mation (80 °C, 20 torr) to afford **12** as a colorless solid (26 mg, 60%): mp 267–269 °C; IR (KBr) 2920, 1465, 1435, 1265, 1120, 1020, 865, 825, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6–2.9 (m, 3 H), 2.7–0.8 (m, 13 H); MS, *m/e* (%) 169 (16), 168 (M^+, 61), 167 (33), 135 (23), 93 (44), 92 (23), 91 (50), 81 (28), 79 (64), 77 (33), 87 (39), 58 (40), 57 (33), 55 (28), 44 (44), 43 (100), 41 (56).

Anal. Calcd for $C_{10}H_{16}S$: C, 71.37; H, 9.58. Found: C, 71.16; H, 9.39.

Registry No. **1**, 30860-11-8; **2**, 87114-49-6; **4**, 87114-50-9; **5**, 87114-51-0; **6**, 87114-52-1; **7**, 87114-53-2; **8**, 87114-54-3; **9**, 87114-55-4; **10**, 87114-56-5; **11**, 87172-12-1; **12**, 87114-57-6.

2,2′:5′,2″-Terthiophene-5-carboxylic Acid and 2,2′:5′,2″-Terthiophene-5,5″-dicarboxylic Acid

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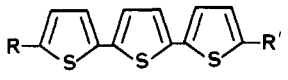
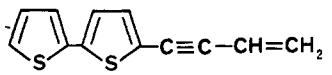
2,2′:5′,2″-Terthiophene-5-carboxylic acid was obtained in excellent yield by treating 2,2′:5′,2″-terthiophene with lithium diisopropylamide, followed by carboxylation of the lithium salt with solid carbon dioxide. The 5,5″-dicarboxylic acid was obtained similarly, when 2 equiv of base were used. Attempted syntheses of the monoacid, based on the oxidation of the corresponding aldehyde or the acetyl derivative, were unsuccessful. Both the monoacid and the 5,5′-diacid sensitized the hemolysis of human erythrocytes in the presence of ultraviolet light.

The unknown 2,2′:5′,2″-terthiophene-5-carboxylic acid (**1**) was of interest for some photosensitization experiments.



1, R = H; R′ = COOH
2, R = R′ = H
3, R = R′ = COOH
4, R = H; R′ = $COOCH_3$
5, R = R′ = $COOCH_3$
6, R = H; R′ = CHO
7, R = H; R′ = $COCH_3$



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2,2′-Bithiophene had been successfully converted into its 5-carboxylic acid by treatment with phenyllithium in ether, followed by carboxylation of the lithium salt,[1] but several attempts with the terthiophene **2** under identical conditions met with failure, and success was achieved only when lithium diisopropylamide (LDA) in tetrahydrofuran was substituted for phenyllithium in ether. The experimental conditions were critical. When **2** was reacted with 1 equiv of LDA and solid carbon dioxide was added, a solid material was obtained. Its time-resolved mass spectrometric analysis revealed a mixture of two components, identified as the desired carboxylic acid **1** and its dicarboxylic acid homologue **3**.

This result suggested that proton transfer between 2 mol of the monoanion of **2** had occurred, favoring a mixture of the dianion with an equivalent amount of unreacted starting material. In principle, this equilibrium should be repressed by maintaining a relatively high concentration of **2** in the mixture. Indeed, a good yield of the monocarboxylic acid **1** was obtained when only 0.5 equiv of LDA was used and the lithium derivative treated with solid carbon dioxide without delay.

As anticipated from the original observations, the treatment of **2** with 2 equiv of LDA, followed by carbon dioxide, led to the production of the diacid **3** almost quantitatively.

The structural assignments are based on mass spectral and elemental analyses, infrared spectra, and conversion with diazomethane into the methyl esters **4** and **5**, which had satisfactory NMR, mass spectra, and elemental analyses. These results left no doubt about the presence and the number of the carboxyl groups attached to the terthiophene system in each case. Their assignment to the 5 and 5,5″ positions, respectively, is supported by the following arguments: (a) the acidity of the thiophene hydrogens is greater in the α than in the β positions,[1] (b) the NMR spectra of the methyl esters **4** and **5** did not show any ring protons without vicinal coupling, required if any β-carboxylation of **4** had occurred, and (c) the reduction with Raney nickel of **1** and **3** yielded the unbranched tridecanoic acid and 1,12-dodecanedicarboxylic acids, respectively. The former was shown to be identical with an authentic sample by direct comparison (IR, NMR, melting point, mixture melting point). The latter was characterized not only on the basis of the melting point and mass spectrum but also by its NMR data. For any carboxylation which occurred at one β-position in **2**, one α-position would have remained unsubstituted, and thus converted into a methyl group in the reductive degradation with Raney nickel. The NMR showed no such methyls in the product obtained.

Both carboxylic acids **1** and **3** were surprisingly insoluble in organic solvents and in base. While the former could be recrystallized from ethanol and the latter from dimethylformamide, only 1 mg of **1** dissolved when a 7-mg sample was treated with 10 mL of 1 N NaOH solution at room temperature for 24 h. Under exactly the same conditions, 0.5 mg of **3** could be dissolved. The solid recovered from these experiments was the unreacted acid in each case. In similar experiments, the solubility of **1** in pure ethanol was found to be 0.3 g per liter at room temperature, and that of **3** was 0.1 g/L.

The very slow and limited solubility of **1** in base perhaps explains the difficulties that were encountered in early attempts to oxidize the aldehyde **6** with the following reagents: chromium trioxide,[2] silver oxide, either alone[3]

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or in the presence of hydrogen cyanide,[4] potassium permanganate, either alone[5] or in the presence of dibenzo-18-crown-6,[6] and ozone.[7] In all cases either the starting material was recovered or untractable products were produced, from which no organic acids were obtained when the crude mixtures were extracted with dilute base in the customary manner. Likewise, the hypochlorite oxidation[8] of 5-acetyl-2,2′:5′,2″-terthiophene (**7**) failed to produce **1**, but a very small amount of desired product was observed in the Cannizzaro reaction of **6**.[9]

The very low solubility of **1** also suggests that this compound could have escaped detection in plants, had it been a natural product. Actually, **1** had been suggested[10] to be the immediate precursor for **2** in the biosynthesis starting from **8** in *Eclipta erecta*. This view contrasts with the claim that in *Echinops sphaerocephalus* the loss of the thirteenth carbon atom had taken place prior to the cyclization of the third thiophene ring.[11] The availability of **1** should allow a more rigorous determination of the biosynthetic pathway(s) leading from **8** to **2**.

A number of terthiophene derivatives have been reported to have powerful photosensitizing properties by a mechanism which is oxygen dependent. Human erythrocytes provide a convenient substrate for the detection of photodynamic molecules,[12] and we have now observed that the carboxylic acids **1** and **3**, as well as their methyl esters **4** and **5**, led to the hemolysis of the red blood cells in the presence of long-wavelength ultraviolet light. Identical mixtures of red blood cells, sensitizer, and buffer solution were photolyzed simultaneously in the beam of a Hanovia 1000-W lamp that had been filtered through Pyrex. The time required for achieving about 50% hemolysis of the cells was 5 min for **1** and **2**, 10 min for **3**, 15 min for **5**, and 35 min for **4**. The two new acids and their esters also showed photoantibiotic activity against *E. coli B*, *Saccharomyces cerevisiae*, and *Candida utilis*.[13]

Experimental Section

The melting points were determined with a Kofler apparatus and are not corrected. The NMR spectra were recorded on a Varian T-60, with an internal standard of tetramethylsilane. The mass spectra were recorded on a Hewlett-Packard 5985. The microanalyses were performed by Micro-Tech Laboratories, Skokie, IL.

Hemolysis Experiments. Erythrocytes obtained by centrifugation of 0.2 mL of blood were washed 3 times with 1 mL of buffer (0.02 M NaH_2PO_4, 0.084 M Na_2HPO_4, pH 7.42) and resuspended in 1.8 mL of buffer. The sensitizers (1 mg/mL in Me_2SO, 0.150 mL) in buffer (1.9 mL) were added, and the mixtures were gently shaken for 18 h in the dark prior to the photolyses. The progress of the photolyses was followed by taking aliquots which were centrifuged and the supernatent analyzed spectroscopically.[14]

Carboxylation of 2 with 1 equiv of LDA. Under nitrogen, a solution of diisopropylamine (1 mmol) in dry THF (10 mL) was treated with *n*-BuLi (1 mmol, 1.6 M solution in hexane) at −78 °C with stirring. After 15 min, a solution of **2** (0.250 g, 1 mmol) in dry THF (10 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, 2 h at the same temperature after addition of an excess of solid CO_2, and finally overnight at room temperature. The yellow solid obtained after neutralization with 3% aqueous HCl was washed with water and crystallized from dimethylformamide to yield 110 mg (33%) of diacid **3**, mp >330 °C. Ethyl acetate (100 mL) was added to the remaining THF solution. The mixture was washed with 3% HCl (3 × 10 mL) and with water (3 × 10 mL), dried over $MgSO_4$, and concentrated to dryness. The residue, which showed two components on TLC, was flash chromatographed by using acetone–hexane (1:9) and yielded 50 mg (20%) of unreacted starting material **2** as well as 60 mg (21%) of monoacid **1**, mp 239–240 °C after recrystallization from EtOH.

Synthesis of 1. A solution of **2** (2.480 g, 0.01 mol) in dry THF (50 mL) was added dropwise over 10 min to a solution of LDA prepared from 0.5 g (0.005 mol) of diisopropylamine and 0.32 g (0.005 mol) of *n*-BuLi in hexane, which was kept at −78 °C. After 1 h, solid carbon dioxide was added. The mixture was stirred at −78 °C for 2 h and then overnight at room temperature. The mixture was carefully neutralized with 3% aqueous HCl. Filtration yielded 100 mg (3%) of **3**, identified by comparison of its IR and mass spectra. Ethyl acetate (100 mL) was added to the filtrate, which was washed with 3% HCl (3 × 10 mL) and with water (3 × 25 mL), dried over $MgSO_4$, and concentrated to dryness. The residue was flash chromatographed (acetone–hexane, 1:9) to yield 1.100 g of starting material **2** and 1.000 g of **1** (3.425 mmol, 68.5% yield based on the LDA used). An analytical sample had mp 239–240 °C; IR (KBr) 1670 cm^{-1}; mass spectrum, *m/e* 292; UV (MeOH) 370, 255 nm. Anal. Calcd for $C_{13}H_8O_2S_3$: C, 53.40; H, 2.75; S, 32.89. Found: C, 53.47; H, 2.68; S, 32.71. A small sample of **1** was treated with diazomethane in ether. The methyl ester **4** (95% yield) was recrystallyzed from MeOH. It had mp 180–182 °C; NMR ($CDCl_3$) 3.65 (s, 3 H) and 6.95–7.35 ppm (m, 7 H); IR (KBr): 1710 cm^{-1}; UV (MeOH) 375, 245; mass spectrum, *m/e* 306 (M^+, 100%). Anal. Calcd for $C_{14}H_{10}O_2S_3$:C, 54.87; H, 3.28; S, 31.39. Found C, 54.83; H, 3.19; S, 31.07.

Synthesis of 3. To a solution of LDA in 10 mL of THF, prepared from 2 mmol of *n*-BuLi and 2 mmol of diisopropylamine at −78 °C, was added dropwise a solution of **2** (0.248 g, 1 mmol) in THF (10 mL). The mixture was stirred for 1 h at −78 °C, solid carbon dioxide was added, and stirring was continued for 2 h at −78 °C and overnight at room temperature. The solid produced was filtered, washed with 3% HCl and with water, and dried. An analytical sample was prepared from this material (0.305 g, 90%) by recrystallization from DMF: mp >330 °C; UV (MeOH) 380, 275 nm; IR (KBr) 1670 cm^{-1}; mass spectrum, *m/e* 336 (M^+, 100%). Anal. Calcd for $C_{14}H_8O_4S_3$: C, 49.98; H, 2.39; S, 28.59. Found: C, 49.92; H, 2.34; S, 28.53.

A sample was treated with an excess of diazomethane in ether, giving the dimethyl ester **5** in 90% yield. After recrystallization from DMF it had mp 220 °C; UV (MeOH) 385, 274 nm; IR (KBr) 1720 cm^{-1}; mass spectrum, *m/e* 364 (M^+, 100%). Anal. Calcd for $C_{16}H_{12}O_4S_3$: C, 52.72; H, 3.31; S, 26.39. Found: C, 52.69; H, 3.27; S, 26.19.

Reductive Desulfurization of 1. To a suspension of freshly prepared Raney nickel (4 g) in water (100 mL) was added 0.300 g of **1**. The mixture was stirred and refluxed for 20 h. The nickel was filtered off and washed several times with water, using ultrasonic agitation. The filtrate and the water extracts were combined and concentrated under vacuum to ca. 5 mL. The concentrated solution was cooled, acidified with concentrated HCl, and filtered to give 0.200 g (91%) of tridecanoic acid, mp 41–42 °C (lit.[15] mp 41.8 °C), identical with an authentic sample (IR, NMR, mixture melting point).

Reductive Desulfurization of 5. The above procedure was followed exactly and afforded 1,12-dodecanedicarboxylic acid in 85% yield, mp 127–128 °C (lit.[16] mp 126 °C). The NMR showed

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no methyl groups.

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Registry No. 1, 87145-85-5; 2, 1081-34-1; 3, 87145-86-6; 4, 87145-87-7; 5, 87145-88-8; tridecanoic acid, 638-53-9; 1,12-dodecanedicarboxylic acid, 821-38-5.

Synthesis of 4-(Acylacetyl)-1-phenyl-2-pyrazolin-5-ones from 3-Acyl-2*H*-pyran-2,4(3*H*)-diones. Their Synthetic Applications to Functionalized 4-Oxopyrano[2,3-*c*]pyrazole Derivatives

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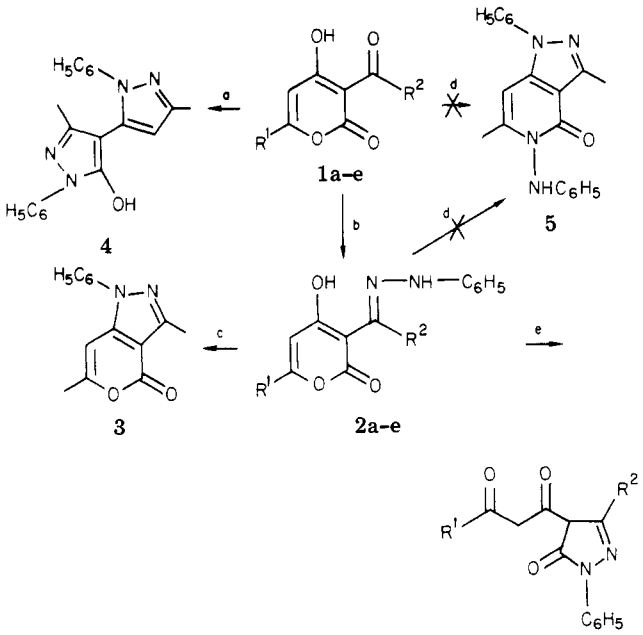
The phenylhydrazones of 3-acyl-2*H*-pyran-2,4(3*H*)-diones (**2**), in refluxing acetic acid, underwent rearrangement to 4-(acylacetyl)-1-phenyl-2-pyrazolin-5-ones (**6**), from which some functionalized 4-oxopyrano[2,3-*c*]pyrazole derivatives were synthesized. This finding showed that the phenylhydrazone of dehydroacetic acid (**2a**) gave **6a** instead of the reported pyridinopyrazole (**5**). The tautomerism of the β-tricarbonyl compounds (**6**) was studied by NMR spectroscopy.

Recent work from our laboratory has shown that the phenylhydrazones of 3-acyl-4-hydroxycoumarins were capable of cyclizing by three different processes, depending upon the conditions employed. Two of these cyclizations led to the 4-oxo-1*H*- or -2*H*-[1]benzopyrano[4,3-*c*]pyrazole derivatives[1] and the other one to the 1-aryl-4-(2-hydroxybenzoyl)pyrazol-5-ones.[2] We now wish to report on the ring transformation of the phenylhydrazones **2** of 3-acyl-2*H*-pyran-2,4(3*H*)-diones (**1**).

Some years ago, the formation of 3,6-dimethyl-1-phenyl-4-oxopyrano[4,3-*c*]pyrazole (mp 158 °C) (**3**) and 5-hydroxy-3-methyl-1-phenyl-4-(3-methyl-1-phenylpyrazol-5-yl)pyrazole (mp 260 °C) (**4**) was reported.[3,4] Surprisingly, in a more recent paper,[5] 5-anilino-3,6-dimethyl-4-oxo-1-phenylpyrazolo[4,3-*c*]pyridine (**5**) (named as pyridinopyrazole by the authors) was described from the reaction of dehydroacetic acid (**1a**) and phenylhydrazine (Scheme I). The melting point reported for this product is consistent with its formulation as **4** previously encountered by Stolle.[3] We repeated the treatment of dehydroacetic acid with phenylhydrazine following the literature method[5] and obtained the pyrazolylpyrazole (**4**) identical with the one prepared by repeating the pioneering work of Stolle. Consequently, structure **5** should be revised to **4**.

Formally, 3-acyl-2*H*-pyran-2,4(3*H*)-diones (**1**) possess four sites for nucleophilic attack.[6] As early as 1884 Perkin[7] reported that phenylhydrazine reacts readily with dehydroacetic acid, in ethanol solution, to yield 3-(1-phenylhydrazonoethyl)dehydroacetic acid (**2a**). We now report a new successful conversion of the phenylhydrazones (**2a–e**) to 3-substituted-4-(acylacetyl)-1-phenyl-2-pyrazolin-5-ones (**6a–e**) and their subsequent transformation directed toward the synthesis of 1*H*-pyrano[2,3-*c*]pyrazol-4-one derivatives, a class of compounds which has received very limited attention in the literature.[8–10]

Scheme I[a]



a, $R^1 = R^2 = Me$; b, $R^1 = Me$, $R^2 = Et$; c, $R^1 = Me$, $R^2 = Ph$; d, $R^1 = Ph$, $R^2 = Me$; e, $R^1 = Ph$, $R^2 = Ph$

[a] (a) $R^1 = R^2 = Me$, 2 $PhNHNH_2$, ref 3; (b) 1 $PhNHNH_2$; (c) $R^1 = R^2 = Me$, HCl, ref 3, 4; (d) ref 5; (e) CH_3COOH, reflux.

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