Synthesis of Pyrrolo[2,3-*b*]pyrrole Derivatives[1]

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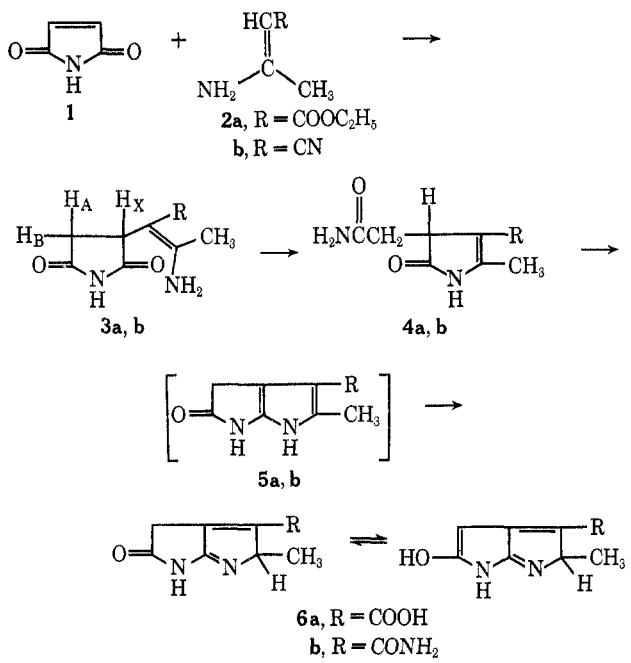
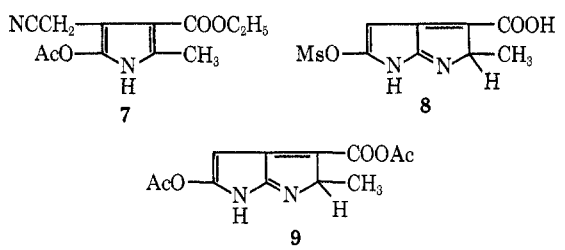
Reaction of maleimide and ethyl 3-aminocrotonate gives the aminovinylsuccinimide **3a**. On heating, **3a** is converted to the pyrrolinonacetamide **4a**. Treatment of **4a** with Ac_2O gives the 2-acetoxypyrrole-3-acetonitrile **7**. In base, **4a** undergoes cyclization to the pyrrolopyrrole **6**. Analogous compounds were obtained from maleimide and 3-aminocrotononitrile.

In recent years considerable attention[2] has been given to the applicability of the Nenitzescu synthesis[3] for the preparation of 5-hydroxy-3-carbalkoxyindole derivatives. The general route involves the condensation of a 1,4-benzoquinone with an appropriate 3-aminocrotonate. Our interest in the construction of various nitrogen, oxygen, and sulfur isosteres of biologically active indole-containing compounds led us to investigate the feasibility of extending this reaction to the synthesis of pyrrolo[2,3-*b*]pyrrole derivatives.

When one considers that the sulfur atom is isosteric with a vinyl group (ring equivalents)[4] and that the oxygen and nitrogen (–NH–) atoms are isosteric with sulfur or the vinyl group, then maleimide, maleic anhydride, or thiomaleic anhydride[5] may be expected to behave chemically as isosteres of 1,4-benzoquinone. In fact, maleimide and maleic anhydride have been described as pyrrolequinone and furanquinone in some early work.[6] Maleimide (**1**) was chosen for our initial studies, and its reaction with ethyl 3-aminocrotonate (**2a**) gave a product (**3a**), mp 156–158°. Structural assignment was made from infrared, nmr, and elemental analysis data. From previous experience with the Nenitzescu reaction, one would have anticipated direct isolation of the pyrrolo[2,3-*b*]pyrrole (**5**), but in this case a possible intermediate (**3a**) proposed to occur in the reaction sequence was isolated and characterized. Heating of **3a** in xylene (or organic solvents boiling above 100°) gave a product (**4a**), mp 231–234°, as anticipated when an amine is heated with an imide.[7] Intermediates analogous to **3a** and **4a** have been described by Robson and Marcus[8] when maleic anhydride was treated with 3-methylaminocrotonate. Structural assignment for **4a** was confirmed by infrared, elemental analysis, and nmr data. The coupling for **4a** (see Experimental Section) was similar to that observed for 3-carbomethoxy-1,2-dimethyl-5-oxo-2-pyrroline-4-acetic acid[8] and 3-carbethoxy-2,4-dimethyl-5-oxo-2-pyrroline.[9]



Conditions designed to convert **4** into **5** (*e.g.*, refluxing in ethylene glycol with a trace of sulfuric acid or acid alone) gave almost quantitatively recovery of starting material. When **4a** was refluxed in acetic anhydride, an enol acetate **7**[10] resulted with dehydration of the



amido function. However, in basic solutions (30% potassium hydroxide, concentrated ammonium hydroxide, or alcoholic potassium *tert*-butoxide), a reaction was achieved, and the product from **4a** was identified as **6a**. This substance (**6a**) was probably formed *via* the intermediate **5a**, which hydrolyzed to the carboxylic acid upon work-up. Protonation of **5a** to give a hydrogen at the 2 position can occur through enamine behavior of the pyrrole ring upon work-up under acidic

(1) This work was supported by Research Grant MH-16422 from the National Institutes of Health. Presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, Abstract ORGN 78.

(2) (a) M. J. Weiss, G. R. Allen, Jr., G. J. Gibs, C. Pidacks, J. F. Poletto, and W. A. Remers in "Topics in Heterocyclic Chemistry," R. N. Castle, Ed., Wiley-Interscience, New York, N. Y., 1969, p 178; (b) S. A. Monti, *J. Org. Chem.*, **31**, 2669 (1966); (c) R. Littell, G. O. Morton, and G. R. Allen, Jr., *J. Amer. Chem. Soc.*, **92**, 3740 (1970); (d) J. F. Poletto and M. J. Weiss, *J. Org. Chem.*, **35**, 1190 (1970).

(3) C. D. Nenitzescu, *Bull. Sci. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930).

(4) V. B. Schatz in "Medicinal Chemistry," 2nd ed, A. Burger, Ed., Interscience, New York, N. Y., 1960, p 72.

(5) (a) J. Z. Mortensen and S. O. Lawesson, *Acta Chem. Scand.*, **22**, 1056 (1968); (b) H. D. Scharf and M. Verbeek, *Angew. Chem., Int. Ed. Engl.*, **6**, 874 (1967).

(6) (a) P. Pfieffer and T. Bottler, *Ber.*, **51**, 1819 (1918); (b) G. Plancher and F. Cattadori, *Atti Accad. Naz. Lincei*, **13**, 489 (1904); *J. Chem. Soc.*, **86**, 770 (1904).

(7) (a) A. L. J. Beckwith in "The Chemistry of Amides," J. Zabicky, Ed., Interscience, New York, N. Y., 1970, pp 116–117; (b) H. Zimmer, *Tetrahedron Lett.*, 2839 (1970).

(8) J. H. Robson and E. Marcus, *Chem. Ind. (London)*, 1022 (1970).

(9) J. H. Atkinson, R. S. Atkinson, and A. W. Johnson, *J. Chem. Soc.*, 5999 (1964).

(10) T. Kato, M. Sato, and T. Yoshida, *Chem. Pharm. Bull.*, **19**, 292 (1971).

conditions. Although the alkaline conditions employed for conversion of **4** to **5** are not common in ring closure procedures utilized for synthesis of pyrroles or indoles, they are often useful for preparation of compounds with the –NCN– moiety. For example, numerous 4-oxoquinazolines,[11] benzimidazoles,[12] and purines[13] can be prepared by heating amides in aqueous or alcoholic alkali for base-catalyzed dehydrocyclization.[14] Furthermore, it is possible that **4** may be reconverted to **3** under the alkaline conditions since the process is reversible,[7a] and that **3** is the actual substance which undergoes base-catalyzed cyclodehydration Many examples may be cited[12,14,15] for reaction of an amide carbonyl with an amine. Compound **6a** was, in fact, prepared directly from **3a** (method B).

Structural assignment for **6** was confirmed by nmr spectroscopy where an enol form appears to predominate in highly polar solution while the keto form appears to be favored in solid phase infrared studies. The facility of the enolization is substantiated by deuterium exchange studies. The C-4 proton(s) at δ 5.79 in the enol form is exchanged, as well as the NH and OH protons for **6a** (and **6b**), but, when O-substituted derivatives (*e.g.*, mesylate **8** and acetate **9**) are prepared and tautomerism is prohibited, the C-4 proton at δ 6.86 (**8**) or 7.48 (**9**) is not exchanged. (In addition to elemental and spectral data, structural assignment for **7** and **9** was supported by observation that **7** did not react with 2,4-dichloroaniline, but the anhydride **9** gave 2,4-dichloroacetanilide.) The carboxyl (**6a**) proton is not easily assigned because of exchange with solvent. Irradiation of the doublet at δ 1.40 (**6a**) led to collapse of the quartet at 4.45, with similar results being obtained for **6b**.

From the elemental analysis of **6a**, it was difficult to obtain a sample completely devoid of all traces of water, the presence of moisture being confirmed by the Karl Fischer method. (For an analytical sample devoid of water and acceptable for elemental analysis, it was necessary to dry the material *in vacuo* at 100° over phosphorus pentoxide for 2 weeks.) To eliminate this problem and obtain acceptable elemental analysis, without the need to include water in the calculated values, a derivative was prepared to avoid the presence of a carboxylic acid moiety (the hygroscopic moiety). Maleimide was allowed to react with 3-aminocrotonitrile (**2b**) in the hope that the cyano moiety would reduce or eliminate the affinity of the analytical sample to retain moisture. Intermediates similar to **3a** and **4a** were isolated and characterized. The conversion of **4b** to **6b** was achieved in basic solution with alcoholic potassium *tert*-butoxide giving best results. Again, work-up conditions gave a hydrolysis product; nitrile converted to the amide. An nmr spectrum supported the structural assignment and the analytical sample was devoid of moisture contamination.

Preliminary evidence indicated that the ring system was quite stable under acidic or basic condition. For example, **6a** dissolved in warm concentrated sulfuric acid and precipitated as a sulfate salt on addition of cold ethyl acetate. Upon addition of this salt to water or alcohol, solution was immediately achieved, followed in a short period by precipitation of the starting product (**6a**). A weak salt complex was apparently formed and readily hydrolyzed to the parent material without destruction or alteration of the basic ring system. However, **6a** was observed to be quite susceptible to oxidative or thermal decomposition. Routine decarboxylation attempts or warming in dimethyl sulfoxide gave black or blue-purple amorphous material with the odor of dimethyl sulfide being detected in the latter instance. Structural assignment has not been made for the product of these reactions.

With the successful application of the modified Nenitzescu reaction for the synthesis of the pyrrolo[2,3-*b*]-pyrrole ring, the parent nucleus with suitable functional groups is now available for the preparation of various indole isosteres of biologically active agents. The results of these studies, as well as additional data on the chemical behavior of the new heterocycle and applicability of maleic anhydride and thiomaleic anhydride[16] in the reaction, will constitute future communication.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Hitachi Perkin-Elmer R 20A high-resolution nmr spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference. Elemental analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn., or Atlantic Microlab, Inc., Atlanta, Ga. Infrared spectra were measured on a Perkin-Elmer 237 B grating spectrophotometer using the potassium bromide technique, and ultraviolet spectra were determined in methanol solution with a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Tlc was performed on Eastman chromatogram sheets, type 6060.

Ethyl 3-[α-(1-Aminoethylidene)]-2,5-dioxopyrrolidineacetate (3a).—A solution of 77.6 g (0.08 mol) of maleimide and 100 g of ethyl 3-aminocrotonate in 450 ml of acetone was heated at reflux for 18–24 hr with continuous stirring. The acetone was removed *in vacuo*, and the white solid was collected, washed with petroleum ether (80–93% yield), and crystallized from ethanol (homogeneous on tlc, $CHCl_3$): mp 156–158°; ir (KBr) 3450, 3400, 3300, 3250, 1780, 1720, 1650, 1620, 1540 cm^{-1}; nmr δ 1.10 (t, 3 H, J = 7.5 Hz, CH_3 of ethyl), 2.00 (s, 3 H, vinyl methyl), 2.35 (CH_A, 1 H, J_{AX} = 6.0 Hz), 2.92 (CH_B, 1 H, J_{AB} = −17.0 Hz), 3.73 (CH_X, 1 H, J_{BX} = 9.0), 3.95 (q, 2 H, J = 7.5; CH_2 of ethyl), 6.5–8.5 (broad d, 2 H, NH_2), and 10.8 (broad s, 1 H, NH) (NH_2 and NH exchanged by D_2O); uv max (MeOH) 205 mμ (ε 4970) and 284 (14,800).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.05; H, 6.19; N, 12.38. Found: C, 53.07; H, 6.19; N, 12.43.

3-Carbethoxy-2-methyl-5-oxo-2-pyrroline-4-acetamide (4a).—A suspension of **3a** (25 g, 0.111 mol) in 150 ml of xylene with a trace of piperidine was refluxed and stirred for 2 hr. (Dissolution of the starting material was not achieved.) Upon cooling, a lavender-colored product (mp 218–226°) was filtered from a reddish blue mixture (85–90% yield). The product was crystallized from ethanol–DMF (9:1) or from hot water as a tan material and found to be homogenous on tlc ($CHCl_3$; substance had

(11) W. L. F. Armarego in "Quinazolines: Fused Pyrimidines, Part I," D. J. Brown, Ed., Interscience, New York, N. Y., 1967, pp 78–80.

(12) (a) G. McCoy and A. R. Day, *J. Amer. Chem. Soc.*, **65**, 2159 (1943); (b) J. D. Loundon in "Chemistry of Carbon Compounds," Vol IVa, E. H. Rodd, Ed., Elsevier, New York, N. Y., 1957, p 322.

(13) (a) E. Shaw, *J. Biol. Chem.*, **185**, 439 (1950); (b) T. Ichikawa, T. Kato, and T. Takenishi, *J. Heterocycl. Chem.*, **2**, 253 (1965); (c) G. A. Howard in "Chemistry of Carbon Compounds," Vol. IVc, E. H. Rodd, Ed., Elsevier, New York, N. Y., 1960, p 1647.

(14) (a) B. R. Baker and D. V. Santi, *J. Heterocycl. Chem.*, **4**, 216 (1967); (b) W. J. Haggerty, Jr., R. H. Springer, and C. C. Cheng, *J. Med. Chem.*, **8**, 797 (1965).

(15) (a) R. G. Glushkov and O. Yu Magidson, *Zh. Obshch. Khim.*, **30**, 1855 (1960); *J. Gen. Chem. USSR*. **30**, 1838 (1960); (b) A. J. Hill and S. R. Aspinall, *J. Amer. Chem. Soc.*, **61**, 822, 3195 (1939); (c) H. Bredereck and G. Theilis, *Ber.*, **86**, 88 (1953); *Angew. Chem.*, **71**, 753 (1959).

(16) Reference 8 and an abstract[17] have appeared describing the preparation of 5-oxo-2-pyrrolines by reaction of 3-alkylaminocrotonates with maleic anhydride. These reports may indicate a limited scope in the modified Nenitzescu reaction for synthesis of furo[2,3-*b*]pyrroles.

(17) S. G. Agbalyan and L. A. Nersesyan, *Arm. Khim. Zh.*, **22**, 40 (1969); *Chem. Abstr.*, **71**, 91195 (1969).

a greenish fluoresence in solution and bluish on paper under uv light): mp 231–234° dec; ir (KBr) 3350, 3230, 3175, 2975, 1740, 1660, 1625 cm^{-1}; nmr δ 1.20 (t, 3 H, J = 7.5 Hz, CH_3 of ethyl), 2.25 (d, 3 H, J = 2.0 Hz 2-CH_3), 2.52 (d, 2 H, J = 5.0 Hz, 4-CH_2), 3.31 (t, 1 H, J = 5.0 Hz, C_4H) (triplet split into multiplet, J = 2.0 Hz), 4.06 (q, 2 H, J = 7.5 Hz, CH_2 of ethyl), 7.2–6.61 (broad d, 2 H, amido NH_2), and 10.2 (broad s, 1 H, NH) (NH and NH_2 protons exchanged by D_2O); uv max (MeOH) 205 mμ (ϵ 4070), 220 (3840), and 282 (10,500).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.05; H, 6.19; N, 12.38. Found: C, 52.77; H, 6.20; N, 12.41.

5-Acetoxy-3-carbethoxy-2-methylpyrrole-4-acetonitrile (7).—The amide **4a** (2 g) was suspended in 50 ml of acetic anhydride and refluxed for 2 hr. Solution occurred after 45 min when the oil bath temperature had reached 150°. After standing overnight, the solvent was concentrated *in vacuo*. The residual oil was washed with petroleum ether, treated with a few milliliters of ethanol, and diluted with water. On standing, a pale yellow solid separated. The analytical material (25–45%) was crystallized from 95% ethanol: mp 139–141°; ir (KBr) 3200, 2260, 1775, 1700, 1630 cm^{-1}; nmr δ 1.30 (t, 3 H, J = 7.5 Hz, CH_3 of ethyl), 2.3 (s, 3 H, 2-CH_3), 2.38 (s, 3 H, CH_3 of acetoxy), 3.65 (s, 2 H, 4-CH_2), 4.20 (q, 2 H, J = 7.5 Hz, CH_2 of ethyl), 11.70 (broad s, 1 H, NH, exchanged by D_2O).

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.60; H, 5.60; N, 11.20. Found: C, 57.52; H, 5.79; N, 11.08, 11.16.

2,4,5,6-Tetrahydro-2-methyl-5-oxopyrrolo[2,3-b]pyrrole-3-carboxylic Acid (6a). Method A.—**4a** (15 g, 0.067 mol) suspended in 200 ml of *tert*-butyl alcohol was treated with 8 g of potassium *tert*-butoxide and refluxed for 4.5 hr. (The solid dissolved almost immediately on heating, then the reaction mixture became cloudy, and eventually a thick voluminous brown product precipitated.) A major portion of the *tert*-butyl alcohol was removed *in vacuo* leaving a pale yellow solid residue. The semidry residue was added to 200 ml of cold 2 *N* H_2SO_4 and then diluted to 400 ml with water. The resulting yellow solution was stirred and chilled to achieve precipitation of a pale yellow product from the dark greenish solution. Addition of potassium chloride facilitated precipitation of the desired product. After standing overnight, the yellow-tan product was collected (70–85% yield). After crystallization from hot water, the compound which was bicarbonate soluble, melted at 253–255° dec (sealed tube) and was homogenous on tlc (MeOH–Et_2NH, 19:1). For analysis, a sample was repeatedly purified by dissolution in sodium hydroxide, subsequent acidification with dilute sulfuric acid, and drying over P_2O_5: mp 255–257° dec (sealed tube); ir (KBr) 3300, 3150–2700 (broad, m), 1700, 1650, 1600 cm^{-1}; nmr δ 1.40 (d, 3 H, J = 6.5 Hz, 2-CH_3), 4.45 (q, 1 H, J = 6.5 Hz, C_2H), 5.79 (s, 1 H, C_4H), 8.90 (s, 1 H, NH) (peaks at 5.79 and 8.90 exchanged by D_2O); mol wt (mass spectrometry) 180 (calcd 180); uv max (MeOH) 209 mμ (ϵ 12,300), 233 (9810), and 339 (6660).

Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.44; N, 15.55. Found (0.5 H_2O): C, 50.38; H, 5.04; N, 14.66. Found (after drying 10 days *in vacuo* and over P_2O_5): C, 53.16; H, 4.51; N, 15.54.

Method B.—In this procedure, **3a** was substituted for **4a** in method A with the result that **6a** was obtained in 71–87% yield. The product from either method had identical ir, nmr, and melting point.

Preparation of a solid ester derivative from phenacyl bromide[18] gave a disubstituted product, *i.e.*, reaction with the 3-carboxylic acid and the 5-enolic moiety. Upon crystallization from ethanol–DMF, a white product was obtained, melting at 260–262° (seal tube): ir (KBr) 3350, 1700 (broad), 1680, 1600 cm^{-1}.

Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.23; H, 4.81; N, 6.74. Found: C, 69.34; H, 4.89; N, 6.68.

2,6-Dihydro-3-carboxyl-2-methylpyrrolo[2,3-b]pyrrole-5-mesylate (8).—**6a** (5 g, 0.028 mol) was suspended in 50 ml of water and treated with 1.22 g (0.031 mol) of sodium hydroxide. This solution was treated with 2.4 ml (0.031 mol) of methanesulfonyl chloride. A brown solid began to precipitate almost immediately. After the solution was stirred for 30 min, product was collected (65–95%) and recrystallized from 95% ethanol: mp 205° dec; ir (KBr) 3360, 3000–2600 (broad), 1690, 1650, 1625, 1350, 1180 cm^{-1}; uv max (MeOH) 207 mμ (ϵ 14,300), 218 (10,900), 242 (4930), and 295 (6220); nmr δ 1.40 (d, 3 H, J = 6.5 Hz, 2-CH_3), 3.52 (s, 3 H, CH_3 of mesyl), 4.65 (q, 1 H, J = 6.5 Hz, C_2H), 6.86 (s, 1 H, C_4H), 9.08 (s, 1 H, NH), and 12.25 (broad s, 1 H, COOH, undergoes slow exchange with solvent on standing) (Peaks at 9.08 and 12.25 exchanged with D_2O).

Anal. Calcd for $C_9H_{10}N_2O_5S$: C, 41.86; H, 3.87; N, 10.85; S, 12.40. Found: C, 42.02; H, 3.99; N, 10.78; S, 12.33.

5-Acetoxy-2,6-dihydro-2-methylpyrrolo[2,3-b]pyrrole-3-carboxylic Ethanoic Anhydride (9).—The pyrrolopyrrole **6a** (1 g) was suspended in 35 ml of acetic anhydride and heated at 75–80° for 1.5 hr. The grey suspension became yellowish and as the temperature was increased to 110° over 0.5 hr a red solution occurred. After an additional 20 min at 110°, the hot solution was filtered and allowed to stand overnight. Excess acetic anhydride was removed *in vacuo* and the residual syrup treated with 5 ml of ethanol and 50 ml of water. After salting with NaCl, a pale purplish material separated, mp 122–130°, 0.98 g. An analytical sample crystallized from $CHCl_3$–ligroine: mp 149–151° (sealed tube); ir (KBr) 3180, 3140, 3100, 3075, 1775, 1760, 1724, 1710, 1625, 1580 cm^{-1}; nmr δ ($CDCl_3$) 1.49 (d, 3 H, J = 6.5 Hz, 2-CH_3), 2.33 (s, 3 H, C_5 acetoxy), 2.35 (s, 3 H, CH_3 of anhydride), 4.70 (q, 1 H, J = 6.5 Hz, C_2H), 7.48 (s, 1 H, C_4H), and 8.72 (s, 1 H, NH, exchanged by D_2O).

Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.55; N, 10.61. Found: C, 54.65; H, 4.57; N, 10.73.

3-[α-(1-Aminoethylidene)]-2,5-dioxopyrrolideneacetonitrile (3b).—The procedure described for preparation of **3a** was utilized in the condensation of maleimide and 3-aminocrotonitrile. The product (40–50% yield) was crystallized from ethanol: mp 173–175°; ir (KBr) 3450, 3350, 3250–3100 (broad), 2200, 1800, 1700, 1660, 1625 cm^{-1}; nmr δ 2.02 (s, 3 H, vinyl methyl), 2.35 (CH_A, 1 H, J_{AX} = 5.5 Hz), 3.05 (CH_B, 1 H, J_{AB} = −18.0 Hz), 3.89 (CH_X, 1 H, J_{BX} = 9.0 Hz), 6.55 (s, 2 H, NH_2), and 11.25 (s, 1 H, NH); uv max (MeOH) 204 mμ (ϵ 3400) and 259 (10,400).

Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.03; N, 23.46. Found: C, 53.43; H, 5.11; N, 23.33.

3-Cyano-2-methyl-5-oxo-2-pyrroline-4-acetamide (4b).—This product (**4b**) could be prepared by the procedure described for **4a** in refluxing xylene. However, it was more convenient to prepare **4b** directly without isolating **3b**. A solution containing 1 mol of maleimide was treated with 1.2 mol of 3-aminocrotonitrile in 400 ml of dioxane and refluxed for 48 hr. The dioxane was then removed *in vacuo* and the remaining brown gummy residue was boiled with ethanol. The insoluble substance was collected by filtration, washed with ethanol, and dried (mp 252–253°). Crystallization from ethanol–DMF (yield 37–51%) gave a product which melted at 253–255°: ir (KBr) 3400, 3300, 2200, 1720, 1670, 1620 cm^{-1}; nmr δ 2.10 (d, 3 H, J = 2 Hz, 2-CH_3), 2.55 (d, 2 H, J = 5 Hz, 4-CH_2), 3.45 (t, 1 H, J = 5 Hz, C_4H) (triplet split into multiplet, J = 2.0 Hz), 7.15 (broad d, 2 H, amido NH_2), and 10.50 (broad s, 1 H, NH); uv max (MeOH) 206 mμ (ϵ 2540), 270 (5150), 275 (5520), and 279 (5300).

Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.03; N, 23.46. Found: C, 53.50; H, 4.95; N. 23.59.

The alcoholic filtrate was concentrated to 1/3 the original volume and then diluted with water to give an off-white product melting at 300–304°. Upon crystallization from dioxane this substance melted at 302–304° and was homogenous on tlc ($CHCl_3$–CH_3OH, 2:1). This product was assigned the structure 2,6-dimethyl-4-oxonicotinonitrile:[19] ir (KBr) 3000–2700 (broad), 2215, 1680, 1620, 1570 cm^{-1}; nmr δ 2.2 (d, 3 H), 2.4 (s, 3 H), 6.18 (m, 1 H), 12.2 (broad, 1 H, NH) (both CH_3 peaks are weakly coupled to the CH at 6.18).

Anal. Calcd for $C_8H_8N_2O$: C, 64.86; H, 5.41; N, 18.92. Found: C, 65.20; H, 5.63; N, 18.79.

2,4,5,6-Tetrahydro-2-methyl-5-oxopyrrolo[2,3-b]pyrrole-3-carboxamide (6b).—**4b** (15 g, 0.083 mol) suspended in 150 ml of *tert*-butyl alcohol was treated with 10.1 g (0.09 mol) of potassium *tert*-butyl alcohol and refluxed for 14 hr under constant stirring. The mixture was concentrated *in vacuo* and the solid residue added

(18) (a) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1960, p 200; (b) J. B. Hendrickson and C. Kandall, *Tetrahedron Lett.*, 343 (1970).

(19) E. V. Meyer and C. Irmscher, *J. Prakt. Chem.*, **78**, 523 (1908). In this reference, the 2,6-dimethyl-4-oxonicotinonitrile was reportedly synthesized from 3-aminocrotonitrile (diacetonitrile) and ethyl acetoacetate in presence of pyridine. No mention was made of synthesis from self-condensation of 3-aminocrotononitrile, which can be easily accomplished (60–70% yield) by refluxing in 90% ethanol with piperidine catalysis. Structural assignment also supported by comparison with known[20] 4,6-dimethyl-2-oxonicotinonitrile.

(20) H. O. Fitton and R. K. Smalley in "Practical Heterocyclic Chemistry," Academic Press, New York, N. Y., 1968, p 71.

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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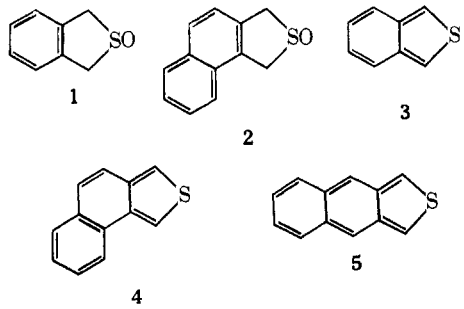
Benzo[c]thiophene (isothianaphthene, **3**) was obtained when 1,3-dihydrobenzo[c]thiophene 2-oxide (**1**) was heated with neutral alumina to 120–130°. Thiophene **3** was generated *in situ* when sulfoxide **1** was heated with acetic anhydride, as shown by the isolation of the exo and endo Diels–Alder 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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