0.152 g (19.2 $10^{-2}$ mmol, 42%) of the porphyrin **7** as a purple microcrystalline product: mp over 360 °C; UV-vis $\lambda_{max}$ nm ($\epsilon$ mol·L$^{-1}$·cm$^{-1}$) 243 (27000, 284 (46000), 412 (14 × $10^4$), 506 (10400), 540 (2600), 580 (3500), 635 (629); $^1$H NMR (200 MHz, $\delta$ ppm ref $CHCl_3$) 10.14 (s, 2 H, $H_{methene}$), 9.24 (d, $J$ = 4 Hz, 4 H, $H_b$), 8.92 (d, $J$ = 4 Hz, 4 H, $H_a$), 8.77 (d, $J$ = 6.5 Hz, 2 H, $H_c$), 7.94 (d, $J$ = 8.5 Hz, 2 H, $H_{4,5}$), 7.91 (m, 6 H, $H_{d,e,f}$), 7.52 (d, $J$ = 8.5 Hz, 2 H, $H_{4,7}$), 7.48 (s, 2 H, $H_{5,6}$), 6.71 (d, $J$ = 8.0 Hz, 4 H, $H_o$), 6.43 (d, $J$ = 8 Hz, 4 H, $H_m$), -2.90 (s, 2 H, $H_{N-H}$); mass spectrum FAB, NBA matrix, $I$ = 233 mV, $M^+$ at $m/e$ 791.4 (100). Anal. Calcd for $C_{56}H_{42}N_6 \cdot C_7H_8 \cdot {}^5/_2H_2O$: C, 81.55; H, 5.01; N, 9.06. Found: C, 81.77; H, 4.71; N, 8.96.

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**Registry No.** **1**, 129265-60-7; **2**, 34824-58-3; **3**, 137964-68-2; **4**, 40138-16-7; **5**, 129265-61-8; **6**, 21211-65-4; **7**, 137946-82-8; 2-$BrC_6H_4CHO$, 6630-33-7.

## Pyrazolo[3,4-*c*]pyridazines from Hydrazine and Aminothiophenecarboxylates[1]

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As part of another project we required several thiophene analogues of the protected anthranilic acid hydrazide **1**. Reaction of the 3-aminothiophene-2-carboxylic acid esters **2** with hydrazine gave the expected hydrazides **3** which were easily converted to their benzylidene derivatives **4**. Application of this sequence to the isomeric 2-aminothiophene-3-carboxylic esters **5**, however, failed to yield hydrazides **6** and under more severe conditions led to ring rupture as evidenced by the evolution of $H_2S$.

This, and a similar observation made by Gewald some years ago,[2] can be rationalized by the decreased reactivity of the carbonyl group to nucleophilic attack due to $\pi$-electron donation from the two $\beta$-situated heteroatoms. Such reactivity is well-known for a variety of related heterocyclic $\beta$-enamino esters.[3]

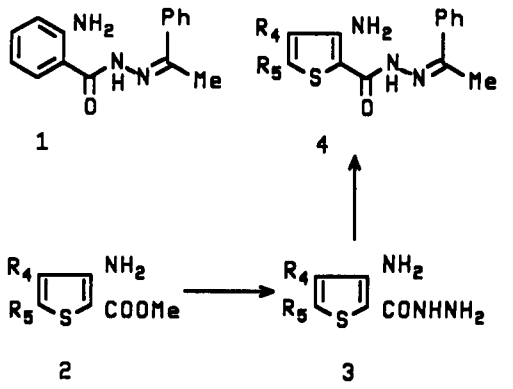
Although the desired protected hydrazides **7** were eventually made by a Gewald cyclization[4] of the protected cyanoacetohydrazide **8**, the nature of the apparent ring-opening reaction was examined further because of the potential utility of such transformations in heterocyclic chemistry.[5]

### Results

Esters **5a** and **5b** reacted with 97% hydrazine to give the crude hydrazonium salts **9a** and **9b** in 69 and 87% yield, respectively. Heating the solid salt with soda lime liberated hydrazine while treatment with glacial acetic acid gave the parent amphoteric pyrazolo[3,4-*c*]pyridazines **10a** and **10b** in 64 and 46% overall yield, respectively. The former compound is known but characterized only by its melting point,[6] so structure assignments were based on mass and especially $^{13}$C spectra (Table I) which were compared to that of the related pyrazolo[3,4-*c*]pyridazine hydrochloride **10h**·HCl.[7]

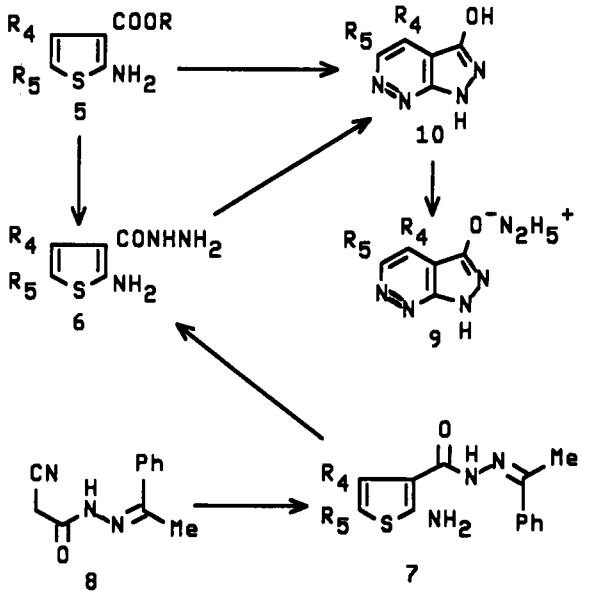
Because formation of this latter compound was the sole example of the transformation **5** → **10** when the five 2-amino-3-carboalkoxythiophenes **5d-h** were treated with

**Scheme I**[a]




[a] Key: (a) $R_4 = R_5 = H$; (b) $R_4 = R_5 = -CH{=}CHCH{=}CH-$

**Scheme II**




| | $R_4$ | $R_5$ | R |
|---|---|---|---|
| **a:** | H | H | Me |
| **b:** | $-CH_2-CH_2-CH_2-CH_2-$ | | Et |
| **c:** | $-CH_2-CH_2-CH_2-CH_2-$ | | Me |
| **d:** | H | Ph | Et |
| **e:** | Ph | H | Et |
| **f:** | H | H | ? |
| **g:** | H | Et | ? |
| **h:** | H | Me | Me |

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Table I. NMR Parameters of Pyrazolo[3,4-c]pyridazines 9 and 10[a]

| | 10a | | 9a | 10b | | 9b | | 10h·HCl[b] | |
|---|---|---|---|---|---|---|---|---|---|
| atom | C | H | H | C | H | C | H | C | H |
| 3 | 154.5 | | | 155.7 | | 156.7 | | 153.7 | |
| 3a | 105.8 | | | 105.7 | | 105.5 | | 113.0 | |
| 4 | 118.5 | 8.13[c] | 7.72[d] | 131.3 | | 131.3 | | 127.2 | 8.71 |
| 5 | 141.7 | 9.11[c] | 8.50[d] | 148.6 | | 147.8 | | 146.8 | |
| 7a | 153.3 | | | 154.7 | | 155.1 | | 151.0 | |
| $CH_3$ | | | | | | | | | 2.89 |
| $CH_2$ | | | | 21.4 | 1.80 | 21.1 | 1.82 | | |
| | | | | 22.4 | | 22.5 | | | |
| | | | | 24.3 | 3.15 | 24.2 | 3.10 | | |
| | | | | 28.9 | | 28.9 | | | |
| OH/NH | | 12.3[e] | 4.7[e] | | 5.15 | | | | 6.50 |

[a] DMSO-$d_6$. [b] Reference 7. [c] (d, $J$ = 5.6 Hz). [d] (d, $J$ = 5.4 Hz). [e] Broad, 2 H, $D_2O$ exchangeable.

hydrazine (**5d** gave a normal hydrazide and **5e–g** did not react), Gewald concluded that this reaction was not general.[7] However, since methyl ester **5a** reacts under our conditions while the possibily identical **5f** (alkoxy group unspecified) does not under his conditions,[8] this preparation of pyrazolo[3,4-*c*]pyridazines may be general after all.[6,9]

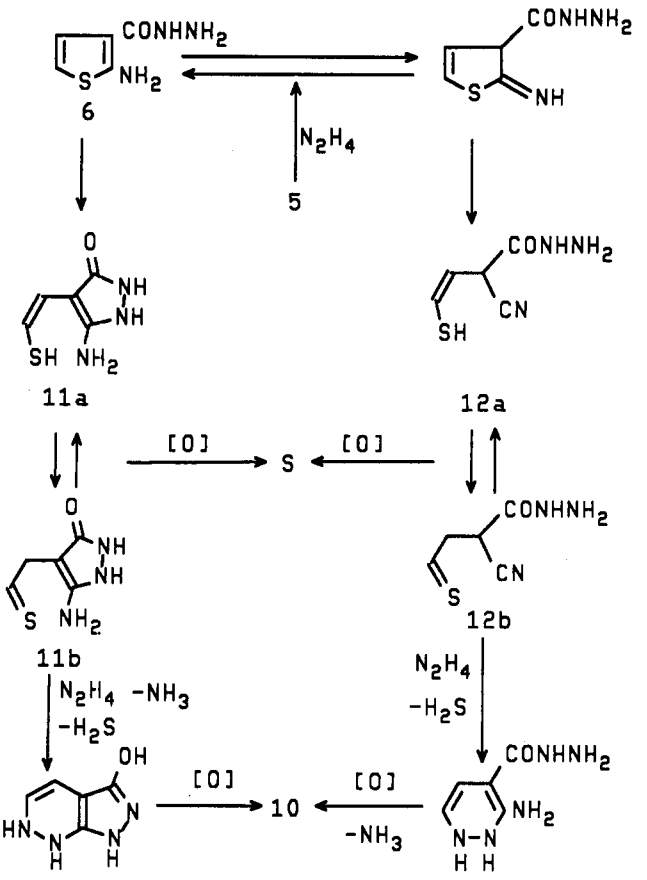
## Mechanism

The reaction **5** → **10** involves conversion of an *o*-amino ester moiety to a pyrazole ring and a thiophene to a pyridazine ring in either order. Precedent exists for the generation of pyrazoles from 3-acyl derivatives of furan,[10] pyrrole,[11] benzo[*b*]thiophene,[12] and indole.[13] An analogous mechanism for **5** proceeding via hydrazide **6** and the enethiol/thiocarbonyl compound **11** is supported by the singular example (**6d**) of normal hydrazide formation cited above.

Pyridazine formation is known from furans[14] and pyrroles,[15] but not from thiophenes. However, ring opening of 2-aminothiophenes with bases to enethiol/thiocarbonyl compounds such as **12** is a general reaction[16] which with hydrazine could lead to **10**. The formation of sulfur by oxidation[17] of species such as **11** or **12** is consistent with either mechanism.

In an attempt to detect any intermediates, the reaction was followed by NMR. With **5a** the $^1H$ spectrum showed a transient species, possibly the hydrazide **6a**, which could not be isolated. No intermediates were detected by $^{13}C$ NMR with **5b** suggesting that initial attack on this ester was slower than subsequent steps. The more reactive[18] methyl ester **5c**, however, revealed an intermediate which was shown to be the hydrazide **6b** by independent synthesis from the protected hydrazide **7b**. Furthermore, reaction of hydrazide **6b** under conditions used for the ethyl ester **5b** gave hydrazonium salt **9b** in 94% yield thereby demonstrating that hydrazide **6** formation precedes thiophene ring opening in the conversion of 2-amino-3-carboalkoxythiophenes **5** to pyrazolo[3,4-*c*]-pyridazines **10** as shown in Scheme III.

Scheme III




## Experimental Section

**General.** Melting points were measured on a Thomas-Hoover or a Mel-Temp apparatus and are certified.[19] Analyses were performed by M-H-W laboratories of Phoenix, AZ. GC/MS analyses were obtained in a Finnigan 1020 OWA instrument at 70 eV containing a DB-1 30 m × 0.25 mm capillary column with helium as the carrier gas. Base peaks and all those above $m/z$ 100 with relative intensity >10% are reported. The HRMS was taken at the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (Grant No. CHE 8211164). Proton and carbon NMR spectra were obtained on Varian EM-390, JEOL JNM-FX-60, or Varian XL-300 in-

(8) 80% hydrazine hydrate (51% hydrazine) for 2 h vs 97% hydrazine and alcohol for several days, all at reflux.

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struments. $J_{H,H}$ values are as observed, and carbon multiplicities were determined by the SFORD method. Ir spectra were measured on Beckman IR 33 or IR 4250 instruments in KBr disks.

**3-Aminothiophene-2-carbohydrazide (3a).** A solution of 6.90 g (44 mmol) of methyl 3-aminothiophene-2-carboxylate (**2a**),[20,21] 12.5 mL of 95% ethanol, and 13 mL of 85% aqueous hydrazine was heated under reflux for 24 h. The crystals which formed upon removal of the ethanol on a rotary evaporator were washed with water and air-dried to give 5.83 g (86%) of **3a**: mp 157–158.5 °C (abs EtOH); $^1$H NMR (DMSO-$d_6$) $\delta$ 8.55 (s, br, 1), 7.26 (d, 1 $J$ = 5.4 Hz), 6.49 (d, 1 $J$ = 5.4 Hz), 6.29 (s, br, 2), 4.2 (s, br, 2); $^{13}$C NMR (DMSO)-$d_6$) $\delta$ 165.4, 153.2, 128.1 (d), 120.4 (d), 99.5; IR (cm$^{-1}$) 3440, 3325, 3225, 3100, 1590; MS $m/z$ 157 (53), 127 (11), 126 (100). Anal. Calcd for $C_5H_7N_3OS$: C, 38.2; H, 4.5; N, 26.7. Found: C, 38.4; H, 4.6; N, 26.5.

**3-Amino-*N*′-(1-phenylethylidene)thiophene-2-carbohydrazide (4a).** To a stirred solution of 6.90 g (44 mmol) of **3a** in 83 mL of glacial HOAc was added 5.65 g (47 mmol) of acetophenone. The crystals which deposited after 3.5 h were washed with water and 95% ethanol to give, when combined with a second crop from the filtrate, 10.43 g of **4a** (92%): mp 209–210 °C (EtOH); $^1$H NMR ($CDCl_3$) $\delta$ 8.58 (s, br, 1), 7.73 (m, 2), 7.45–7.18 (m, 3), 7.40 (d, 1 $J$ = 5.4 Hz), 6.52 (d, 1, $J$ = 5.4 Hz), 6.05 (s, br, 2), 2.28 (s, 3); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 165.7, 157.2, 147.0, 138.3, 134.4 (d), 128.7 (d), 128.3 (d, 2), 126.4 (d, 2), 119.1 (d), 96.7, 13.5 (q); IR (cm$^{-1}$) 3450, 3400, 3350, 3150, 1610; MS $m/z$ 260 (12), 259 (69), 228 (10), 127 (11), 126 (100), 103 (11). Anal. Calcd for $C_{13}H_{13}N_3OS$: C, 60.2; H, 5.1; N, 16.2. Found: C, 60.5; H, 5.3; N, 16.4.

**3-Aminobenzo[*b*]thiophene-2-carbohydrazide (3b).** A solution of 4.49 g (21.7 mmol) of methyl 3-aminobenzo[*b*]-thiophene-2-carboxylate (**2b**),[22] 23 mL of 95% ethanol, and 9 mL of 64% aqueous hydrazine was heated under reflux for 20 h. The solution was added to 400 mL of water, and the precipitated crystals were washed with water and dried to give 4.25 g (95%) of **3b**: mp 181.5–182.5 °C (abs EtOH) (lit.[23] 180–182 °C); $^1$H NMR (DMSO-$d_6$) $\delta$ 8.84 (s, br 1), 7.97 (m, 1), 7.74 (m, 1), 7.35 (m, 2), 6.96 (s, br, 2), 4.37 (s, br, 2); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 165.8, 147.4, 137.6, 132.1, 127.4 (d), 123.6 (d), 122.8 (d), 122.3 (d), 97.1; IR (cm$^{-1}$) 3280, 1595; MS $m/z$ 208 (10), 207 (71), 192 (6), 178 (13), 177 (28), 176 (100), 149 (14), 148 (71), 146 (17), 122 (12), 121 (87), 104 (21). Anal. Calcd for $C_9H_9N_3OS$: C, 52.2; H, 4.4; N, 20.3. Found: C, 52.1; H, 4.3; N, 20.2.

**3-Amino-*N*′-(1-phenylethylidene)benzo[*b*]thiophene-2-carbohydrazide (4b).** To a stirred solution of 510 mg (2.5 mmol) of **3b** in 4 mL of glacial HOAc and 4 mL of MeCN was added 300 mg (2.5 mmol) of acetophenone. The crystals which deposited after the addition of 40 mL of water at the end of 1 h were washed with water to give 640 mg of **4b** (84%): mp 240 °C (dioxane); $^1$H NMR (DMSO-$d_6$) $\delta$ 10.32 (s, br, 1), 8.2–7.3 (m, 9), 7.65 (s, br, 2) 2.33 (s, 3); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 166.4, 151.6, 147.6, 141.5, 138.2, 130.6, 128.8 (d), 128.3 (d, 2), 127.9 (d), 126.6 (d, 2), 123.3 (d), 122.4 (d, 2), 94.4, 13.6 (q); IR (cm$^{-1}$) 3480, 3360, 3180, 3050, 1595; MS $m/z$ 309 (26), 177 (16), 176 (100), 148 (32), 121 (42), 104 (14), 103 (10). Anal. Calcd for $C_{17}H_{15}N_3OS$: C, 66.0; H, 4.9; N, 13.6. Found: C, 65.6; H, 5.0; N, 13.6.

**3-Hydroxypyrazolo[3,4-*c*]pyridazine (10a) and Its Hydrazinium Salt 9a.** A mixture of 1 g (6.4 mmol) of methyl 2-aminothiophene-3-carboxylate (**5a**),[21] 2 mL of 97% hydrazine, and 4 mL of abs methanol was heated under reflux ($CaSO_4$ drying tube) for 37 h. To the violet solid remaining after removal of the solvents on a rotary evaporator was added 3 mL of glacial HOAc and 20 mL of water and the resulting solid washed with water and dried to give 550 mg (64%) of crude **10a** as an orange solid which charred at 297–305 °C (water, Norit) (lit.[6] 280–300 °C; $^1$H and $^{13}$C NMR cf. Table I; IR (cm$^{-1}$) 3400–2600; MS $m/z$ 136 (73), 38 (100). Anal. Calcd for $C_5H_4N_4O$: C, 44.1; H, 3.0; N, 41.2. Found: C, 43.9; H, 3.2; N, 41.2.

Impure sulfur (mp 114–120 °C, 96 mg (47%)) in the condenser was identified from its mass spectrum.

A similar reaction on 412 mg (2.6 mmol) of **5a** carried out in a 90 °C water bath was monitored by $^1$H NMR for 16 h by which time the pair of doublets of **5a** at $\delta$ 6.85 and 6.18 were replaced first by a pair at 6.95 and 6.23 ($J$ = 6.0 Hz) assigned to the hydrazide **6a** and then by a pair at $\delta$ 7.88 and 8.60 from the hydrazonium salt **9a**. The dark red reaction evolved $H_2S$ as detected by moist $Pb(OAc)_2$ paper. Removal of the solvents under vacuum at room temperature left 305 mg of a red solid (69%), a 162-mg portion of which was separated by preparative TLC (silica, MeOH) $R_f$ = 0.66 to give 56 mg (43%) of **9a** as an orange red solid which charred at 250 °C but did not melt up to 315 °C. Heating **9a** with soda lime gave a gas that smelled of hydrazine and turned red litmus blue: $^1$H NMR cf. Table I; MS $m/z$ identical to **10a**.

***N*′-(1-Phenylethylidene)cyanoacetohydrazide (8).** The colorless needles which formed in a solution of 1 g (10 mmol) of cyanoacetohydrazide,[24] 10 mL of glacial HOAc, and 1.25 g (10.4 mmol) of acetophenone after 15 min were washed with water and EtOH to give 1.45 g (71%) of **8**: mp 155–156.5 °C (lit.[25] mp 149–150 °C); $^1$H NMR (acetone-$d_6$) $\delta$ 9.85 (s, br, 1), 7.8 (m, 2), 7.35 (m, 3), 4.03 (s, 2), 2.32 (s, 3); $^{13}$C NMR (acetone-$d_6$) $\delta$ 166.0, 150.2, 138.9, 130.1 (CH), 129.1 (2), 127.2 (2), 115.7, 25.0, 13.6; IR (cm$^{-1}$) 3200, 3120, 2970, 2940, 2340, 2270, 1690.

**2-Amino-*N*′-(1-phenylethylidene)thiophene-3-carbohydrazide (7a).** A mixture of 12.8 g (64 mmol) of the protected hydrazide **8**, 4.85 g (32 mmol) of 2,5-dihydroxy-1,4-dithiane,[26] 6.7 mL of triethylamine, and 29 mL of DMF was heated at 65 °C for 1.5 h with stirring. Recrystallization (abs EtOH) of the solid which formed upon adding the dark reaction mixture to 200 mL of water gave (two crops) 12.15 g (74%) of **7a**: mp 188.5–189 °C; $^1$H NMR (acetone-$d_6$) $\delta$ 9.18 (s, br, 1), 7.80 (m, 2), 7.34 (d, 1, $J$ = 5.7 Hz), 7.34 (m, 3), 7.10 (s, br, 2), 6.20 (d, 1, $J$ = 5.7 Hz), 2.34 (s, 3); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 163.4, 163.2, 151.3, 138.3, 128.9 (d), 128.2 (d, 2), 126.0 (d, 2), 124.8 (d), 105.8, 105.6 (d), 13.9 (q); IR (cm$^{-1}$) 3380, 3240, 3150, 1630, 1590; MS $m/z$ 260 (11), 259 (68), 228 (14), 126 (100), 103 (11). Anal. Calcd for $C_{13}H_{13}N_3OS$: C, 60.2; H, 5.1; N, 16.2. Found: C, 60.2; H, 5.2; N, 16.0.

**2-Amino-*N*′-(1-phenylethylidene)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbohydrazide (7b).** A mixture of 2.01 g (10 mmol) of the protected hydrazide **8**, 320 mg (10 mmol) of sulfur, 990 mg (10 mmol) of cyclohexanone, 1 mL of morpholine, and 8 mL of abs EtOH was heated under reflux for 45 min. The precipitate which formed upon cooling the reaction to 3 °C was washed with abs EtOH to give 1.17 g (37%) of **7b**: mp 221–221.5 °C (abs EtOH); $^1$H NMR (4:1 DMSO-$d_6$/$CDCl_3$) $\delta$ 9.60 (s, br, 1), 7.73 (m, 2), 7.30 (m, 3), 6.68 (s, br, 2), 2.7–2.4 (m, 3), 2.28 (s, 3), 1.72 (m, 5); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 162.8, 158.2, 150.0, 138.3, 130.5, 128.8 (d), 128.1 (d), 126.1 (d), 117.1, 108.7, 26.1 (t), 24.0 (t), 22.6 (t, 2), 13.7 (q); IR (cm$^{-1}$) 3390, 3280, 2935, 2830, 1635, 1575; MS $m/z$ 314 (14), 313 (69), 181 (12), 180 (100), 151 (10), 119 (10), 118 (21), 104 (25), 103 (16). Anal. Calcd for $C_{17}H_{19}N_3OS$: C, 65.2; H, 6.1; N, 13.4. Found: C, 65.4; H, 5.9; N, 13.3.

**Methyl 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5c).** A solution of 5.0 g of **5b**[26] in 70 mL of dry methanol containing 50 mg of sodium metal was heated under reflux in a nitrogen atmosphere for 3 days. The solution was cooled to 0 °C and the resulting precipitate collected to give 2.56 g (55%) of the methyl ester **5c**. Recrystallization from methanol gave an analytical sample: mp 127–128 °C; $^1$H NMR ($CDCl_3$) $\delta$ 5.89 (bs, 2 H), 3.73 (s, 3 H), 2.63 (m, 2 H), 2.45 (m, 4 H), 1.70 (m, 4 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 166.5, 161.8, 132.4, 117.7, 105.7, 50.6, 26.9, 24.5, 23.3, 22.8; MS $m/z$ 211 (66), 180 (17), 179 (100), 151 (53). Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.9; H, 6.2. Found: C, 56.7; H, 6.4.

**2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbohydrazide (6b).** A solution of 2.0 g of the protected hydrazide **7b** in 30 mL of ice-cold concd HCl was stirred for 5 min, 60 mL of water added, and the reaction mixture left at room temperature for 12 h. Basification with 10% NaOH gave 800 mg (57%) of

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product **6b**: mp 151–152 °C dec (lit.[2] mp 165–168 °C); $^1$H NMR (DMSO-$d_6$) δ 8.04 (bs, 1 H), 6.49 (bs, 2 H), 4.30 (bs, 2 H), 2.38–2.52 (m, 4 H), 1.58–1.65 (m, 4 H); $^{13}$C NMR (DMSO-$d_6$) δ 166.2, 157.0, 130.1, 116.4, 102.4, 25.6, 23.9, 22.7, 22.4; MS *m/z* 211 (9), 180 (100). Anal. Calcd for $C_9H_{13}N_3OS$: C, 51.2; H, 6.2. Found: C, 51.0; H, 6.1.

**3-Hydroxy-4,5-cyclohexanopyrazolo[3,4-*c*]pyridazine (10b) and Its Hydrazinium Salt (9b). A. From Ethyl 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5b).** A mixture of 1.43 g of **5b**,[26] 2 mL of 97% hydrazine, and 4 mL of abs ethanol was heated under reflux ($CaSO_4$ drying tube) for 12 days during which aliquots were removed for NMR analysis. The only peaks observed in the aromatic region of the $^{13}$C spectrum were due to either the reactant or the product. A solid in the condenser was identified by MS as sublimed **5b** containing a small amount of sulfur. Removal of the solvent on a rotary evaporator left the hydrazonium salt **9b** (87% taking into account the removed aliquots): mp 227–231 °C dec; $^1$H and $^{13}$C NMR cf. Table I.

The salt **9b** was acidified with glacial acetic acid to give the pyrazolo[3,4-*c*]pyridazine **10b** (total yield 57% taking into account the removed aliquots): mp slowly decomposes above 200 °C; $^1$H and $^{13}$C NMR cf. Table I; MS *m/z* 190 (100), 189 (16), 175 (5), 134 (5), 119 (14), 118 (9). It was not possible to get a satisfactory analysis on this compound: HRMS *m/z* 190.0863, theory for $C_9H_{10}N_4O$ is 190.0856.

**B. From Methyl 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (5c).** A mixture of 1.0 g of **5c**, 1.5 mL of 97% hydrazine, and 3 mL of methanol was heated under reflux ($CaSO_4$ drying tube), and aliquots were removed for $^{13}$C NMR analysis over a period of 8 days. The presence of hydrazide **6b** was clearly evident in the aromatic region. Isolation as described above gave the pyridazine **10b** in 46% yield, taking into account the removed aliquots.

**C. From 2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbohydrazide (6b).** A solution of 500 mg of the hydrazide **6b**, 1.5 mL of 97% hydrazine, and 3 mL of abs ethanol was heated under reflux ($CaSO_4$ drying tube) for 2 days. The solvents were removed on a rotary evaporator to give 500 mg (94%) of the pyrazolo[3,4-*c*]pyridazine hydrazonium salt **9b** with $^1$H and $^{13}$C spectra identical to the product of the reaction of the ethyl ester **5b** and hydrazine.

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**Registry No.** **2a**, 22288-78-4; **2b**, 35212-85-2; **3a**, 137844-98-5; **3b**, 99027-29-9; **4a**, 137844-99-6; **4b**, 137845-00-2; **5a**, 4651-81-4; **5b**, 4506-71-2; **5c**, 108354-78-5; **6b**, 22721-28-4; **7a**, 137845-01-3; **7b**, 137845-02-4; **8**, 4974-47-4; **9a**, 137845-03-5; **9b**, 137845-05-7; **10a**, 2125-85-1; **10b**, 137845-04-6; acetophenone, 98-86-2; hydrazine, 302-01-2.

## Construction of the Bicyclo[6.3.0]undecane Skeleton via Ring Opening of Tricyclo[6.3.0.0$^{1,4}$]undecan-5-ones

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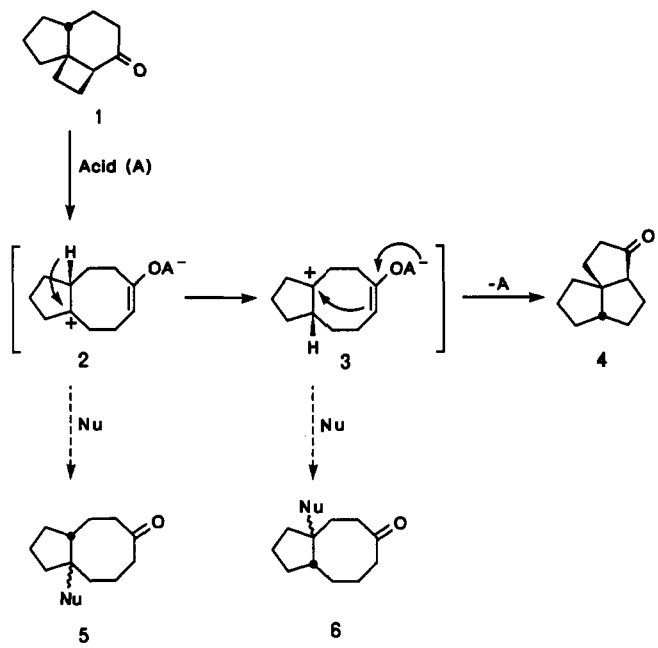
Considerable attention has been paid to the development of methodologies for the construction of 5-8 and 5-8-5 fused ring compounds because of the recent isolation and identification of many biologically active natural products containing these carbocyclic skeletons.[1] Recently we reported that tricyclo[6.3.0.0$^{1,4}$]undecan-2-one (**1**) rearranged under the action of acid catalysts through a new pathway to give the 5-5-5 angularly fused ketone, tricyclo[6.3.0.0$^{1,5}$]undecan-4-one (**4**).[2] This novel rearrangement has been applied to the total syntheses of some triquinane natural products[2,3] and to the construction of tetra- and spiroquinane skeletons.[4,5] We also proposed the mechanism shown in Scheme I in which the fission of the central cyclobutane bond takes place in the initial step to generate eight-membered-ring cation **2**. Subsequent 1,2-hydride shift and transannular cyclization of the cation **3** give **4**.[2] On the basis of this mechanism, we envisaged that if the cation intermediates **2** and **3** could be intercepted efficiently by a nucleophile (Nu) leading to bicyclo[6.3.0]undecane derivatives such as **5** and **6**, a new method for construction of the 5-8 fused ring system would be provided. From this viewpoint, we have investigated the reactions of **1** and its methyl derivatives **11** and **15** with a variety of acid (electrophile)–nucleophile combinations and found that the 5-8 fused compounds **7a,b**, **8a,b**, **12**, and **16** are obtained as dienol esters instead of the expected products like **5** and **6** arising from nucleophilic capture.

**Scheme I**




We first carried out reactions of **1** under the conditions which had been employed in the acid-catalyzed rearrangement of bicyclo[4.2.0]octanones[6] to intercept the respective cation intermediates. Starting ketone **1** was, however, recovered unchanged in reactions with 35% HCl in ether at 35 °C for 100 h and TsOH in acetic acid at 55 °C for 120 h. Treatment with 50% $H_2SO_4$ in THF at 55 °C gave a complex mixture of products after prolonged reaction time (120 h). Furthermore, with TMSOTf[7] in $CHCl_3$ at rt for 60 h, ketone **1** was recovered unchanged.

(1) For example, see: Feldman, K. S.; Come, J. H.; Kosmider, B. J.; Smith, P. M.; Rotella, D. P.; Wu, M.-J. *J. Org. Chem.* **1989**, *54*, 592 and references cited therein.

(2) Kakiuchi, K.; Ue, M.; Tsukahara, H.; Simizu, T.; Miyao, T.; Tobe, Y.; Odaira, Y.; Yasuda, M.; Shima, K. *J. Am. Chem. Soc.* **1989**, *111*, 3707.

(3) Ue, M.; Ohnishi, Y.; Kobiro, K.; Kakiuchi, K.; Tobe, Y.; Odaira Y. *Chem. Lett.* **1990**, 149.

(4) Kakiuchi, K.; Hirano, N.; Shimizu, T.; Suwa, M.; Kobiro, K.; Tobe, Y.; Odaira, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3039.

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(6) Kakiuchi, K.; Kumanoya, S.; Kobiro, K.; Tobe, Y.; Odaira, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3358 and references cited therein.

(7) It has been reported that this reagent was useful for the ring opening of cyclopropyl ketones, see: Demuth, M.; Mikhail, G. *Tetrahedron* **1983**, *39*, 991.

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