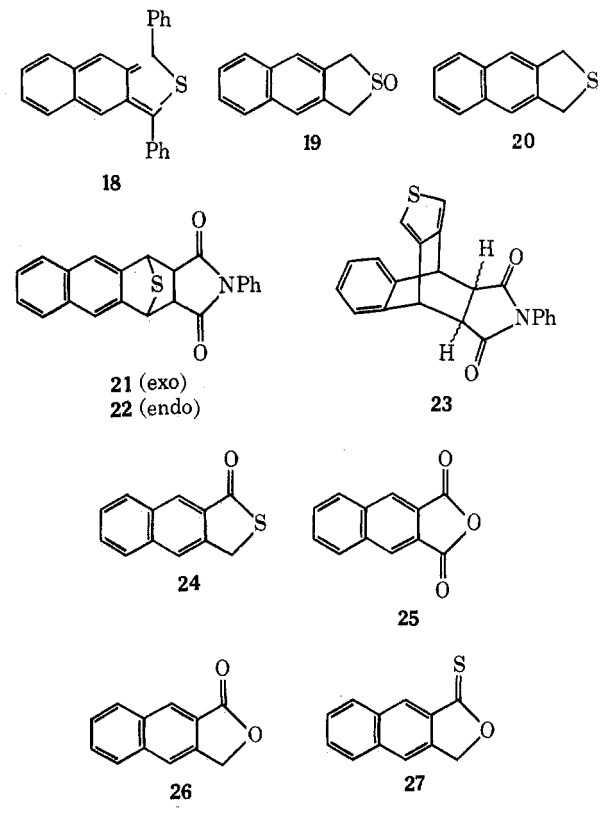
The ultraviolet spectra of adducts A and B are almost identical, each showing absorption up to 330 mμ, consistent with the presence of a naphthalene nucleus. Adducts A and B were formed, therefore, by addition of NPM to the thiophene ring of **5**. The exo configuration **21** was assigned to A on the basis of its nmr spectrum, which revealed the protons α to the imide carbonyls at δ 3.46 and the bridgehead protons at δ 5.13, both sets appearing as sharp singlets. In the nmr spectrum of endo isomer **22** (adduct B), the protons α to the carbonyls appear downfield at δ 4.10, while the bridgehead protons appear at δ 5.05; both signals are multiplets, consistent with the endo configuration. Also, the two phenyl protons ortho to the nitrogen atom in **22** are shielded by the naphthalene nucleus and appear centered at δ 6.08.

Adduct C was assigned structure **23**, in which a molecule of NPM has added to the central ring of **5**. In accord with this formulation, the adduct shows no ultraviolet maxima above 269 mμ. Its nmr spectrum is quite similar to that of the NPM–anthracene adduct **10**.[8] Thus, the protons α to the carbonyls and the bridgehead protons appear as singlets at δ 3.34 and 4.87 respectively, while the two phenyl protons ortho to the nitrogen appear as a shielded multiplet around δ 6.51; the thiophene protons are seen as a sharp singlet at δ 7.06. Unfortunately, these values do not reveal whether the imide ring of **23** lies over the benzene ring or over the thiophene ring.

In an attempt to isolate naphtho[2,3-*c*]thiophene (**5**), sulfoxide **19** was mixed with neutral alumina and heated to 200° under reduced pressure in a sublimer. A thin film of yellow sublimate was obtained on the cold finger, which was maintained at −78°. The sublimate was dissolved in a benzene solution of NPM and the products were analyzed by tlc, revealing the presence of none of the NPM adducts of **5**, but only a small amount of sulfide **20**. Extraction of the alumina residue from the pyrolysis, followed by chromatographic separation, afforded only two products in very low (*ca.* 1%) yield. One product was sulfide **20**; the second product, $C_{12}H_8OS$, was shown to be 1,3-dihydronaphtho[2,3-*c*]thiophen-1-one (**24**). Thiolactone **24** was prepared also by an independent synthesis from 2,3-naphthalic anhydride (**25**) *via* lactone **26** and the isomeric thiolactone **27** as intermediates, as described in detail in the Experimental Section.[16]

It was observed that a solution of sulfoxide **19** in chloroform or ethylene dichloride developed a yellow color and a strong yellow-green fluorescence on heating; a similar color possibly attributable to **5** was produced by the slow passage of a chloroform solution of **19** through a neutral alumina column at room temperature. An attempt to isolate **5** from the column eluate of the latter experiment afforded mostly starting sulfoxide **19** along with smaller amounts of sulfide **20** and thiolactone **24**. In addition, immediate treatment of the yellow eluate with NPM, followed by tlc analysis, failed to give any indication of the presence of adducts of **5**.

Positive evidence was obtained, however, for the slow generation of **5** from **19** in hot ethylene dichloride in the presence of alumina. When a mixture of **19**, NPM, and alumina was heated under nitrogen in ethylene dichloride solution for 24 hr at 85–90°, low yields (*ca.* 6% total) of the NPM adducts of **5** were isolated, along with traces of sulfide **20** and thiolactone **24**.



Discussion

The formation of benzo[*c*]thiophene by the dehydration of sulfoxide **1** may be viewed as a variation of the Pummerer reaction.[17] The sulfonium ion **28** is proposed as an intermediate in this process,[17c] although the acetoxy sulfide **29** may also be involved in acetic anhydride solution.[17b] In the naphtho[2,3-*c*]thiophene case, the intermediate sulfonium ion **30** also is attacked by the nucleophilic oxygen of unchanged sulfoxide **19**; collapse of

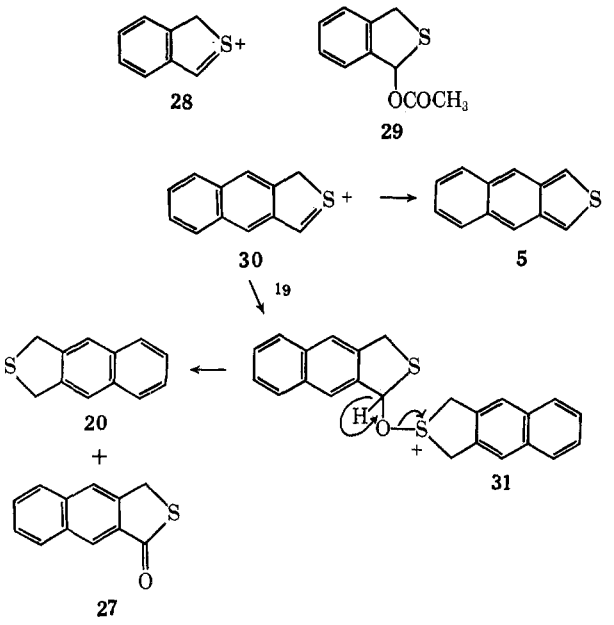
(14) (a) M. P. Cava and J. P. Van Meter, *J. Amer. Chem. Soc.*, **84**, 2008 (1962); (b) *J. Org. Chem.*, **34**, 538 (1969).

(15) M. P. Cava and R. L. Shirley, *J. Amer. Chem. Soc.*, **82**, 654 (1960).

(16) The preparation of related thiophthalides has been reported: (a) V. Prey and P. Kondler, *Monatsh. Chem.*, **89**, 505 (1958); (b) V. Prey, B. Kerres, and H. Berbalk, *ibid.*, **91**, 319 (1960); (c) *ibid.*, **91**, 774 (1960).

(17) (a) L. Horner and P. Kaiser, *Justus Liebigs Ann. Chem.*, **626**, 19 (1959); (b) S. Oae, T. Kitao, S. Kawamura, and Y. Kitaoka, *Tetrahedron*, **19**, 817 (1963); (c) C. R. Johnson, J. C. Sharp, and W. G. Phillips, *Tetrahedron Lett.*, 5299 (1967).

the resulting oxysulfonium ion **31** leads to the observed by-products **20** and **27**. The relative reluctance of ion **30** to lose a proton (as compared to ion **28**) may be attributed to the fact that thiophene **5** is a high-energy 2,3-napthoquinonoid system.[14]



It is of interest to compare the addition of the dienophile NPM to the condensed thiophenes **3**, **4**, and **5**. In all three compounds addition to the thiophene ring was observed; formation of the exo isomer was somewhat favored. Indeed, addition of NPM to a benzenoid ring was observed only in the formation of the minor adduct (**23**) from naphtho[2,3-*c*]thiophene (**5**). Some dienophile addition to the central ring of **5** is not surprising, in view of the fact that **5** is a thiophene analog of anthracene.[18]

Experimental Section

General.—Melting points are uncorrected. Microanalyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. Spectra were recorded on a Perkin-Elmer Model 137 ir spectrophotometer, a Perkin-Elmer Model 202 uv-visible spectrophotometer, a Varian A-60A nmr spectrometer, and a Perkin-Elmer Model 270B mass spectrometer.

1,3-Dihydrobenzo[*c*]thiophene 2-Oxide (1).[6]—Molten 1,3-dihydrobenzo[*c*]thiophene[3,4] (27.2 g, 0.20 mol) was added dropwise to a stirred solution of 46.0 g (0.215 mol) of sodium periodate in 900 ml of 50% aqueous methanol. After being stirred for 12 hr at room temperature, the reaction mixture was filtered to remove inorganic salts. Evaporation afforded a solid residue which was recrystallized from ethyl acetate–cyclohexane to give 24.2 g (80%) of sulfoxide **1**, mp 85–87°. The analytical sample, mp 90–91°, was recrystallized three times from the same solvent mixture.

Anal. Calcd for C_8H_8OS: C, 63.13; H, 5.29; S, 21.06. Found: C, 63.05; H, 5.38; S, 20.80.

Benzo[*c*]thiophene (3).—An intimate mixture of 2.00 g (13.2 mmol) of 1,3-dihydrobenzo[*c*]thiophene 2-oxide (**1**) and 3.0 g of grade I neutral alumina (Woelm) was heated under 25-mm pressure at 120–130° in a sublimer to give 1.67 g (94%) of benzo[*c*]-thiophene, mp 47–56°, formed during 1 hr as a pure white crystalline solid. An analytical sample, mp 53–55° (lit.[10] mp 50–51°), was prepared by resubliming the crystalline solid at 40–45° (6.0 mm) (15% recovery).

(18) After the submission of our manuscript, an independent study appeared describing the generation of **5** and the isolation of its adducts **21** and **22** (but not **23**): D. W. H. MacDowell, A. T. Jeffries, and M. B. Meyers, *J. Org. Chem.*, **36**, 1416 (1971).

Adducts 8 and 9 of Benzo[*c*]thiophene (3) with *N*-Phenylmaleimide. A. Generation of 3 *in Situ*.—An intimate mixture of 0.456 g (3.00 mmol) of 1,3-dihydrobenzo[*c*]thiophene 2-oxide and 0.692 g (4.00 mmol) of *N*-phenylmaleimide was heated in an oil bath at 220° (vigorous reaction, loss of water). The reaction product was subjected to fractional crystallization to give 0.438 g (48%) of the exo adduct **8**, mp 194–202°, obtained in two crops from benzene. Recrystallization from benzene–ether gave the analytical sample, mp 203–204°.

Anal. Calcd for $C_{18}H_{13}NO_2S$: C, 70.34; H, 4.26; N, 4.56; S, 10.43. Found: C, 70.53; H, 4.36; N, 4.44; S, 10.24.

Fractional crystallization of the residual material obtained by evaporating the mother liquor gave 0.221 g (24%) of the endo adduct **9**, mp 150–190° (from benzene–cyclohexane). Recrystallization from ethanol–ethyl acetate and then from benzene–cyclohexane gave the analytical sample, mp 236–239°.

Anal. Calcd for $C_{18}N_{13}NO_2S$: C, 70.34; H, 4.26; N, 4.56; S, 10.43. Found: C, 70.61; H, 4.36; N, 4.71; S, 10.42.

Similar results were obtained when the reaction was carried out in acetic anhydride. Thus, a mixture of 1.00 g (6.58 mmol) of the sulfoxide **1**, 1.14 g (6.59 mmol) of *N*-phenylmaleimide, and 20 ml of acetic anhydride was heated under reflux for 2 hr and was worked up in the usual way to give 1.75 g (86%) of adduct mixture, mp 170–200°, which was shown by ir analysis to be made up of the exo and endo adducts (**8** and **9**) in the ratio 1.2:1.

B. Use of Pure 3.—Benzo[*c*]thiophene (402 mg, 3 mmol) was added to a solution of 519 mg (3.00 mmol) of *N*-phenylmaleimide and a trace of hydroquinone in 15 ml of benzene. The reaction mixture was allowed to stand at room temperature for 3 days and was then worked up to give a product consisting of the usual ratio of isomers **8** and **9** as shown by tlc and ir analysis.

Adducts 11 and 12 of Benzo[*c*]thiophene (3) with Maleic Anhydride. A. Generation of 3 *in Situ*.—A mixture of 0.610 g (4.00 mmol) of the sulfoxide **1**, 0.390 g (4.00 mmol) of maleic anhydride, and 25 ml of acetic anhydride was heated at reflux for 15 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residue was taken up in benzene and precipitated with ether to give 0.450 g (49%) of crude crystalline product. Recrystallization from benzene–ether afforded 0.225 g (24%) of adduct mixture **11** and **12**, white crystals, mp 148–152° (lit.[10] mp 153–154°).

B. From Pure 3.—A solution of 0.536 g (4.00 mmol) of benzo[*c*]thiophene (**3**), 0.392 g (4.00 mmol) of maleic anhydride, and a trace of hydroquinone in 30 ml of benzene was allowed to stand at room temperature for 12 hr and was then heated under reflux for 1 hr. Evaporation of the reaction mixture and crystallization of the residue from benzene–ether gave 0.419 g (52%) of adduct mixture **11** and **12**, mp 141–155° (lit.[10] mp 153–154°).

1,3-Dihydronaphtho[1,2-*c*]thiophene 2-Oxide (2).—Adding a solution of 7.00 g (32.7 mmol) of sodium periodate in 170 ml of water to a stirred solution of 5.44 g (29.2 mmol) of 1,3-dihydronaptho[1,2-*c*]thiophene (**15**)[18] in 500 ml of ethanol and stirring the reaction mixture for 15 hr at room temperature gave, after the usual work-up (evaporation to half-volume, extraction with benzene, etc.), 3.05 g (52%) of the product, mp 135–142° (crystallized from benzene). Recrystallization from ethyl acetate gave 2.22 g (38%) of pure **2**, mp 141–143°.

Anal. Calcd for $C_{12}H_{10}OS$: C, 71.26; H, 4.98; S, 15.86. Found: C, 71.52; H, 4.84; S, 15.96.

Naphtho[1,2-*c*]thiophene (4).—A mixture of 500 mg (2.48 mmol) of sulfoxide **2** and 800 mg of neutral grade I alumina (Woelm) was heated under 25-mm pressure at 160–180° in a sublimer. After 1 hr, the crude product was scraped from the cold finger and was resublimed at 100° under 25-mm pressure to give 216 mg (47%) of analytically pure naphtho[1,2-*c*]thiophene (**4**): transparent plates; mp 110–112°; ultraviolet spectrum λ_{max}^{MeOH} 208 mμ (log ε 4.45), 223 (4.32), 253 sh (4.38), 257 (4.39), 266 (4.43), 271 (4.53), 277 (4.56), 314 sh (3.78), 318 (3.79), 326 sh (3.71), 332 (3.67), 348 (3.27).

Anal. Calcd for $C_{12}H_8S$: C, 78.20; H, 4.37; S, 17.40. Found: C, 78.15; H, 4.30; S, 17.23.

Adducts 16 and 17 of Naphtho[1,2-*c*]thiophene (4) with *N*-Phenylmaleimide. A. Generation of 4 *in Situ*.—A mixture of sulfoxide **2** (1.010 g, 5.00 mmol) and 0.865 g (5.00 mmol) of *N*-phenylmaleimide in 20 ml of acetic anhydride was heated under reflux for 5 hr. After standing at room temperature for 4 days, the reaction mixture was decanted from a crystalline precipitate of 0.515 g of exo adduct **16**, mp 244–246°. Evapora-

tion of the mother liquor and recrystallization of the resulting residue from benzene–cyclohexane afforded additional product (0.209 g, total 0.724 g, 41%), mp 243–245°. Pure exo adduct, mp 246–247°, was obtained by recrystallization from ethyl acetate–ethanol.

Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97. Found: C, 73.93; H, 4.46; N, 4.01; S, 9.12.

Evaporation of the mother liquors and recrystallization of the residual material from ethanol afforded 0.559 g (31%) of the endo adduct **17**, mp 172–174°. Attempts to obtain a second crop of **17** yielded only an impure mixture of adducts. The analytical sample, mp 174–175°, was recrystallized from ethanol and then from benzene–cyclohexane.

Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97. Found: C, 74.20; H, 4.06; N, 3.87; S, 9.18.

B. Use of Pure 4.—A mixture of 40 mg (0.21 mmol) of **4** and 38 mg (0.22 mmol) of *N*-phenylmaleimide in 10 ml of benzene was heated under reflux for 4 hr. Work-up of the reaction product gave 26 mg (37%) of pure **16**, mp 250–252° (recrystallized from methanol). Tlc and ir analysis of the mother liquor residues showed that they were composed of the usual mixture of **16** and **17**.

1,3-Dihydronaphtho[2,3-*c*]thiophene 2-Oxide (19).—A solution of 1.49 g (8.01 mmol) of 1,3-dihydronaphtho[2,3-*c*]thiophene (**20**)[15] in 350 ml of hot ethanol was mixed with a solution of 1.90 g (8.89 mmol) of sodium periodate in 65 ml of water. The reaction mixture was heated and stirred under reflux for 15 hr. Work-up in the usual way and crystallization from ethyl acetate afforded 1.21 g (75%) of sulfoxide **19**, mp 198–204°. The analytical sample, mp 198–201°, was obtained by recrystallization from ethyl acetate.

Anal. Calcd for $C_{12}H_{10}OS$: C, 71.26; H, 4.98; S, 15.86. Found: C, 71.03; H, 5.15; S, 15.84.

Attempted Preparation of Naphtho[2,3-*c*]thiophene (5) by Dehydration of the Sulfoxide 19 with Alumina. A. At Elevated Temperature.—An intimate mixture of 100 mg (0.50 mmol) of sulfoxide **19** and 200 mg of neutral grade I alumina (Woelm) was heated under 25-mm pressure at 200° in a sublimer provided with a cold finger at −78°. After 10 min the cold finger, which was coated with a thin film of pale yellow sublimate, was dipped into a solution of 100 mg of *N*-phenylmaleimide in 15 ml of benzene. After standing for 1 hr at room temperature, the solution was evaporated to dryness *in vacuo* to give 101 mg of residue. Tlc analysis of the residue showed that adducts **21** and **22** (see below) were not present in detectable quantity; only two spots, corresponding to *N*-phenylmaleimide and the sulfide **20**, could be detected.

The alumina from the attempted preparation of **5** (wt 296 mg) was extracted with methanol–chloroform. Evaporation of the extract *in vacuo* gave 39 mg of an orange glass which was subjected to plc on silica gel (20 × 20 cm plate, 1 mm in thickness) developed twice with benzene. A multiplicity of zones was obtained from which only two products could be isolated, namely 1,3-dihydronaphtho[2,3-*c*]thiophene [**20**, 1.0 mg (*ca.* 1%, purified by sublimation at 90° (0.5 mm), mp 162–164° (lit.[15] mp 169–170°); R_f (0.60 on silica gel eluted with benzene) and ir spectrum identical with those of authentic **20**] and 1,3-dihydronaphtho[2,3-*c*]-thiophen-1-one [**24**, 0.6 mg (<1%); R_f (0.27 on silica gel eluted with benzene) and ir spectrum identical with those of authentic **24** (see preparation below)].

B. At Room Temperature.—A solution of 0.050 g (0.25 mmol) of sulfoxide **19** in *ca.* 0.25 ml of alcohol-free chloroform was passed through a small column of alumina (1.5 g of neutral grade I Woelm alumina, column dimensions: diameter, 1 cm; length, 1.5 cm). The column was eluted first with 20 ml of alcohol-free chloroform (prepared by passing reagent grade chloroform through 25 g of neutral grade I alumina), and then with 25 ml of 3% methanol–chloroform. The eluate was evaporated to a small volume and was subjected to plc on one 20 × 20 cm silica gel plate (1 mm thickness) to give a number of zones, from which only three compounds could be isolated in appreciable amounts, namely the starting material [**19**, 0.036 g (72% recovery)], 1,3-dihydronaphtho[2,3-*c*]thiophene [**20**, 0.004 g (31% yield, based on unrecovered starting material), purified by sublimation, mp 162–165° (lit.[15] mp 169–170°), R_f and ir spectrum identical with those of authentic material], and 1,3-dihydronaphtho[2,3-*c*]thiophen-1-one [**24**, 0.0005 g (3.5% yield, based on unrecovered starting material), R_f and ir spectrum identical with those of authentic **24** (see preparation below)].

Adducts 21, 22, and 23 of Naphtho[2,3-*c*]thiophene (20) with *N*-Phenylmaleimide. A. Generation of 20 by Dehydration of the Sulfoxide 19 with Acetic Anhydride.—A mixture of 3.20 g (16.0 mmol) of sulfoxide **19**, 3.0 g (17.0 mmol) of *N*-phenylmaleimide, and 20 ml of acetic anhydride was heated under reflux for 4 hr. After standing at room temperature for 12 hr, the reaction mixture was decanted from a crystalline precipitate; recrystallization of this material from ethyl acetate–chloroform gave 1.7 g (30%) of pure exo adduct **21**, mp 279–282°, and an impure second crop, 0.20 g (4%), mp 275–281°. The analytical sample of **21**, mp 280–282°, was recrystallized from ethyl acetate.

Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97. Found: C, 73.93; H, 4.46; N, 4.01; S, 9.12.

Evaporation of the acetic anhydride mother liquors (see above) afforded a solid residue which was recrystallized from benzene–ether to give 1.10 g (19%) of endo adduct **22**, mp 190–205°. Repeated recrystallization of this material from ethyl acetate and benzene–cyclohexane gave the analytical sample (0.30 g, 5%), mp 212–215°.

Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97. Found: C, 73.96; H, 4.40; N, 4.08; S, 9.19.

The mother liquors from the crystallization of **22** were concentrated to a small volume and diluted with ether to give 0.30 g (5%) of crude adduct **23**, mp 215–235°, which was recrystallized alternately from ethyl acetate and benzene–cyclohexane to give the analytical sample (0.13 g, 2%), mp 243–246°.

Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97. Found: C, 74.13; H, 4.47; N, 4.15; S, 9.02.

When the work-up of the adducts was carried out by plc instead of by fractional crystallization, the yields of **21** and **22** were improved. Thus, heating 0.202 g (1.00 mmol) of sulfoxide **19**, 0.173 g (1.00 mmol) of *N*-phenylmaleimide, and 2.0 ml of acetic anhydride in a sealed tube under nitrogen for 3 hr at 145°, followed by the usual preliminary crystallization, afforded 0.111 g crude exo adduct **21**, which was recrystallized from chloroform–ethyl acetate to give 0.077 g of pure material, mp 281–281.5°, obtained in two crops. Evaporation of the combined mother liquors gave 0.269 g of residue which was chromatographed on two 20 × 40 × 0.2 cm silica gel plates (E. Merck) developed four times with 0.25% methanol in benzene. Elution of the resulting zones and crystallization of the solid material so obtained gave an additional 0.056 g of **21**, mp 281–282° (total yield, 0.133 g, 37.3%), and 0.040 g (11.2%) of **22**, mp 214–215°. The purity of the **23** obtained by plc work-up (0.028 g, 7.8%, mp 219–221°) was inferior to that obtained by fractional crystallization (see above).

B. Generation of 20 by Dehydration of the Sulfoxide 19 with Alumina.—A mixture of 0.101 g (0.5 mmol) of sulfoxide **19**, 0.087 g (0.5 mmol) of *N*-phenylmaleimide, 0.050 g of neutral grade I alumina (Woelm), and 3 ml of ethylene dichloride was heated in a sealed tube under nitrogen at 85–90° for 24 hr. Preparative layer chromatographic separation of the product mixture on one 20 × 20 cm silica gel plate (Merck, 2-mm thickness), eluted twice with benzene, gave the three adducts, **21** [0.008 g (4.5%), mp 280.5–281° (recrystallized from chloroform–ethyl acetate)], **23** [trace amount; R_f identical with that of authentic **23**], and **22** [0.003 g (1.7%), mp 191–198° (recrystallized from chloroform–ethyl acetate)], together with trace quantities of 1,3-dihydronaphtho[2,3-*c*]thiophene (**20**) and 1,3-dihydronaphtho[2,3-*c*]thiophen-1-one (**24**).

1,3-Dihydronaphtho[2,3-*c*]furan-1-one (26).—A suspension of 40.0 g (0.20 mol) of naphthalene-2,3-dicarboxylic anhydride (**25**) and 10.0 g (0.26 mol) of sodium borohydride in 1 l. of THF was boiled under reflux for 15 min. The reaction mixture was evaporated to dryness *in vacuo* and the solid residue was dissolved in 500 ml of ice water. Acidification with dilute hydrochloric acid gave a crystalline precipitate which was mixed with xylene and heated for 2 hr to complete the lactonization. Addition of pentane and cooling gave a crystalline solid which was recrystallized from THF to give 30.0 g (80%) of pure **26**, mp 207–209°.

Anal. Calcd for $C_{12}H_8O_2$: C, 78.25; H, 4.38. Found: C, 78.33; H, 4.37.

1,3-Dihydronaphtho[2,3-*c*]furan-1-thione (27).—A suspension of 11.1 g of phosphorus pentasulfide and 9.2 g (0.05 mol) of lactone **26** in xylene was refluxed for 2 hr. The reaction mixture was filtered while hot and the filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from THF gave an orange precipitate which was chromatographed on a column of silica gel with 1:1 benzene–cyclohexane to give 4.25 g (45%) of

the thiolactone **27**, mp 192–193°. The analytical sample was recrystallized from benzene, mp 194–195°.

Anal. Calcd for $C_{12}H_8OS$: C, 71.97; H, 4.02; S, 16.01. Found: C, 71.93; H, 4.09; S, 15.83.

1,3-Dihydronaphtho[2,3-*c*]thiophen-1-one (24).—A mixture of 0.100 g (1.00 mmol) of 1,3-dihydronaphtho[2,3-*c*]furan-1-thione (**27**) and 1.8 ml of pyridine was heated under nitrogen in a sealed tube at 190° for 8 hr. The reaction mixture was diluted with chloroform, washed with dilute aqueous hydrochloric acid, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. Recrystallization of the residue from benzene gave 0.072 g (72%) of the product, mp 174–175°, obtained in two crops.

Anal. Calcd for $C_{12}H_8OS$: C, 71.97; H, 4.02; S, 16.01. Found: C, 71.85; H, 4.30; S, 15.84.

The product was also obtained when quinoline was used as the solvent but in lesser yield and poorer quality.

Registry No.—**1**, 3533-72-0; **2**, 31739-49-8; **3**, 270-82-6; **4**, 232-81-5; **8**, 13129-12-9; **9**, 13129-13-0; **11**, 31736-38-6; **12**, 31790-98-4; **16**, 13129-15-2; **17**, 13129-16-3; **19**, 28238-02-0; **21**, 31736-40-0; **22**, 31736-41-1; **23**, 31739-52-3; **24**, 31739-53-4; **26**, 4711-50-6; **27**, 31739-55-6.

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The Synthesis, Properties, and Base-Catalyzed Interactions of 8-Substituted 6,7-Dimethyllumazines[1]

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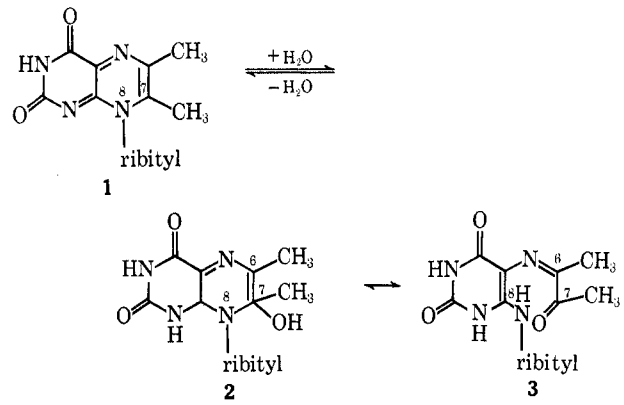
Alkaline solutions of 6,7-dimethyllumazines substituted at position 8 with groups bearing a 2′-hydroxyl group exhibit no long wavelength absorption; analogs without a 2′-hydroxyl group show absorption in the visible range. In H_2O, at alkaline pH, analogs with a 2′-hydroxyl substituent show nmr absorption of the 7-methyl group at −1.37 ppm, while the 6-methyl group exhibits singlets at −2.17 and −2.07 ppm. Analogs lacking the 2′-hydroxyl group do not absorb at −1.37 ppm but exhibit two resonance peaks between −3.90 and −4.30 ppm and a single absorption peak of the 6-methyl group at −2.07 ppm. These data suggest that 8-substituted 6,7-dimethyllumazines which bear a 2′-hydroxyl group form an equilibrium mixture in alkaline solutions containing primarily an intramolecular ether formed between the 2′-hydroxyl group of the side chain at position 8 and carbon 7 of the pyrazine ring (7-methyl group at −1.37 ppm, 6-methyl group at −2.17 ppm) and a minor amount of the 7-exo methylene form (6-methyl group at −2.07 ppm). Without a 2′-hydroxyl on the group at position 8, the intramolecular ether cannot form and the 7-exo methylene form predominates in basic media. The synthesis and properties of eight new 6,7-dimethyllumazine derivatives bearing D- and L-erythrityl, D- and L-threityl, 2′-deoxy-D-ribityl, DL-glycerityl, and 3′-hydroxypropyl substituents at position 8 and their corresponding 4-(1′-alditylamino)-5-nitroso-2,6-dihydroxypyrimidine precursors are reported. The preparation and characterization of the oximes of D- and L-erythrose, D- and L-threose, 2-deoxy-D-ribose, 3-deoxy-D-ribose, and the corresponding amines formed by reduction are described. These syrupy amines are characterized as their crystalline salicylidene derivatives.

The mechanism for conversion of 6,7-dimethyl-8-ribityllumazine to riboflavin chemically[3–7] and enzymically[8,9] has been studied in some detail over the past decade. It was thought originally that the conversion occurred by an aldol condensation involving an α-methyl ketone resulting from hydration and ring opening of the pyrazine ring.[3,5]

More recent work strongly suggests a 7-exo methylene intermediate **7** described below[6–9] rather than the α-methyl ketone **3**. Pfleiderer[10] has interpreted the spectra of alkaline solutions of various lumazines as evidence of hydration and the ring-opening reaction sequence. This report presents nuclear magnetic resonance data substantiating the presence of the 7-exo methylene (**7**) structure and the absence of the open ring (**3**) form in basic solution.



Nuclear magnetic resonance spectra of a number of selected and newly synthesized 6,7-dimethyllumazines substituted at position 8 with various groups indicate that, if the substituent at position 8 bears a 2′-hydroxyl group, an equilibrium mixture results. This is predominantly an intramolecular ether resulting from the base-catalyzed interaction of the 2′-hydroxy group and carbon 7 of the pyrazine ring, with a minor amount of 7-exo methylene form which may result from either the addition of hydroxide ion from the solvent to carbon 7

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(2) The data presented in this publication were derived from a Ph.D. Thesis by R. L. Beach submitted to Rutgers University, 1970. Summaries of more detailed results can be obtained from this author upon request.

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