ln (k_{obsd}/k_w) vs. m_A is calculated as +0.62. This large and positive value deviates strongly from the experimental slope (-0.24). This deviation is significant, even when allowance is made for the approximations inherent in the Savage-Wood treatment. The most likely explanation again emphasizes the idea that the equatorial OH groups of D-glucose fit well into water structure and make them (almost) indistinguishable from those of bulk water. As a consequence, the term $-5G_{OH\leftrightarrow OH}$ in eq 2 is much too large. Good agreement between the experimental and calculated slope is obtained by taking 0.6 OH groups into account in eq 2, indicating that 4.4 OH groups fit into the water structure. This value is in satisfactory agreement with the experimental value of 3.7 equatorial OH moieties.[24] However, we note that much more work will be necessary to further substantiate the Savage-Wood approach (including the applicability of the "additivity principle") in the analysis of carbohydrate medium effects in aqueous solution.

In summary, we submit that the subtle influences which simple carbohydrates exert on water structure and which are largely determined by their stereochemistry are indeed revealed in the isobaric activation parameters of the pH-independent hydrolysis of 1-acyl-1,2,4-triazoles. Thermodynamic parameters for transfer of a model substrate from water to aqueous solutions of D-glucose and D-ribose as well as an analysis of the rate inhibition in the presence of D-glucose in terms of a Savage-Wood treatment support the interpretation.

Experimental Section

Materials. The carbohydrates were high quality commercial samples: D-glucose (Merck), D-xylose (Merck), maltose (Janssen), D-ribose (Janssen), and D-arabinose (Janssen). The 1-acyl-1,2,4-triazoles **1–3** were prepared by acylation of the corresponding 1,2,4-triazole. The model substrate **5** was prepared from the reaction of phenacyl bromide with 3-phenyl-1,2,4-triazole. The product was purified by chromatography over neutral alumina using ether–methanol (9:1) as the eluent. 6-Nitrobenzisoxazole-3-carboxylate (**4**) was synthesized according to the literature procedure.[30]

Products. ^{1}H NMR spectroscopic analysis revealed that carboxylic acid and (substituted) 1,2,4-triazole are the sole products formed after hydrolysis of **1–3**. In the presence of D-glucose (4 mol %) no other reaction products were formed as indicated by UV spectroscopy.

Kinetics. Pseudo-first-order rate constants, k_{obsd}, for the neutral hydrolysis of **1–3** under atmospheric pressure were measured at five different temperatures between 25 and 45 °C by monitoring the disappearance of **1** (at 273 nm) and **2** and **3** (at 225 nm) with a Varian Cary 210 or Perkin-Elmer lambda 5 spectrophotometer. All reactions were followed to completion. In a typical experiment, 10 μL of a stock solution in MeCN (containing 5×10^{-2} M of substrate) was added to 2.5 mL of the reaction medium in the cell. The rate constants were reproducible to within 1.5%. Isobaric activation parameters were obtained by using the Eyring equation (least-squares program). Errors in $\Delta^{\ddagger}H^{\ominus}$ and $\Delta^{\ddagger}S^{\ominus}$ were estimated from the standard deviation of the regression. In all cases $\Delta^{\ddagger}$Cp values were negligible, and correlation coefficients were better than 0.999. The volumes of activation for neutral hydrolysis of **1** were determined by using the method described previously.[16]

Transfer Parameters. Thermodynamic parameters for transfer of **5** from water to aqueous carbohydrate solutions were obtained from solubility measurements in the temperature range 15–45 °C. The experimental procedure has been described before.[31] Solubilities, calculated from the absorbance at 248 nm, were reproducible to within 6%.

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Notes

Stereoselective Reaction of Dithio-Substituted Crotylmetal with α-Oxy Carbonyl Compounds

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Received January 15, 1987

Diastereoselective reaction of crotylmetals with carbonyl compounds has been extensively investigated as a useful method in the synthesis of macrolide antibiotics and polyether ionophores.[2] In previous papers,[3] we have reported the regio- and stereochemistry regarding the reaction of (*E*)-2-(1-propen-1-yl)-1,3-dithiane (**1**) with various carbonyl compounds. In order to further exploit this method in organic synthesis, it is important to test the reactivity of α-oxy carbonyl compounds with the crotylmetal generated from **1**. We report here the result of reactions of (benzyloxy)acetaldehyde (**2**), D-glyceraldehyde acetonide (**3**) and ethyl pyruvate (**4**).

Results and Discussion

Metalation of the vinyl dithiane **1** was effected by treatment with *n*-BuLi in THF. The resulting crotyllithium was subsequently treated with (benzyloxy)acetaldehyde at −78 °C to give exclusively the γ-addition products of **5a** and **5s** in a ratio of 78:22 (Chart I). The predominance of the 3,4-anti adduct **5a** was predictable by considering a chair-like transition state (A) involving in the reaction.[2,3] While exclusive anti adduct was found in analogous reactions, e.g., with *n*-pentanal,[3] the increased syn adduct in this reaction with (benzyloxy)acetaldehyde might be attributed to a double chelate transition state (B, see below).

The reaction of **1** with D-glyceraldehyde acetonide under similar conditions afforded three γ-addition products, **6aa**, **6as**, and **6sa**, in a ratio of 44:43:13. The letter/s following the number of compounds indicates the stereochemistry at $C_{3,4}$ and $C_{4,5}$, i.e., **a** represents anti, while **s** represents syn configuration. The stereostructure of isomers of **6**

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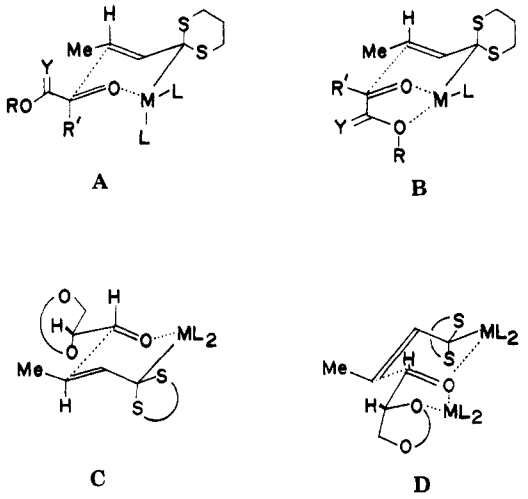
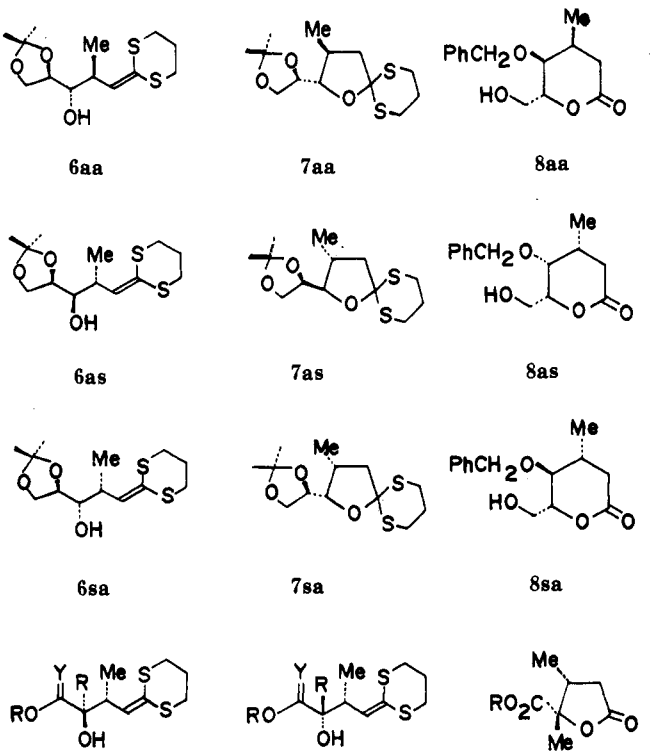


could not unambiguously determined by analysis of the ^1H and ^{13}C NMR spectra.[4] Alternatively, the assignment was made by correlation with their cyclic derivatives **7** and **8**. The spirodithianes **7** were readily obtained by treating **6** with a trace amount of acid.[3,5] The δ-lactones **8** were prepared by hydrolysis (60% aqueous HOAc, 3 h reflux) of the corresponding benzyl ethers of **6** (NaH, $PhCH_2Br$). Spirodithianes **7aa** and **7as**, having the trans configuration at C-3 and C-4, showed the resonance of C-4 protons at relatively higher fields of δ 2.9 and 3.2 due to the shielding effect of the adjacent methyl group,[3,6] whereas the cis isomer **7sa** exhibited the corresponding resonance at a relatively low field of δ 3.9. Consistently, the methyl resonance of **7sa** appeared at a higher field than those of the trans isomers. The relative relationship of three substituents at carbons 3, 4, and 5 was further deduced by analysis of the ^1H NMR spectra of lactones **8**. For example, three pseudoaxial protons in **8sa** were inferred by the large coupling constants of 7.0 and 8.7 Hz attributable to $J_{3,4}$ and $J_{4,5}$, respectively. Therefore, the diastereogenic selectivity at $C_{3,4}$ (anti/syn) equaled 87/13, while the diastereofacial selectivity at $C_{4,5}$ (anti/syn) equaled 57/43. This stereochemical outcome is in qualitative agreement with the result obtained by Roush from the reaction of (*E*)-crotylboronates.[7] The trivial facial selectivity might reflect two competing pathways of the Felkin model (C) and the chelate model (D), giving 4,5-syn and 4,5-anti adducts, respectively.[4b,8]

The reaction of vinyldithiane **1** and ethyl pyruvate resulted in two γ-addition products **9a** and **9s**. As shown in Table I, the ratio of the two products was influenced by the reaction temperature and the counter cation. By using lithium as the counter ion, the reaction at −78 °C gave a small preference of the syn adduct. The syn selectivity was greatly enhanced to 85% in the presence of a 1-equiv amount of zinc chloride. Lowering the reaction temperature to −100 °C finally led to 96% of syn adduct **9s**. Conceivably, this selectivity could be accounted on the strong chelate ability of zinc cation and oxygen atoms as depicted in the double chelate model B.[9] Compound **9s** was easily converted to the γ-lactone **10** by hydrolysis with $HgCl_2$.[3] Subsequent treatment of **10** with LiOH thus produced crobarbatic acid (**11**), mp 175–177 °C (lit.[10] mp 177–178 °C), having two methyl groups in the trans configuration. Crobarbatic acid is a degradative product of the macrolide pyrrolizidine alkaloid, crobarbatine.[10] While our method provides an efficient preparation of crobarbatic acid, a related approach using the pyruvate with a bulky alcoholic group culminates in selective synthesis of the cis isomer.[9]

Chart I



5a R = $C_6H_5CH_2$, R′ = H, Y = H, H
9a R = C_2H_5, R′ = Me, Y = O
5s
9s
10 R = C_2H_5
11 R = H

In summary, the reaction of α-oxy carbonyl compounds with the crotylmetal generated from the vinyldithiane **1** probably proceeded via the double chelate transition state. The increased percentage of syn addition could be attributed to the secondary chelation of the oxo substituent.

Experimental Section

General information concerning instrumentation and material was described previously.[3] An exemplary procedure of the reaction of vinyldithiane and ethyl pyruvate is demonstrated as following:

Under an atmosphere of nitrogen, 3.0 mmol of *n*-BuLi (1.6 M in hexane) was added dropwise to a solution of dithiane **1** (3.0 mmol) in THF (6 mL) at −30 °C. After stirring for 15 min, a suspension of anhydrous $ZnCl_2$ (3.0 mmol) in THF (5 mL) was added. The solution was cooled to −78 °C, and a solution of ethyl pyruvate (3.1 mmol) in THF (0.5 mL) was added. The mixture was stirred for 20 min at −78 °C and quenched by addition of MeOH. The mixture was extracted with EtOAc. The combined organic phase was washed with brine, concentrated, and separated

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by chromatography to give an 86% yield of products **9a** and **9s** in a ratio of 15:85. The physical and spectroscopic properties of adducts **9a** and **9s** have been reported.[3b]

Anti adduct 5a: HPLC (15% EtOAc in hexane) t_R 8.7 min; ^{1}H NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 7 Hz), 2.00–2.30 (3 H, m, CH_2CS and OH), 2.65–3.00 (4 H, m, SCH_2), 3.20–3.80 (3 H, m, OCH_2 and *CH*OH), 4.60 (2 H, s, OCH_2Ph), 5.98 (1 H, d, J = 10 Hz), 7.30–7.42 (5 H, m); ^{13}C NMR ($CDCl_3$), 75 MHz) δ 16.8 (q, CH_3), 25.1 (t, $SCCH_2$), 29.6 (t, SCH_2), 30.2 (t, SCH_2), 36.8 (d, C-3), 72.8 (d, C-4), 73.4 (t, C-5), 73.7 (t, CH_2Ph), 127.0 (s), 127.7 (3 C), 128.4 (2 C), 135.0 (d, C-2), 137.9 (s, C-1); IR (neat) 3487, 3035, 2965, 2922, 2870, 1548 cm^{-1}; EIMS, m/z (relative intensity) 310 (37, M^+), 219 (13), 204 (21), 197 (7), 186 (9), 161 (41), 160 (53), 159 (100), 145 (6), 130 (12), 91 (27). Anal. Calcd for $C_{16}H_{22}O_2S_2$: C, 61.90; H, 7.14. Found: C, 61.72; H, 7.18.

Syn adduct 5s: HPLC (15% EtOAc) t_R 7.8 min; ^{1}H NMR ($CDCl_3$) δ 1.05 (3 H, d, J = 7 Hz), 1.57 (1 H, s, OH), 2.00–2.25 (2 H, m), 2.70–3.00 (4 H, m), 3.30–3.70 (3 H, m), 4.55 (2 H, s), 5.80 (1 H, d, J = 10 Hz), 7.30–7.45 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 16.1 (q), 25.1 (t), 29.5 (t), 30.2 (t), 37.3 (d), 72.9 (d), 73.4 (t), 73.7 (t), 127.0 (s), 127.7 (3 C), 128.4 (2 C), 135.2 (d), 140.0 (s); IR (neat) 3500, 2980, 2940, 1548 cm^{-1}; EIMS, m/z (relative intensity) 310 (34, M^+), 219 (10), 204 (11), 197 (2), 186 (5), 161 (29), 160 (35), 159 (100), 145 (5), 130 (8), 106 (8), 97 (8), 91 (16). Anal. Calcd for $C_{16}H_{22}O_2S_2$: C, 61.90; H, 7.14. Found: C, 62.09; H, 7.17.

Compound 6aa: HPLC (10% EtOAc) t_R 12.0 min; $[\alpha]^{25}_D$ +1.0° (c 0.024, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.06 (3 H, d, J = 6 Hz), 1.30 (3 H, s), 1.36 (3 H, s), 1.90–2.40 (3 H, m, $SCCH_2$ and OH), 2.55–2.97 (5 H, m), 3.32 (1 H, m, *CH*OH), 3.48–4.10 (3 H, m), 5.89 (d, 1 H, J = 10 Hz); ^{13}C NMR ($CDCl_3$) δ 17.3 (q), 25.1 (d), 25.5 (q), 26.7 (q), 29.5 (t), 30.1 (t), 36.4 (d, C-3), 66.2 (t, C-6), 75.9 (d, C-4), 77.7 (d, C-5), 109.0 (s), 126.4 (s, C-1), 133.7 (d, C-2); IR (neat) 3500, 2990, 2950, 1580 cm^{-1}; EIMS, m/z (relative intensity) 290 (6, M^+), 275 (4), 232 (2), 215 (2), 161 (10), 160 (11), 159 (100). Anal. Calcd for $C_{13}H_{22}O_3S_2$: C, 53.77; H, 7.63. Found: C, 53.73; H, 7.69.

Compound 6as: HPLC (10% EtOAc) t_R 18.4 min; $[\alpha]^{25}_D$ +19.6° (c 0.042, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.05 (3 H, d, J = 6 Hz), 1.30 (3 H, s), 1.36 (3 H, s), 1.98–2.30 (3 H, m), 2.50–3.00 (5 H, m), 3.59 (1 H, m), 3.72–4.10 (3 H, m), 5.80 (1 H, d, J = 10 Hz); ^{13}C NMR ($CDCl_3$) δ 17.1 (q), 25.0 (t), 25.4 (q), 26.5 (q), 29.4 (t), 29.9 (t), 36.9 (d), 65.0 (t), 74.6 (d), 77.4 (d), 108.0 (s), 126.7 (s), 133.9 (d); IR (neat) 3500, 2990, 2950, 1580 cm^{-1}; EIMS, m/z (relative intensity) 290 (7, M^+), 275 (4), 232 (3), 215 (6), 161 (10), 160 (11), 159 (100), 132 (6), 126 (7), 106 (5). Anal. Calcd for $C_{13}H_{22}O_3S_2$: C, 53.77; H, 7.63. Found: C, 53.65; H, 7.67.

Compound 6sa: HPLC (10% EtOAc) t_R 16.2 min; $[\alpha]^{25}_D$ +32.7° (c 0.016, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.05 (3 H, d, J = 6 Hz), 1.30 (3 H, s), 1.36 (3 H, s), 1.90–2.30 (3 H, m), 2.40–2.97 (5 H, m), 3.52 (1 H, m), 3.73–4.10 (3 H, m), 5.66 (1 H, d); IR (neat) 3500, 2990, 2950, 1580 cm^{-1}; EIMS, m/z (relative intensity) 290 (6, M^+), 275 (6), 232 (6), 161 (13), 160 (14), 159 (100). Anal. Calcd for $C_{13}H_{22}O_3S_2$: C, 53.77; H, 7.63. Found: C, 53.47; H, 7.62.

Spirodithiane 7aa: ^{1}H NMR ($CDCl_3$) δ 1.30 (3 H, d, J = 6 Hz), 1.55 (3 H, s), 1.62 (3 H, s), 1.75–2.15 (4 H, m), 2.45–3.00 (6 H, m), 3.60–4.30 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 17.6 (q), 25.1 (t), 25.8 (q), 26.5 (q), 28.3 (t), 28.7 (t), 34.3 (t, C-2), 50.6 (d, C-3), 65.7 (t, C-6), 75.5 (d, C-4), 86.0 (d, C-5), 90.4 (s, C-1), 109.3 (s); IR (neat) 2990, 2950 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3S_2$: C, 53.77; H, 7.63. Found: C, 53.59; H, 7.53.

Spirodithiane 7as: ^{1}H NMR ($CDCl_3$) δ 1.15 (3 H, d, J = 6 Hz), 1.30 (3 H, s), 1.36 (3 H, s), 1.60–2.80 (7 H, m), 3.10–3.70 (3 H, m), 3.80–4.20 (3 H, m); ^{13}C NMR ($CDCl_3$) δ 18.1 (q), 24.7 (t), 25.5 (q), 26.2 (q), 27.6 (t), 28.7 (t), 38.0 (t), 50.6 (d), 67.4 (t), 75.6 (d), 87.0 (d), 90.1 (s), 109.0 (s); IR (neat) 2990, 2950 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3S_2$: C, 53.77; H, 7.63. Found: C, 53.69; H, 7.65.

Spirodithiane 7sa: ^{1}H NMR ($CDCl_3$) δ 1.10 (3 H, d, J = 6 Hz), 1.30 (3 H, s), 1.36 (3 H, s), 1.70–2.85 (7 H, m), 3.10–3.55 (2 H, m), 3.65–4.25 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 15.6 (q), 24.8 (t), 25.7 (q), 27.0 (q), 28.5 (t), 28.9 (t), 34.7 (t), 50.0 (d), 68.1 (t), 73.5 (d), 83.1 (d), 89.8 (s), 109.3 (s); IR (neat) 2990, 2950 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3S_2$: C, 53.77; H, 7.63. Found: C, 53.80; H, 7.55.

Table I. Reaction of Dithiane 1 and α-Oxy Carbonyl Compounds

compd	reactn conditns	products (%)	total yield, %
2	*n*-BuLi, −78 °C	**5a** (78), **5s** (22)	90
3	*n*-BuLi, −78 °C	**6aa** (44), **6as** (43), **6sa** (13)	91
4	*n*-BuLi, −78 °C	**9a** (48), **9s** (52)	86
4	*n*-BuLi, $ZnCl_2$, −78 °C	**9a** (15), **9s** (85)	88
4	*n*-BuLi, $ZnCl_2$, −100 °C	**9a** (4), **9s** (96)	85

Benzyl ether of 6aa: ^{1}H NMR (CCl_4) δ 1.00 (3 H, d, J = 6 Hz), 1.30 (3 H, s), 1.36 (3 H, s), 1.90–2.25 (2 H, m), 2.60–2.90 (4 H, m), 3.10–3.30 (1 H, m), 3.45–4.10 (3 H, m), 4.55 (1 H, d, J = 12 Hz), 4.85 (1 H, d, J = 12 Hz), 5.96 (1 H, d, J = 10 Hz), 7.10–7.40 (5 H, m); IR (neat) 3020, 2990, 2950, 1580 cm^{-1}; EIMS, m/z (relative intensity) 380 (5, M^+), 365 (1), 289 (3), 274 (2), 231 (2), 161 (10), 160 (10), 159 (100), 132 (19), 91 (16).

Benzyl ether of 6as: ^{1}H NMR (CCl_4) δ 1.03 (3 H, d, J = 6 Hz), 1.25 (3 H, s), 1.32 (3 H, s), 1.95–2.25 (2 H, m), 2.70–2.89 (4 H, m), 2.90–3.15 (1 H, m), 3.40–4.10 (3 H, m), 4.62 (2 H, s), 5.82 (1 H, d, J = 10 Hz), 7.15–7.30 (5 H, m); IR (neat) 3020, 2990, 2950, 1580 cm^{-1}; EIMS, m/z (relative intensity) 380 (6, M^+), 161 (12), 160 (10), 159 (100).

Benzyl ether of 6sa: ^{1}H NMR (CCl_4) δ 1.00 (3 H, d, J = 6 Hz), 1.27 (3 H, s), 1.33 (3 H, s), 1.95–2.30 (2 H, m), 2.70–3.00 (4 H, m), 3.30–3.50 (1 H, m), 3.75–4.15 (3 H, m), 4.50 (1 H, d, J = 12 Hz), 4.67 (1 H, d, J = 12 Hz), 5.73 (1 H, d, J = 10 Hz), 7.20–7.35 (5 H, m); IR (neat) 3020, 2990, 2950, 1580 cm^{-1}; EIMS, m/z (relative intensity) 380 (5, M^+), 161 (11), 160 (11), 159 (100).

Lactone 8aa: HPLC (55% EtOAc) t_R 6.8 min; $[\alpha]^{25}_D$ +4.2° (c 0.024, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.01 (3 H, d, J = 6.7 Hz), 2.07–2.13 (1 H, m, H-3), 2.26 (1 H, br s, OH), 2.41 (2 H, d, J = 9.2 Hz), 3.61 (1 H, d, J = 6.5 Hz, H-4), 3.64 (1 H, dd, J = 11.2, 1.3 Hz, H-6), 3.79 (1 H, dd, J = 11.2, 6.5 Hz, H-6), 4.29 (1 H, td, J = 6.5, 1.3 Hz, H-5), 4.56 (1 H, d, J = 11.2 Hz), 4.61 (1 H, d, J = 11.2 Hz), 7.19–7.29 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 17.6 (q), 32.2 (d, C-3), 33.4 (t, C-2), 62.0 (t, C-6), 73.9 (t, $PhCH_2$), 76.7 (d, C-5), 83.4 (d, C-4), 128.0 (2 C), 128.2 (d), 128.6 (2 C), 137.5 (s), 169.8 (s, C=O); IR (neat) 3420, 2950, 1720 cm^{-1}; EIMS, m/z (relative intensity) 250 (7, M^+), 207 (2), 161 (17), 144 (8), 133 (6), 126 (39), 107 (16), 99 (52), 91 (100). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.34; H, 7.18.

Lactone 8as: HPLC (55% EtOAc) t_R 7.0 min; $[\alpha]^{25}_D$ +13.1° (c 0.084, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 6.6 Hz), 2.22–2.27 (1 H, m, H-3), 2.36–2.45 (2 H, m, H-2), 3.37 (1 H, br s, OH), 3.62 (1 H, dd, J = 8.6, 4.2 Hz, H-4), 3.66 (1 H, d, J = 12.0 Hz, H-6), 3.71 (1 H, dd, J = 12.0, 4.2 Hz, H-6), 4.41 (1 H, dd, J = 8.6, 4.2 Hz, H-5), 4.46 (1 H, d, J = 11.6 Hz), 4.52 (1 H, d, J = 11.6 Hz), 7.18–7.27 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.9 (q), 27.8 (d), 34.1 (t), 62.3 (t), 71.5 (t), 73.4 (d), 80.6 (d), 127.6 (2 C), 127.8 (d), 128.3 (2 C), 137.5 (s), 171.2 (s); IR (neat) 3400, 2920, 1710 cm^{-1}; EIMS, m/z (relative intensity) 250 (5, M^+), 161 (3), 144 (6), 126 (15), 107 (6), 99 (60), 91 (100). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.40; H, 7.21.

Lactone 8sa: HPLC (55% EtOAc) t_R 6.6 min; $[\alpha]^{25}_D$ +37.2° (c 0.083, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.97 (3 H, d, J = 6.4 Hz), 2.10–2.17 (1 H, m, H-3), 2.16 (1 H, dd, J = 15.0, 8.2 Hz, H-2), 2.61 (1 H, br s, OH), 2.69 (1 H, dd, J = 15.0, 4.1 Hz, H-2), 3.41 (1 H, dd, J = 8.7, 7.0 Hz, H-4), 3.67 (1 H, br d, J = 12.3 Hz, H-6), 3.81 (1 H, br d, J = 12.3 Hz, H-6), 4.06 (1 H, dt, J = 8.7, 2.5 Hz, H-5), 4.52 (1 H, d, J = 11.2 Hz), 4.56 (1 H, d, J = 11.2 Hz), 7.15–7.25 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 18.8 (q), 32.2 (d), 35.7 (t), 61.5 (t), 73.5 (t), 76.7 (t), 82.0 (d), 128.0 (2 C), 128.1 (d), 128.5 (2 C), 137.3 (s), 171.2 (s); IR (neat) 3420, 2950, 1720 cm^{-1}; EIMS, m/z (relative intensity) 250 (4, M^+), 235 (4), 161 (7), 144 (8), 126 (30), 107 (12), 99 (82), 91 (100).

Ethyl crobarbatate (10): ^{1}H NMR ($CDCl_3$) δ 1.02 (3 H, d, J = 7 Hz), 1.26 (3 H, t, J = 7 Hz), 1.57 (3 H, s), 2.15–2.74 (3 H, m), 4.20 (2 H, q, J = 7 Hz); IR (neat) 2939, 2868, 1792, 1735 cm^{-1}. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.82; H, 7.60.

Acknowledgment. We thank the National Science Council (ROC) for financial support.

Oxidative Decarboxylation of Alcohol Hemiacetals of α-Keto Carboxylic Acids with *N*-Iodosuccinimide

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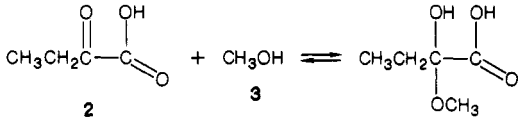
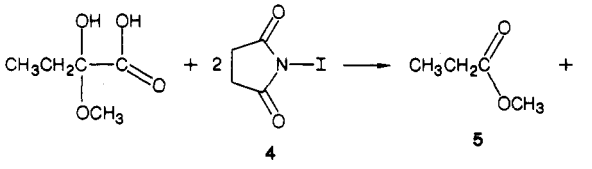
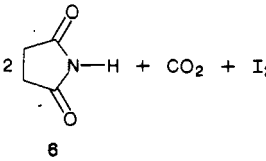
Received November 17, 1986

Recently,[1] we found that α-hydroxy carboxylic acids were easily decarboxylated with *N*-iodosuccinimide (NIS). At this time, we report that the methyl and ethyl alcohol hemiacetals of α-keto carboxylic acids also give good yields of bond-cleavage products when treated with NIS. Similar oxidative cleavage of α-keto carboxylic acid hemiacetals using lead tetracetate was observed by Baer,[2] although the pathways are undoubtably different. Both NIS and lead tetraacetate convert hemiacetals of α-keto carboxylic acids to esters with the loss of carbon dioxide.

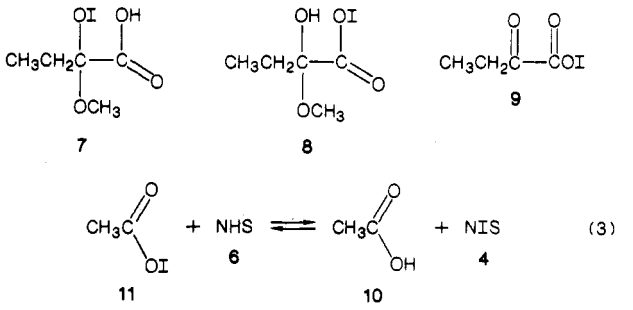
This new reaction with NIS can be illustrated by using the methyl alcohol hemiacetal **1** of α-ketobutyric acid (**2**). When the acid **2** and methyl alcohol (**3**) (20 mol excess) in benzene was treated with NIS (**4**), good yields of methyl propionate (**5**) could be obtained by using three different sets of reaction conditions: (1) heating the reaction mixture in the dark (probable radical pathway), (2) irradiating the reaction mixture (probable radical pathway), and (3) stirring the reaction mixture in the dark at ambient temperatures for long time periods (probable pericyclic decomposition pathway for the hemiacetal hypoiodite). The stoichiometry shown in eq 1 and 2 is supported by good yields of iodine and succinimide (**6**). The carbon dioxide product was determined by running the reaction on a vacuum rack. The carbon dioxide filled a gas-collecting bulb, and the molecular weight of the collected gas was 43.8. Mass spectrometer analysis confirmed the presence of CO_2 as a product in the NIS oxidation of the hemiacetals.







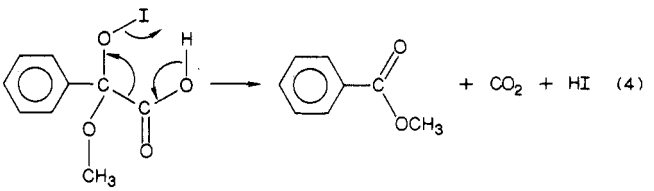
Three hypoiodite intermediate products are possible when the α-keto carboxylic acids react with NIS. Either the hemiacetal hypoiodite **7** or the acyl hypoiodites **8** and **9** could be intermediates. There is good evidence[3,4] for the formation of alkyl hypoiodites from the reaction of alcohols and NIS and the subsequent decomposition of the alkyl hypoiodites with heat or light to produce alkoxy radicals. The chemistry of the reaction of simple carboxylic acids with NIS to form acyl hypoiodites has not been established. Quantitative yields[5] of *N*-iodosuccinimide (**4**) and acetic acid (**10**) are produced when acetyl hypoiodite (**11**) and succinimide (**6**) are mixed (eq 3), which indicates that little acyl hypoiodite is present when succinimide is available to be iodinated. Radical decomposition of the acyl hypoiodite **9** would involve the formation of an acyl iodide intermediate which would react with the alcohol present to produce the ester and HI.



Intermediate methyl ester or dimethyl ketal products of the α-keto carboxylic acid were ruled out because of the speed of the light- and heat-catalyzed reactions. Without the presence of strong mineral acids, esters and ketals are formed very slowly when alcohols and carboxylic acids or alcohols and ketones, respectively, are heated together.

The methyl and ethyl alcohol hemiacetals of three α-keto carboxylic acids (α-ketobutyric acid, pyruvic acid, and benzoylformic acid) were subjected to NIS oxidative decarboxylation. Table I outlines these oxidative cleavages.

Product formation was fastest for the reactions that were heated and irradiated. We believe that the decomposition of the hemiacetal hypoiodite with irradiation follows a radical process to produce the observed products. A concerted, pericyclic pathway (eq 4) is possible for the decarboxylation of the hypoiodite **12** in the room temperature, dark reactions. The methyl alcohol hemiacetal hypoiodite of benzoylformic acid is shown in eq 4. The production of I_2 and NIS in the dark, ambient temperature reactions occurs when the HI decomposes the NIS, a reaction seen in all NIS oxidations where HI is produced.



The stoichiometry of eq 1 indicates a one-to-one mole ratio of keto acid and alcohol is needed to form the hemiacetals. To increase the chance of hemiacetal formation

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