row, and into the first was added, *via* micropipet, one drop, the second two drops, the third three drops, etc., of the first solution, then into the first tube nine drops, the second eight drops, the third seven drops, etc., of the second solution. The ten-drop mixtures were evaporated to dryness at aspirator pressures in a desiccator, and each residue was ground and powdered intimately, with a glass rod, then dried at 0.1 mm over P_2O_5 for several hours. Melting ranges were determined in capillary tubes in a Thomas–Hoover "Unimelt," with a heating rate of *ca.* 0.5°/min during melting. The onset and completion of melting was frequently difficult to estimate, especially when the range was large. With some practice, however, a reproducibility of ±0.5 to 1.0° was generally achievable in duplicate determinations of each set of diagrams.

Raney Nickel and O-Benzyl-(*S*)-(−)-atrolactamide.—A mixture of the above levorotatory amide (0.25 g), Raney nickel catalyst (8 g), and absolute ethanol (25 ml) was heated under reflux for 5 hr, then cooled and filtered with a sintered-glass funnel, and the residual catalyst was rinsed with ethanol. The filtrate was stripped of solvent to yield 0.15 g (100%) of white solid. This was recrystallized from a mixture of benzene (1 ml) and hexane (5 ml), producing 0.12 g of shining white platelets, mp 93.5–94.5°, $[\alpha]_D^{28}$ −35.3° (*c* 1.24, 75% EtOH). Another recrystallization, with intermediate filtration through a Norit bed, gave a sample having mp 94.5–95°, $[\alpha]^{25}D$ −37.4° (*c* 1.44, 75% EtOH) and $[\alpha]^{25}D$ −41.2° (*c* 0.85, absolute EtOH), whose infrared spectrum in $CHCl_3$ solution was identical in all respects with that of authentic hydratropamide. The present product is 88% optically homogeneous, based on $[\alpha]D$ ±46.5° for optically pure hydratropamide.[16] The rotations of the above product in absolute ethanol and 75% ethanol are in a ratio of 1.10:1. This ratio has been used to correct the rotations of our previous hydratropamide samples[2] from 75% ethanol to absolute ethanol in order to make the corrected estimates of the optical purity of these earlier samples noted above.

Registry No.—I, 13479-08-8; (−)-I (+)-DEATC derivative, 13448-64-1; (+)-IVa, 13448-65-2; (+)-IVa (−)-DEATC derivative, 13473-45-5; (−)-IVa, 13448-66-3; (−)-IVa (+)-DEATC derivative, 13448-67-4; (+)-IVb, 13448-68-5; (−)-IVb, 13448-69-6; IVc, 13448-70-9; VIb, 13448-71-0; VIe, 13448-72-1; VIe (+)-DEATC derivative, 13448-73-2; *O*-benzyl-(*S*)-(+)-atrolactic acid, 13448-74-3; O-benzyl-(*S*)-(+)-atrolactic acid (−)-DEATC derivative, 13448-75-4; O-benzyl-(*S*)-(−)-atrolactamide, 13448-76-5; methyl (*R*)-(−)-2-phenyl-2-phenylmercaptopropionate, 13448-77-6; (+)-α-phenylethylammonium (−)-2-phenyl-2-benzylmercaptopropionate, 13448-78-7; (−)-α-phenylethylammonium (+)-2-phenyl-2-benzylmercaptopropionate, 13448-79-8; methyl (*S*)-(+)-atrolactate, 13448-80-1; methyl (*R*)-(−)-atrolactate, 13448-81-2; (*R*)-(−)-α-benzylmercaptophenylacetic acid (−)-DEATC derivative, 13479-09-9; O-benzyl-(*R*)-(−)-mandelic acid (−)-DEATC derivative, 13448-82-3; O-benzyl-(±)-atrolactic acid, 13448-83-4; O-benzyl-(±)-atrolactamide, 13448-84-5; (±)-2-phenyl-2-benzylmercaptopropanoic acid, 13448-85-6; 2-phenyl-3-benzylmercaptopropanoic acid, 13448-86-7.

Acknowledgment.—One of us (W. A. B.) is grateful to the National Institutes of Health (GM-06232-07) for its generous support of a portion of this research during the summer of 1966.

Tautomerism of 2-Substituted Benzo[*b*]thiophenes. Ultraviolet Spectral Correlation of Tautomer Structure with Aromaticity[1a,b]

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Received April 10, 1967

Stepwise methylation of *o*-benzylthiophenylacetonitrile (**2**) conveniently affords a route to the 2-amino-3-methylbenzo[*b*]thiophene (**6**) and the more critically significant dimethyliminodihydrobenzo[*b*]thiophene (**1**). Study of the infrared and nuclear magnetic resonance spectra of **1** and **6** and derivatives in comparison with related compounds previously obtained provides further evidence for imino–amino structural assignments, as well as a firm basis for the assignment of the hitherto uncertain 2-oxygen-substituted derivatives. Strategic confirmation of the 2-aminobenzo[*b*]thiophene structure was accomplished by comparison of the acetyl derivative of **6** with the same material derived from the corresponding 2-nitro intermediate. The synthesis of **6** and **1** in excellent yield further demonstrated the utility of anhydrous aluminum bromide in removal of a masking benzyl group from the sulfur function in the ring tautomeric heterocyclization reaction. Various studies of tautomer chemistry involving Schiff base, hydrochloride, and disulfide formation are described. Convenient differentiation of tautomer structures was discovered possible by correlation of ultraviolet spectral properties with the aromaticity of the ring system.

A major type of tautomerism in heterocyclic systems is that involving proton location between an annular carbon atom and an atom adjacent to the ring.[2] 2-Aminobenzo[*b*]thiophene, recently synthesized in this laboratory,[3] is an example. An opportunity to accumulate persuasive spectroscopic evidence on the tautomerism of these systems was seen in the methylated series **3a** → **6** and **4a** → **1** (Scheme I). Special interest centered on the dimethyliminodihydrobenzo[*b*]thiophene (**1**), as in this case the amino structure, of course, is precluded by methyl substitution at position 3, thus making possible unequivocal assignments consistent with the imino function.

It had been hoped that the synthesis of **1** would be easily accomplished by the appropriate dialkylation of **2**. A procedure for dialkylation of phenylacetonitrile described by Bloomfield[4] unfortunately led to a mixture of mono- and dimethylated derivatives (**3a** and **4a**). However, possible use of benzyl chloride as an alkylating agent suggested a convenient product separation as a consequence of a possibly wider margin in boiling

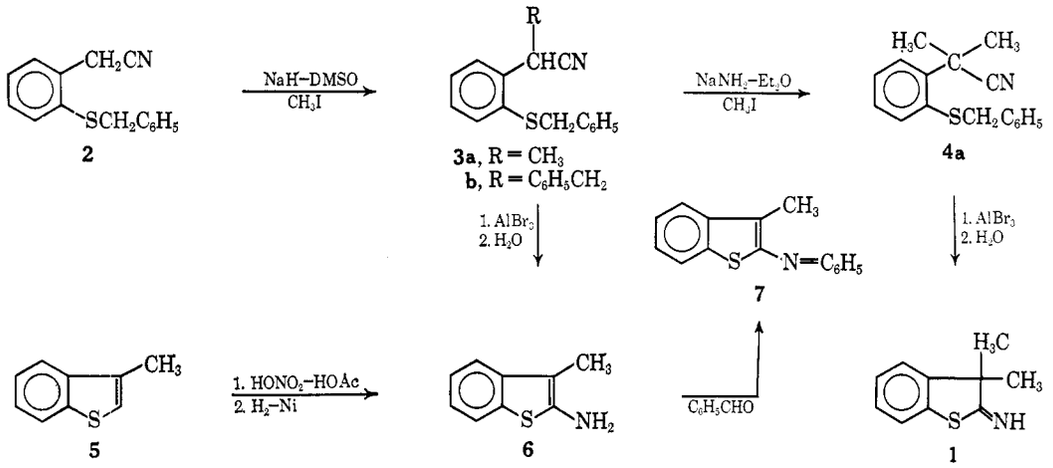
(1) (a) Presented before the Division of Organic Chemistry at the 150th Meeting of the American Chemical Society, Pittsburgh, Pa., April 1966. (b) For paper IV on Tautomerism, see G. W. Stacy and P. L. Strong, *J. Org. Chem.*, **32**, 1487 (1967). (c) National Science Foundation Summer Fellow, 1963; National Science Foundation Cooperative Fellow, 1963–1964. (d) In part from the Ph.D. Thesis of T. E. Wollner, Washington State University, June 1965.

(2) A. R. Katritzky, *Advan. Heterocyclic Chem.*, **1**, 313, 347, 328 (1963).

(3) (a) G. W. Stacy, F. W. Villaescusa, and T. E. Wollner, *J. Org. Chem.*, **30**, 4074 (1965); (b) the enclosure denotes the stable tautomer of the various possibilities under discussion.

(4) J. J. Bloomfield, *J. Org. Chem.*, **26**, 4112 (1961).

SCHEME I



points. This line of experimentation did, in fact, yield favorable results. Use of conditions employing sodium hydride in dimethyl sulfoxide lead to a 76% yield of the monobenzylated product (**3b**). Extension of this procedure to the preparation of **3a** was equally satisfactory (91% yield).

Nevertheless, deployment of this pure monomethyl intermediate (**3a**) for introduction of a second methyl group to form **4a** was still fraught with frustration. After a number of experiments involving sodium hydride–dimethyl sulfoxide or sodium hydride–dimethyl formamide, we finally developed a method bearing similarity to the one reported by Bodroux and Taboury.[5] This superior procedure utilized sodium amide–ether to give 90% yield of the desired dimethylated product (**4a**). Nmr spectra of these mixtures were most useful in following the course of the reaction, as the purity of the product could be determined in reference to the disappearance of a benzyl proton.

In the present investigation, the use of anhydrous aluminum bromide for the cleavage of a benzyl sulfide[6] with simultaneous heterocyclization[3a] again proved to be an effective procedure. Thus, treatment of the appropriate intermediate in benzene with the aluminum bromide, followed by the addition of water for hydrolysis of the complex, gave both the desired iminodihydrobenzo[*b*]thiophene (**1**) from **4a** and the aminobenzo[*b*]thiophene (**6**) from **3a**, both in excellent yield. As expected, spectroscopic data for these two structures were contrasting and completely confirmatory. The infrared spectrum for **1** gave a strong band corresponding to the imino NH stretching region (3200 cm^{-1}) as well as a band for the C=N group (1610 cm^{-1}); on the other hand, for **6** the NH absorption band was expectedly at 3420 and 3340 cm^{-1}, with no band being observed for C=N. Also, there was no evidence for absorption for SH or C≡N groups. The nmr spectra constituted equally impressive evidence. The iminodihydrobenzo[*b*]thiophene (**1**) showed three chemical shifts at δ 9.13, 7.05, and 1.40 with an area ratio of 1:4:6. In earlier work,[7] it had been shown that the chemical shift for the imino proton appears in the region of 9.7. For **6** the characteristic chemical shift for the aromatic amino group[8] was found at 3.5.

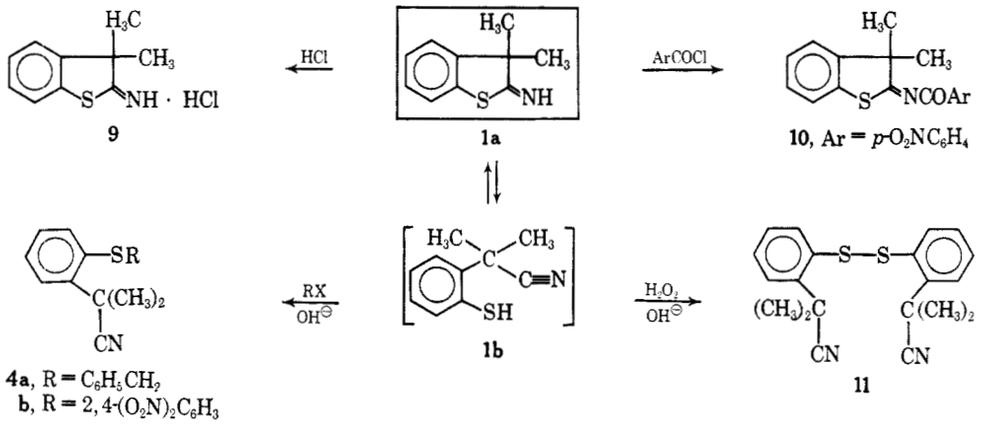
The present series of methylated benzo[*b*]thiophenes provided an advantageous situation for structure confirmation by comparison of an aminobenzo[*b*]thiophene prepared by tautomeric heterocyclization with the same substance from the corresponding nitrobenzo[*b*]-thiophene. The acetyl derivative (**8**) of **6** represented the common reference point, since, in earlier work on aminothiophenes, serious attempts at isolation of these supposedly unstable substances were deferred to separation as derivatives. Accordingly, 2-acetamino-3-methylbenzo[*b*]thiophene (**8**) has been prepared by nitration of 3-methylbenzo[*b*]thiophene (**5**), subsequent Raney nickel reduction of the nitro intermediate, and acetylation of the crude mixture.[9] The melting point (182.5–183°) is identical with that of a sample of **8** prepared from our 2-amino-3-methylbenzo[*b*]thiophene (**6**).

The chemical tautomerism of the aminobenzo[*b*]thiophene (**6**) and the iminodihydrobenzo[*b*]thiophene (**1**) was characterized by several types of reactivity. In accord with the well-known behavior of the amines,[2] **6** reacted with benzaldehyde to give Schiff base (**7**) (91%), whereas the imino group in **1** cannot react in this manner and indeed fails to react at all. Both **6** and **1**, on the other hand, form acyl derivatives (**8** and **10**), respectively.

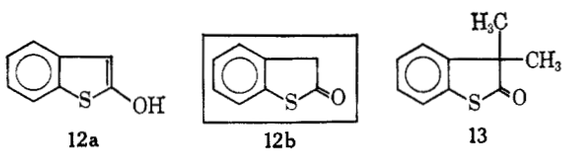
Of much interest was the fact that system **1** showed chemical reactivity consistent with ring–chain tautomerism.[1b] In addition to the acyl derivative (**10**), the ring tautomer (**1**) was also defined by hydrochloride formation (**9**) (Scheme II). Conversely, under alkaline conditions, ring opening occurred to give chain derivatives. With appropriate halides, sulfides (**4a** and **4b**) were formed,[1] **4a** being identical with the intermediate obtained from **3a** by methylation. By treatment of **1** with hydrogen peroxide under alkaline conditions, a disulfide (**11**) resulted in good yield (85%).[1b] The latter reaction is of particular interest when contrasted with the treatment of 2-aminobenzo[*b*]thiophene under identical conditions. As seen previously,[3] ring opening to yield a corresponding disulfide fails to occur in this instance, in keeping with its aromatic stability.

(5) F. Bodroux and F. Taboury, *Bull. Soc. Chim. France*, (**4**)**7**, 667 (1910).
(6) D. P. Harnish and D. S. Tarbell, *J. Am. Chem. Soc.*, **70**, 4123 (1948).
(7) G. W. Stacy, A. J. Papa, F. W. Villaescusa, and S. C. Ray, *J. Org. Chem.*, **29**, 607 (1964).
(8) (a) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 73; (b) H. S. Gutowsky, L. H. Meyer, and A. Saika, *J. Am. Chem. Soc.*, **75**, 4567 (1953).
(9) D. A. Shirley, M. J. Danzig, and F. C. Canter, *ibid.*, **75**, 3278 (1953).

SCHEME II



The 2-oxygen-substituted benzo[*b*]thiophene (**12**) had been reported to have been isolated in both tautomeric forms (**12a** and **12b**).[10] Recently, we reported



the formation of **12** by the acidic hydrolysis of 2-aminobenzo[*b*]thiophene; a preliminary examination of this substance suggested that it existed entirely as the thio lactone (**12b**).[3] Our current work now convincingly confirms this observation. Acidic hydrolysis of **1** comparable with examples previously reported[7,11] produced a similar thio lactone (**13**), which like **12** had a strong infrared absorption peak at 1700 cm^{-1} (thio lactone carbonyl). The spectrum of **12** gave no evidence of an absorption band corresponding to an O–H stretching frequency, while, of course, **13** is incapable of existing in this form and consequently shows no such band. So, **12** and **13** resemble a number of heteroaromatic compounds with an oxygen function α or γ to the heteroatom, which show carbonyl rather than hydroxyl character.[2,12]

By a correlation of the position maxima in the ultraviolet spectra, we found it possible to assign tautomeric structures for all our benzothiophene derivatives with considerable covenience. The spectra are diagnostic of the aromatic or dihydro forms and in this way they distinguish between the amino and imino tautomers. This technique is novel in characterizing a stable tautomer, as compared with classical procedure of examining tautomeric structures in terms of the spectra of alkylated derivatives.[2] The spectrum of the iminodihydrobenzo[*b*]thiophene (**1**) showed λ_{max} 260 mμ (ϵ 7300) and was quite similar to that of dihydrobenzo[*b*]thiophene, λ_{max} 260 mμ (ϵ 6310).[13]

On the other hand, the spectrum of 2-aminobenzo[*b*]thiophene diverges from that of **1**, giving λ_{max} 281 mμ (ϵ 9000), and matches the spectrum of benzo[*b*]thiophene, λ_{max} 288 mμ (ϵ 2300). A comparison of the data in Table I indicates a persuasive correlation

TABLE I

Compound	λ_{max}^{EtOH}, mμ	ϵ
Benzo[*b*]thiophene	288	2,300
2-Aminobenzo[*b*]thiophene	281	9,000
2-Aminobenzo[*b*]thiophene hydrochloride	281	13,500
2-Amino-3-methylbenzo[*b*]thiophene (**6**)	285	9,700
2-Amino-3-methylbenzo[*b*]thiophene hydrochloride	284	12,200
Dihydrobenzo[*b*]thiophene	260	6,310
2-(3H)-Thianaphthenone (**12b**)	260	4,000
2,3-Dihydro-3,3-dimethyl-2-thianaphthenone (**13**)	262	4,350
2,3-Dihydro-3,3-dimethyl-2-iminobenzo[*b*]-thiophene (**1**)	260	7,300
2,3-Dihydro-3,3-dimethyl-2-iminobenzo[*b*]-thiophene hydrochloride (**9**)	261	5,700

of these values with those of related compounds. It should be further noted that ultraviolet spectra of 2-oxygenated benzo[*b*]thiophenes (**12** and **13**) also have absorption maxima at 260 mμ (ϵ 4000) and 262 mμ (ϵ 4350), thus agreeing closely with the spectra of the imino tautomer. This constitutes strong, confirmatory evidence for the thio lactone structures assigned to **12** and **13**.

In conclusion, it is apparent that the 2-nitrogen-substituted benzo[*b*]thiophenes exist as stable amino tautomers rather than in the imino structure. This observation is consistent with the findings of Gronowitz and Hoffman[14] for 2-aminothiophene and those of Dudek and Volpp for enamines in general.[15] Further, these data follow the general trend of α- and γ-nitrogen-substituted heterocycles to show amino rather than imino character.[2] It is of interest to contrast the reluctance of nitrogen to form a double bond in the face of a single-bond alternative[2,15] with the contrary trend that an extranuclear oxygen α or γ to a heteroatom shows carbonyl rather than hydroxyl character, even though the former seemingly has a smaller delocalization energy.[16]

Experimental Section

All melting points are corrected; boiling points at reduced pressures are uncorrected. Microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were determined on Beckman IR-5 or IR-8 spectrophotometers

(10) (a) C. Marschalk, *J. Prakt. Chem.*, **88**, 227 (1913); (b) R. H. Thomson, *Quart. Rev.* (London), **10**, 27 (1956).

(11) A. W. Day and S. Gabriel, *Ber.*, **23**, 2478 (1890).

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(13) H. E. Ungnade, "Organic Electron Spectral Data," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1960, p 138.

(14) S. Gronowitz and R. A. Hoffman, *Arkiv Kemi*, **15**, 499 (1960).

(15) (a) G. O. Dudek and G. P. Volpp, *J. Am. Chem. Soc.*, **85**, 2697 (1963); (b) G. O. Dudek and R. H. Holm, *ibid.*, **84**, 2691 (1962).

(16) R. D. Brown, *Proc. Roy. Australian Chem. Inst.*, **31**, 1 (1964).

with sodium chloride optics throughout; spectra of liquids were run as neat films. The nmr spectra were determined by a Varian A-60 spectrometer using carbon tetrachloride and deuterated chloroform as solvents and tetramethylsilane as an internal reference. The chemical shift in parts per million is followed in parentheses by the splitting pattern: cm = complex multiplet, q = quartet, d = doublet, singlets being otherwise assumed; the number of protons found by integration is then indicated. The "work-up" of most reaction mixtures consisted of extraction with ether, washing of the combined extracts with saturated sodium chloride solution, drying over anhydrous magnesium sulfate, and removal of the ether prior to distillation.

α-Benzyl-o-benzylthiophenylacetonitrile (3b).—A solution of 2.39 g (0.01 mole) of *o*-benzylthiophenylacetonitrile (**2**)[3] in 5 ml of purified dimethyl sulfoxide was added to a stirred suspension of 0.26 g (0.011 mole) of sodium hydride in 7 ml of purified dimethyl sulfoxide (nitrogen). The mixture was allowed to stir 50 min at room temperature and then 1.27 g (0.01 mole) of benzyl chloride was added dropwise. The mixture was stirred at room temperature for 9 hr and was then poured into 50 ml of ice water. After work-up, the viscous residue was molecularly distilled at 180° (0.05 mm) to yield 2.50 g (76%): $n^{25}D$ 1.6192; d^{25}_4 1.1825; ν_{max} 2240 (w, C≡N) cm^{-1}; δ 6.8–7.4 (cm, C_6H_5), 4.3–4.6 (t, CH), 3.9 (SCH_2), 3.8–3.9 (d, CH_2), ratio 14:2:2.

Anal. Calcd for $C_{22}H_{19}NS$: C, 80.22; H, 5.81; S, 9.74. Found: C, 80.13; H, 5.81; S, 9.88.

α-Methyl-o-benzylthiophenylacetonitrile (3a).—A solution of 7.17 g (0.03 mole) of **2** in 15 ml of purified dimethyl sulfoxide was added to a stirred suspension of 0.76 g (0.032 mole) of sodium hydride in 15 ml of purified dimethyl sulfoxide (nitrogen). The mixture was stirred at room temperature for 20 min and then cooled while 4.30 g (0.031 mole) of methyl iodide in 4 ml of dimethyl sulfoxide was added dropwise. The mixture was stirred an additional 12 hr at room temperature and was poured into 150 ml of ice water. After work-up, vacuum distillation gave 7.00 g (91%) of **3a**: bp 140–145° (0.06 mm); $n^{25}D$ 1.6031; d^{25}_4 1.1421; $\nu_{max}^{10\%\ CHCl_3}$ 2040 (m, C≡N) cm^{-1}; δ 7.0–7.5 (cm, C_6H_5), 4.1–4.4 (q, CH), 3.9 (CH_2), 1.2–1.3 (d, CH_3), ratio 9:1:2:3.

Anal. Calcd for $C_{16}H_{15}NS$: C, 75.84; H, 5.97; S, 12.66. Found: C, 75.98; H, 6.05; S, 12.49.

α,α-Dimethyl-o-benzylthiophenylacetonitrile (4a).—A solution of 15.20 g (0.06 mole) of α-methyl-*o*-benzylthiophenylacetonitrile (**3a**) in 60 ml of anhydrous ether was added dropwise to a stirred suspension of 2.42 g (0.062 mole) of sodium amide in 120 ml of anhydrous ether (nitrogen). The mixture was heated under reflux for 0.5 hr and was then cooled while a solution of 8.80 g (0.062 mole) of methyl iodide in 60 ml of anhydrous ether was added dropwise. After the mixture was stirred 17 hr at room temperature, it was then cooled in an ice bath while 50 ml of cold water was added dropwise. After work-up, the solid residue was most readily purified by distillation to yield 14.4 g (90%): bp 141–145° (0.05 mm); mp 61–62° (crystallized from pentane); $\nu_{max}^{10\%\ CHCl_3}$ 2230 (m, C≡N) cm^{-1}; δ 7.0–7.4 (cm, C_6H_5), 4.1 (CH_2), 1.7 (CH_3), ratio 9:2:6.

Anal. Calcd for $C_{17}H_{17}NS$: C, 76.36; H, 6.41; S, 11.99. Found: C, 76.50; H, 6.58; S, 12.12.

2,3-Dihydro-3,3-dimethyl-2-iminobenzo[b]thiophene Hydrochloride (9).—A solution of 2.50 g (0.0094 mole) of α,α-dimethyl-*o*-benzylthiophenylacetonitrile (**4a**) in 20 ml of anhydrous benzene was added dropwise under nitrogen to a cooled, stirred solution of 3.20 g (0.012 mole) of anhydrous aluminum bromide in 20 ml of anhydrous benzene. The solution, which became dark red, was stirred for 24 hr at room temperature. After the mixture had been cooled in an ice bath, 40 ml of ether was added followed by the dropwise addition of 40 ml of cold water. The ether phase was separated and worked up accordingly. The residue was dissolved in 50 ml of dry ether and anhydrous hydrogen chloride was introduced to yield 1.77 g (86%) of **9**: mp 190–195° dec; λ_{max}^{EtOH} 261 mμ (ε 5700). Hydrochloride **9** could, of course, also be prepared from the free base **1**.

Anal. Calcd for $C_{10}H_{12}ClNS$: C, 56.19; H, 5.66; S, 15.00; Cl, 16.59. Found: C, 56.16; H, 5.80; S, 15.10; Cl, 16.66.

2,3-Dihydro-3,3-dimethyl-2-iminobenzo[b]thiophene (1).—A mixture of 1.77 g (0.0083 mole) of **9** and 20 ml of cold 10% sodium hydroxide solution was stirred 15 min and was extracted with three 30-ml portions of ether. After work-up, the residue was molecularly distilled at 115° (0.05 mm) to yield 1.00 g (68%) of the free base: $n^{25}D$ 1.2120; λ_{max}^{EtOH} 260 mμ (ε 7300); ν_{max} 3200 (w, NH), 1610 (w, C=N) cm^{-1}; δ 7.05 (cm, C_6H_5), 1.40 (CH_3), 9.13 (NH), ratio 4:6:1.

Anal. Calcd for $C_{10}H_{11}NS$: C, 67.75; H, 6.26; N, 7.90; S, 18.09. Found: C, 67.62; H, 6.18; N, 7.84; S, 18.20.

2-Amino-3-methylbenzo[b]thiophene (6).—To a cooled, stirred solution of 7.00 g (0.026 mole) of anhydrous aluminum bromide in 40 ml of anhydrous benzene was added dropwise a solution of 4.00 g (0.016 mole) of α-methyl-*o*-benzylthiophenylacetonitrile (**3a**) in 10 ml of anhydrous benzene (nitrogen). The mixture was stirred at room temperature for 28 hr and then cooled in an ice bath while 70 ml of water was added dropwise to hydrolyze the intermediate complex. After work-up, distillation of the residue yielded 2.00 g (78%) of a light yellow oil: bp 96–100° (0.05 mm); $n^{25}D$ 1.6551; d^{25}_4 1.1131; λ_{max}^{EtOH} 285 mμ (ε 9700); ν_{max} 3420 and 3340 (m, NH); δ 7.1–7.5 (cm, C_6H_5), 3.5 (NH_2), 2.0 (CH_3). The hydrochloride of **6** was formed by introduction of anhydrous hydrogen chloride into an ether solution: mp 175–180° dec; λ_{max}^{EtOH} 284 mμ (ε, 12,200); ν_{max}^{KBr} 3390 (m, NH), 2560 (w, $NH_3^+Cl^-$).

Anal. Calcd for $C_9H_{10}ClNS$: C, 54.13; H, 5.05; S, 16.06; Cl, 17.75. Found: C, 54.20; H, 5.06; S, 15.82; Cl, 17.79.

2-Acetamino-3-methylbenzo[b]thiophene (8).—To a solution of 160 mg (1.0 mmole) of **6** in 5 ml of anhydrous benzene was added 100 mg (1.0 mmole) of acetic anhydride dropwise and the mixture was stirred at room temperature for 1 hr. The solid was collected by filtration and was washed with benzene to yield 180 mg (88%), mp 181–182°. Recrystallization from methanol afforded 140 mg (79%) of colorless cubes: mp 182–183° (lit.[9] mp 182.5–183°); $\nu_{max}^{10\%\ CHCl_3}$ 3320 (m, NH), 1680 (w, C=O).

Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; S, 15.62. Found: C, 64.49; H, 5.45; S, 15.81.

2-(N-Benzylidenamino)-3-methylbenzo[b]thiophene (7).—To a solution of 160 mg (1.0 mmole) of 2-amino-3-methylbenzo[*b*]-thiophene (**6**) in 2 ml of 95% ethanol was added 110 mg (1.0 mmole) of benzaldehyde; the resulting mixture was heated on a stream bath for 5 min. After the mixture had been cooled, the product was filtered off: yield 230 mg (91%), mp 88–89°. Recrystallization from 95% ethanol produced 200 mg (80%) of yellow crystals: mp 90°; ν_{max}^{KBr} 1615 (m, C=N) cm^{-1}.

Anal. Calcd for $C_{16}H_{13}NS$: C, 76.46; H, 5.21; S, 12.76. Found: C, 76.62; H, 5.40; S, 13.01.

2,3-Dihydro-3,3-dimethyl-2-(N-p-nitrobenzoyl)-iminobenzo[b]-thiophene (10).—A solution of 0.32 g (0.0016 mole) of the imino hydrochloride (**9**) and 0.30 g (0.0016 mole) of *p*-nitrobenzoyl chloride in 4 ml of pyridine was stirred for 2 hr at room temperature and then was heated on a steam bath for 0.5 hr. Cold water (20 ml) was added to the cooled mixture and the resulting solid was collected by filtration to yield 0.33 g (64%): mp 167–170°; ν_{max}^{KBr} 1650 (w, imide C=O), 1610 (w, C=N) cm^{-1}; δ 7.3–7.6, 6.4–6.6 (cm, C_6H_5), 0.8 (CH_3), ratio 4:3.

Anal. Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.56; H, 4.32; S, 9.83. Found: C, 62.32; H, 4.20; S, 9.85.

α,α-Dimethyl-o-benzylthiophenylacetonitrile (4a) from 2,3-Dihydro-3,3-dimethyl-2-iminobenzo[b]thiophene (1).—To 20 ml of absolute ethanol in which 0.46 g (0.02 g-atom) of sodium metal has been carefully dissolved was added 2.14 g (0.01 mole) of hydrochloride (**9**). After the solution had been stirred at room temperature for 1 hr (nitrogen), 1.27 g (0.01 mole) of benzyl chloride was added dropwise. The resulting mixture was stirred overnight at room temperature and was then heated under reflux for 4 hr. After the ethanol had been removed under reduced pressure, the residue was taken up in 80 ml of ether. After work-up, the residue was distilled to yield 2.00 g (75%) of the anticipated product (**4a**), bp 141–145° (0.05 mm), mp 55–58°. Crystallization of this material from pentane yielded 1.32 g (68%), mp 60–61°. The infrared spectrum was identical with that of a sample prepared from α-methyl-*o*-benzylthiophenylacetonitrile (**3a**).

α,α-Dimethyl-o-(2,4-dinitrophenylthio)phenylacetonitrile (4b).—To a stirred solution of 0.64 g (3.0 mmoles) of **9** in 40 ml of absolute ethanol was added 0.24 g (6.0 mmoles) of sodium hydroxide in 3 ml of water (nitrogen). After this solution was added dropwise to a solution of 0.61 g (3.0 mmoles) of 2,4-dinitrochlorobenzene in 10 ml of absolute ethanol, the mixture was stirred 2 hr at room temperature and was then cooled. Filtration of the solid yielded 0.96 g (93%) of glistening yellow crystals, mp 159–161°. Recrystallization of this product from absolute ethanol gave 0.90 g (88%): mp 160–161°; $\nu_{max}^{10\%\ CHCl_3}$ 2210 (w, C≡N), 1520, 1340 (s, NO_2) cm^{-1}.

Anal. Calcd for $C_{16}H_{13}N_3O_4S$: C, 55.96; H, 3.81; S, 9.34. Found: C, 55.66; H, 3.90; S, 9.20.

Bis-o-(2-cyano-2-propyl)phenyl Disulfide (11).—To a mixture of 2.14 g (0.01 mole) of **9** and 1.30 g (0.033 mole) of sodium

hydroxide in 40 ml of of water at 80–90° was added 4 ml of 30% hydrogen peroxide dropwise over a period of 0.5 hr with vigorous stirring. After the mixture had been stirred for an additional 1 hr at 80–90° and cooled, it was extracted with three 30-ml portions of chloroform. The chloroform extracts were washed consecutively with 20 ml of 5% hydrochloric acid, 20 ml of saturated sodium bicarbonate solution, and 20 ml of saturated sodium chloride solution. After the chloroform was removed, the residue was molecularly distilled at 220° (0.05 mm) to yield 1.50 g (85%) of a very viscous product: $\nu_{max}^{10\%\ CCl_4}$ 2240 (m, C≡N) cm^{-1}; δ 7.0–7.8 (cm, C_6H_5), 1.8 (CH_3), ratio 2:3.

Anal. Calcd for $C_{20}H_{20}N_2S_2$: C, 68.14; H, 5.72; S, 18.19. Found: C, 68.06; H, 5.67; S, 18.33.

3,3-Dimethyl-2-thianaphthenone (13).—A solution of 1.07 g (0.005 mole) of **9** in 40 ml of 6 *N* hydrochloric acid was heated under reflux for 2 hr. The mixture was cooled and extracted with three 25-ml portions of ether. The ether solution was washed with 20 ml of saturated sodium chloride solution, 20 ml of saturated sodium bicarbonate solution, and 20 ml of saturated sodium chloride solution. After final work-up, distillation of the residue yielded 0.75 g (84%): bp 54–55° (0.05 mm); $n^{25}D$ 1.5750; ν_{max} 1695 (w, thio lactone C=O) cm^{-1}; λ_{max}^{EtOH} 262 mμ (ϵ 4350); δ 7.1–7.3 (cm, C_6H_5), 1.4 (CH_3), ratio 2:3.

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.56; H, 5.66; S, 17.88.

Registry No.—**1**, 13584-50-4; **3a**, 13584-51-5; **3b**, 13584-52-6; **4a**, 13584-53-7; **4b**, 13584-54-8; **6**, 13584-55-9; **6** hydrochloride, 13584-56-0; **7**, 13584-57-1; **8**, 13584-58-2; **9**, 13584-59-3; **10**, 13584-60-6; **11**, 13584-61-7; **12b**, 496-31-1; **13**, 13584-63-9; benzo[*b*]thiophene, 95-15-8; 2-aminobenzo[*b*]thiophene, 4521-30-6; 2-aminobenzo[*b*]thiophene hydrochloride, 13584-65-1.

Acknowledgment.—We wish to thank donors of the Petroleum Research Fund, administered by the American Chemical Society, for Grant 2403-A1,4 and PRF International Award 1680-D in partial support of this work.

Synthesis of Guanosine and Its Derivatives from 5-Amino-1-β-D-ribofuranosyl-4-imidazolecarboxamide. II. Ring Closure with Sodium Methylxanthate[1]

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Received February 23, 1967

A novel and convenient method for the synthesis of guanosine is described. The reaction of 5-amino-1-β-D-ribofuranosyl-4-imidazolecarboxamide (AICA-riboside) with sodium methylxanthate gave 2-mercaptoinosine (I), in almost quantitative yield, which was oxidized with hydrogen peroxide to afford inosine-2-sulfonic acid (IV). Compound IV was readily aminated to give guanosine (VII) in excellent yield. In a similar fashion, the preparation of N^2-methylguanosine (VIII) and N^2,N^2-dimethylguanosine (IX), the minor constituents of transfer ribonucleic acid, was accomplished. Further, this method was extended to the synthesis of 2′,3′-O-isopropylideneguanosine (XV) and the isopropylidene derivatives of various N^2-substituted guanosines from 5-amino-4-carbamoyl-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)imidazole (Ip-AICA-riboside).

Although several methods for the preparation of guanosine (VII) have been reported by Davoll, *et al.*,[2–4] involving the condensation of a metallic salt of purine base with a blocked halo sugar followed by the variation of substituents of the purine ring, the over-all yield of VII obtained by such a procedure is very low. Furthermore, disodium guanosine 5′-phosphate (5′-guanylic acid as well as disodium inosine 5′-phosphate (5′-inosinic acid) has been found to be a useful seasoning agent.[5] This finding prompted us to investigate a new synthetic route to VII or 2′,3′-O-isopropylideneguanosine (XV) which is an important precursor for the synthesis of 5′-guanylic acid.

As the starting material, we employed the pure 5-amino-1-β-D-ribofuranosyl-4-imidazolecarboxamide (AICA-riboside) which was accumulated in the culture broth of the mutant of *Bacillus subtilis* and purified by ion-exchange chromatography.[6]

In a preceding paper,[7] XV was shown to be obtained by the ring-closure reaction of 5-amino-4-carbamoyl-1-(2′,3′-O-isopropylidene-β-D-ribofuranosyl)imidazole (Ip-AICA-riboside)[8,9] with benzoyl isothiocyanate. This method, however, proceeds with a concomitant formation of an equivalent amount of benzoic acid in the last step and the over-all yield of XV based on Ip-AICA-riboside was not satisfactory.

Shaw[10] reported that attempts to obtain guanine from 5-amino-4-imidazolecarboxamide (AICA) using ring-closing reagents such as guanidine, S-methyl isothiourea, and cyanamide, were unsuccessful. From these results, it seemed to be extremely difficult to convert AICA-riboside directly into VII.

It has been reported that the amination of 2-methylthioinosine (V)[4] prepared by chloromercuri method[11] yielded VII. If 2-mercaptoinosine (I), that is, 2-thioxanthosine, could be obtained from AICA-riboside, a new route for preparing VII would be provided by methylation of I followed by amination. Accordingly, many attempts have been made to convert AICA-riboside into I with thiourea, thiophosgen, thiocyanic acid, O,S-dimethyl xanthate,[12] and carbon disulfide in pyridine,[13] but were found to be unsuccessful in all cases. When sodium methylxanthate was employed, however, a satisfactory result was obtained. By reaction of AICA-riboside with 5 equiv of sodium methyl-

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