α-Iodination of Some Aliphatic Acids. Substituent Effect and Optimum Conditions[1]

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The chlorosulfonic acid promoted α-iodination of some aliphatic acids in 1,2-dichloroethane has been studied. In contrast to the bromination, the effect of substituents on the rate shows not only a polar effect but also a steric effect in view of Taft's equation: $\log k_{rel} = \rho_\sigma \sum E_\sigma + \delta \sum E_\rho$, where $\rho_\sigma = -1.20$ and $\delta = 1.55$ at 80 °C. The transition state is discussed, which involves the electrophilic addition of I_2 to a ketene intermediate. Aliphatic acids with less steric hindrance at the α-position, except acetic acid, are α-iodinated in good yields (ca. 80–100%). The optimum conditions for α-iodination of long-chain aliphatic acids with caprylic acid as a model substrate are described.

The authors recently presented a novel method for α-chlorination of aliphatic acids by a Cl_2–O_2 mixture in the presence of fuming H_2SO_4 or $ClSO_3H$[2] and postulated a mechanism via a ketene intermediate.[3] The kinetic study of the analogous α-bromination suggested the rate-determining addition of molecular bromine to the ketene intermediate.[4] Also, analogous α-iodination of propionic acid has been successful.[5] We wish here to report the α-iodination of some aliphatic acids, the optimum conditions for the reaction, and the effect of substituents on the rate of iodination using chlorosulfonic acid as a promoter.

Results and Discussion

α-Iodination. According to the similar workup as reported previously with propionic acid,[5] aliphatic acids could generally be α-iodinated by molecular iodine in the presence of $ClSO_3H$ as a strong acidic promoter in 1,2-dichloroethane at 80 °C (eq 1).

$$RR'CHCO_2H + 0.5I_2 \xrightarrow[\text{in } ClCH_2CH_2Cl \text{ at } 80\ ^\circ C]{ClSO_3H} RR'ClCO_2H \xrightarrow{CH_3OH} RR'ClCO_2CH_3 \quad (1)$$

The aliphatic acids were in excess to iodine. The yields were calculated on the basis of iodine by assuming that 1 mol of iodine produces 2 mol of α-iodo aliphatic acid in view of the oxidation of HI to I_2.[5] Products were identified after being converted to their methyl esters by comparison of their NMR and GLC peaks with those of the authentic samples. The yields and physical properties of products are listed in Tables I and II, respectively. The yields for aliphatic acids without steric hindrance at the α-position (R = alkyl, R′ = H) are almost quantitative, and the effect of chain length is small with acids of carbon number over 8. But the yields for acids with steric hindrance at the 2-position (R and R′ = alkyl) are much lower than the yields for α-bromination; e.g., α-bromination of isobutyric acid (R = R′ = Me) gave a 95% yield of product, but its α-iodination gave only a 14% yield.

Kinetics. The rates of α-iodination were measured by iodometry of the remaining molecular iodine and by GLC analysis of α-iodo aliphatic acid esters. As reported in the iodination of propionic acid, the rate of α-iodination fits eq 2, although the k values tend to decrease with time.[5]

$$v = k[RR'CHCO_2H][I_2][ClSO_3H]_0 \quad (2)$$

Some examples for the calculation of k are shown in the Experimental Section. Hence the mechanism proposed previously for α-iodination of propionic acid[5] may also be applied to general aliphatic acids. The rate-determining

$$RR'CHCO_2H + ClSO_3H \overset{\text{fast}}{\rightleftharpoons} RR'C{=}C{=}O + HCl + H_2SO_4 \quad (3)$$

$$RR'C{=}C{=}O + I_2 \xrightarrow{\text{slow}} RR'ClCOI \quad (4)$$

$$RR'ClCOI + 0.5H_2SO_4 \rightarrow RR'ClCO_2H + 0.5I_2 + 0.5SO_2 \quad (5)$$

step may be the addition of iodine to the ketene (eq 4).

Substituent Effect. Rate constants k calculated by eq 2 are shown in Table III. As is apparent from Table III, the k value increases with increasing carbon number of R when R′ is H. This is ascribed to the electron-releasing effect of alkyl substituent. But when both R and R′ are alkyl, the k values and yields are very small, which suggests the presence of the steric hindrance. Therefore, the data were analyzed on the basis of Taft's equation (eq 6) in which the steric effect is taken into account.[6] Here,

$$\log k_{rel} = \rho_\sigma \sum E_\sigma + \delta \sum E_s \quad (6)$$

Table I. Yields of α-Iodo Acids by $ClSO_3H$-Promoted Reaction of Aliphatic Acids with I_2 in Dichloroethane at 80 °C[a]

substrate	acid	yield, %
acetic	CH_3COOH	12.3[b]
propionic	CH_3CH_2COOH	79.4[b]
butyric	$CH_3CH_2CH_2COOH$	93.6[b]
isobutyric	$(CH_3)_2CHCOOH$	13.8[b]
isovaleric	$(CH_3)_2CHCH_2COOH$	98.0[b]
diethylacetic	$(CH_3CH_2)_2CHCOOH$	7.1[b]
α-methylvaleric	$CH_3CH_2CH_2CH(CH_3)COOH$	trace[b]
caprylic	$CH_3(CH_2)_6COOH$	100[c]
capric	$CH_3(CH_2)_8COOH$	95.8[c]
lauric	$CH_3(CH_2)_{10}COOH$	97.4[c]
myristic	$CH_3(CH_2)_{12}COOH$	92.1[c]
palmitic	$CH_3(CH_2)_{14}COOH$	96.3[c]
stearic	$CH_3(CH_2)_{16}COOH$	95.3[c]

[a] The yields were estimated from the esters and were measured by means of GLC, but the actual isolation of α-iodo acids gave 30–40% lower yields (see Experimental Section). [b] Substrate (85 mmol) was treated with I_2 (6.5 mmol) in the presence of $ClSO_3H$ (32 mmol) in dichloroethane (50 mL) at 80 °C for 3 h. [c] Substrate (50 mmol) was treated with I_2 (12.5 mmol) in the presence of $ClSO_3H$ (50 mmol) in dichloroethane (50 mL) at 80 °C for 2 h.

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Table II. Physical Properties of Methyl Esters of α-Iodo Acids

ester	bp, °C (mm)	NMR chemical shifts,[a] δ	IR[b] $\nu_{C=O}$, cm^{-1}
$CH_2ICO_2CH_3$[c]	169-171 (760)	3.63 (s, 2 H, α-H), 3.71 (g, 3 H, OCH_3)	1720
$CH_3CHICO_2CH_3$	80-85 (50)	1.93 (d, J = 6.8, 3 H, β-H), 3.70 (s, 3 H, OCH_3), 4.43 (q, J = 6.8, 1 H, α-H)	1730
$CH_3CH_2CHICO_2CH_3$	85-86 (31)	0.97 (t, J = 7.1, 3 H, γ-H), 1.97 (m, J = 7.4, 2 H, β-H), 3.71 (s, 3 H, OCH_3), 4.20 (t, J = 7.4, 1 H, α-H)	1730
$(CH_3)_2CICO_2CH_3$[d]	75-77 (32)[e]	2.05 (s, 6 H, β-H), 3.72 (s, 3 H, OCH_3)	1730
$(CH_3)_2CHCHICO_2CH_3$	95-97 (28)	1.00 (d, J = 6.3, 3 H, γ-H),[f] 1.11 (d, J = 6.3, 3 H, γ'-H),[f] 1.94 (m, 1 H, β-H), 3.67 (s, 3 H, OCH_3), 4.04 (d, J = 8.0, 1 H, α-H)	1730
$CH_3(CH_2)_5CHICO_2CH_3$	81-86 (0.2)	3.68 (s, 3 H, OCH_3), 4.19 (t, J = 7.3, 1 H, α-H)	1735
$CH_3(CH_2)_7CHICO_2CH_3$	108-112 (0.16)	3.69 (s, 3 H, OCH_3), 4.20 (t, J = 7.3, 1 H, α-H)	1735
$CH_3(CH_2)_9CHICO_2CH_3$	134-136 (0.12)	3.68 (s, 3 H, OCH_3), 4.18 (t, J = 7.2, 1 H, α-H)	1740
$CH_3(CH_2)_{11}CHICO_2CH_3$	148-152 (0.19)	3.68 (s, 3 H, OCH_3), 4.19 (t, J = 7.7, 1 H, α-H)	1738
$CH_3(CH_2)_{13}CHICO_2CH_3$	169-172 (0.52)	3.69 (s, 3 H, OCH_3), 4.19 (t, J = 7.3, 1 H, α-H)	1740
$CH_3(CH_2)_{15}CHICO_2CH_3$	184-188 (0.42)	3.68 (s, 3 H, OCH_3), 4.18 (t, J = 7.2, 1 H, α-H)	1740

[a] In CCl_4; J values in hertz. [b] Neat. [c] Prepared by esterification of CH_2ICO_2H. [d] Prepared by iodination in thionyl chloride.[7] [e] Lit.[8] bp 55-57 °C (13.4 mm). [f] Protons γ and γ' are not equivalent magnetically.[9]

Table III. Initial Rate Constants for α-Iodination of Aliphatic Acids in 1,2-Dichloroethane at 80 °C[a]

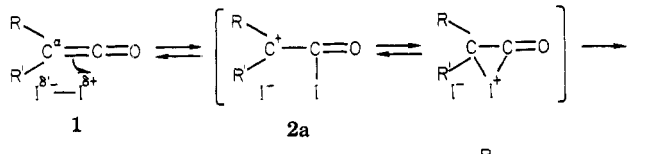
	substrate, $RR'CHCO_2H$ R	R'	third-order rate const 10^3k, M^{-2} s^{-1}	k_{rel}	log k_{rel}	Taft const steric, ΣE_s	polar, ΣE_σ
1	H	H	0.8	0.9	−0.05	2.48	2.44
2	CH_3	H	2.4	2.6	0.41	1.24	1.22
3	CH_3CH_2	H	3.0	3.2	0.51	1.17	0.98
4	$(CH_3)_2CH$	H	3.2	3.5	0.55	0.77	0.75
5	CH_3	CH_3	9.1	1.0	0.00	0.00	0.00
6	CH_3CH_2	CH_3CH_2	2.3	2.6	0.41	−0.14	−0.48

[a] Initial conditions: $RR'CHCO_2H$, 1.3 M; I_2, 0.13 M; $ClSO_3H$, 0.50 M.

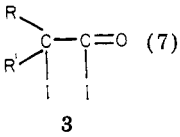
ρ_σ is the polar reaction constant, $\sum E_\sigma$ the sum of the polar substituent constants, δ the steric reaction constant, and $\sum E_s$ the sum of the steric substituent constants.

The value of ρ_σ calculated from sets of aliphatic acids (**2** and **6**, **3**, and **6**, and **4** and **6**) was −1.20. A plot of $\sum E_s$ vs. (log k_{rel} − $\rho_\sigma \sum E_\sigma$), which uses this ρ_σ value, gave a straight line with a slope (δ) of 1.55 (Figure 1). Acetic acid shows a large deviation from the line probably because of the little solubility or instability of the intermediary ketene as observed previously with bromination.[4]

The negative ρ_σ (−1.20) means that acid-promoted α-iodination is accelerated by an electron-releasing group and suggests that an electrophilic addition of iodine to the carbon–carbon double bond of ketene is involved in the rate-determining step. These facts are explained by eq 7 (which is similar to the reaction scheme for α-bromination),[4] where transition state **2a** is much more important than **2b** as described below.



1 2a



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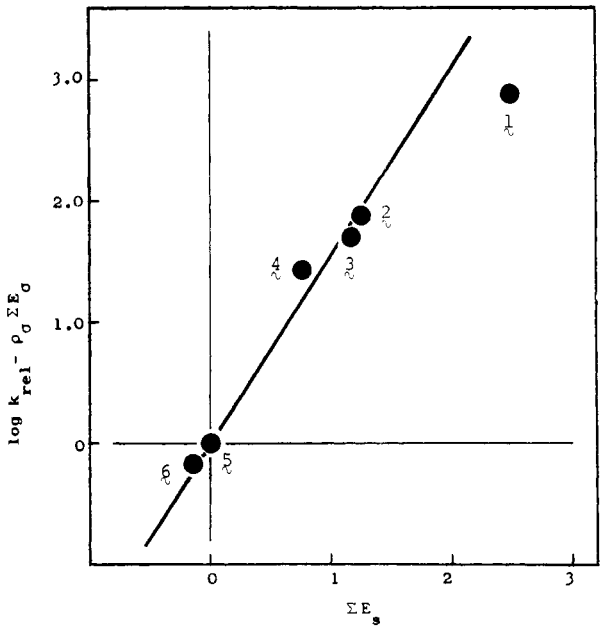

Figure 1. Taft plot of (log k_{rel} − $\rho_\sigma \sum E_\sigma$) vs. $\sum E_s$ for iodination of aliphatic acids in 1,2-dichloroethane at 80 °C. Initial concentrations: $[RR'CHCO_2H]_0$, 1.30 M; $[I_2]_0$, 0.13 M; $[ClSO_3H]_0$, 0.50 M.

Positively polarized iodine should attack on the carbonyl carbon, which is less hindered, and produce cation **2**. The cation **2** is stabilized by steric and polar effects when the iodine atom is located closer to the carbonyl carbon. The other forms, in which the iodine atom is located closer to the α-carbon or is bridged symmetrically to the carbonyl and α-carbons (**2b**), contribute to a lesser extent. However, as opposed to bromination in which δ = 0, a fairly large steric effect (δ = 1.55) is observed in the iodination, because an attack of $I^{\delta+}$, which is bulkier than $Br^{\delta+}$, is retarded by the steric effect. The Stuart model indicates that there is a van der Waals steric interaction between the iodine and methyl groups in the transition state (**2**) for iodination of isobutyric acid but not between the bromine and methyl groups in that for α-bromination of isobutyric acid.

Effects of Conditions on Yields of Caprylic Acid. Aliphatic acids bearing an unsubstituted α-methylene group gave good yields (Table I). α-Iodination of caprylic acid was examined in detail as a model case. The effect of reaction time on yield is shown in Figure 2. Here there is 2 equiv of caprylic acid to 1 equiv of iodine for I and III,

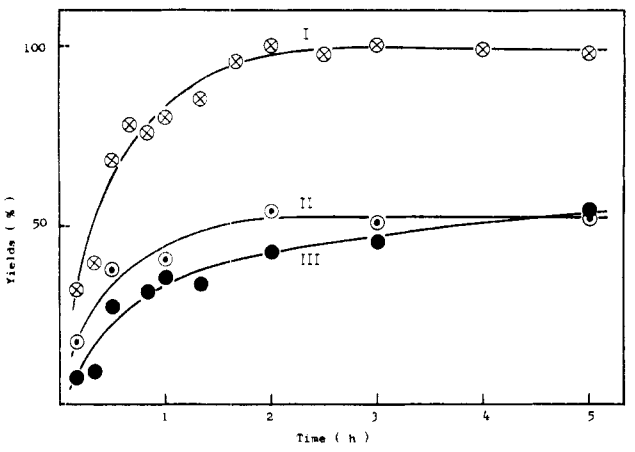

Figure 2. Effect of reactant ratio on the conversion curve in α-iodination of caprylic acid with iodine in the presence of chlorosulfonic acid in 1,2-dichloroethane at 80 °C: curve I, ⊗, $[C_7H_{15}CO_2H]_0$ = 1.0 M, $[I_2]_0$ = 0.25 M, $[ClSO_3H]_0$ = 1.0 M; curve II, ⊙, $[C_7H_{15}CO_2H]_0$ = 0.5 M, $[I_2]_0$ = 0.25 M, $[ClSO_3H]_0$ = 0.5 M; curve III, ●, $[C_7H_{15}CO_2H]_0$ = 1.0 M, $[I_2]_0$ = 0.25 M, $[ClSO_3H]_0$ = 0.5 M.

while there is 1 equiv of each for curve II. Curve I, where the $[\text{caprylic acid}]_0/[I_2]_0/[ClSO_3H]_0$ ratio is 4:1:4, shows that the reaction is complete after 2 h, the yields after 2 h being constant (ca. 100%), so that virtually no decomposition of the products occurs.

Curve II shows the effect of reaction time on the yields when the $[\text{caprylic acid}]_0/[I]_0/[ClSO_3H]_0$ ratio is 2:1:2; here also the yield increases for 2 h and then becomes approximately constant (ca. 50%). In this case, the lower rate of iodination and hence the more appreciable side reactions of caprylic acid with $ClSO_3H$, such as formation of an α-sulfo acid during the iodination, would lower the yield.

Curve III, with a $[\text{caprylic acid}]_0/[I_2]_0/[ClSO_3H]_0$ ratio of 4:1:2, shows that the maximum yield is 50%. Hence, the molar ratio of $[\text{caprylic acid}]_0/[I_2]_0/[ClSO_3H]_0$ of 4:1:4 gives the optimum yields; e.g., the aliphatic acid and $ClSO_3H$ must be in excess to iodine to obtain a high yield. This implies that the concentration of intermediate ketene needs to be much higher for effective reaction of iodine in comparison with chlorination.[2a] No α,α-diiodo acid was detected, which is rational in view of the low electrophilicity of $I^{\delta+}$, the expected large steric hindrance, and the polar effect of the α,α-diiodo acid.

Effect of concentration of $ClSO_3H$ on yields is shown in Figure 3. At lower concentration of $ClSO_3H$, the yield increases with increasing $[ClSO_3H]_0$, and after $[ClSO_3H]_0$ reaches 1.25 M, the yield decreases. This is due to the side reaction producing α-sulfo acid, etc. The produced α-iodo acid might suffer decomposition, but as shown in curve I of Figure 2, virtually no decomposition by $ClSO_3H$ was observed under these conditions.

The effect of temperature on yields is shown in Figure 4. At lower temperatures (40–80 °C) the yield increases with rising temperature, but it decreases gradually at temperatures over 80 °C. This is due to the side reaction as described above. Therefore, the optimum conditions for α-iodination of caprylic acid are that a solution of 1,2-dichloroethane containing 1.0 M of caprylic acid, 0.25 M of iodine, and 1.0 M of $ClSO_3H$ should be heated at 80 °C for 2 h. The yields of α-iodination of long-chain aliphatic acids under these conditions are 92–100% as shown in Table I.

Experimental Section

Materials. Commercial, first grade, aliphatic acids were dried over P_2O_5 and distilled before use; their boiling points are as follows: acetic, 116–117 °C; propionic, 64–66 °C (39 mm); *n*-butyric, 73–74 °C (20 mm); isobutyric, 77–79 °C (42 mm); isovaleric, 98–100 °C (42 mm); diethylacetic, 104–105 °C (27 mm); α-methylvaleric, 103–105 °C (25 mm); caprylic, 147–148 °C (35 mm). Chlorosulfonic acid was also purified by distillation; bp 86–88 °C (33 mm). First grade capric (mp 30.5–31.5 °C), lauric (mp 42.5–43.7 °C), myristic (mp 50.5–51.5 °C), palmitic (mp 63.0–64.0 °C), stearic (mp 69.5–70.5 °C), and iodoacetic acids (mp 81.0–82.5 °C) were used without further purification. Their methyl esters show single peaks upon GLC analysis. Authentic α-iodo acids were prepared by the iodination of aliphatic acids in thionyl chloride.[7] The physical properties of their methyl esters agreed with those prepared by our method, which are shown in Table II.

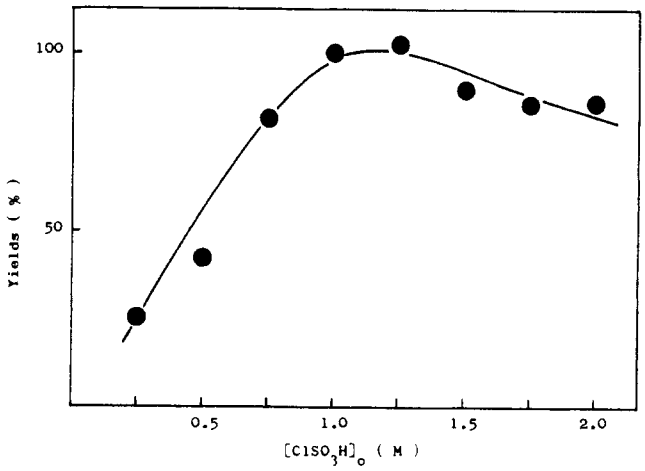

Figure 3. Effect of initial concentration of chlorosulfonic acid on the yield of α-iodination of caprylic acid (1.0 M) with iodine (0.25 M) in 1,2-dichloroethane at 80 °C for 2 h.

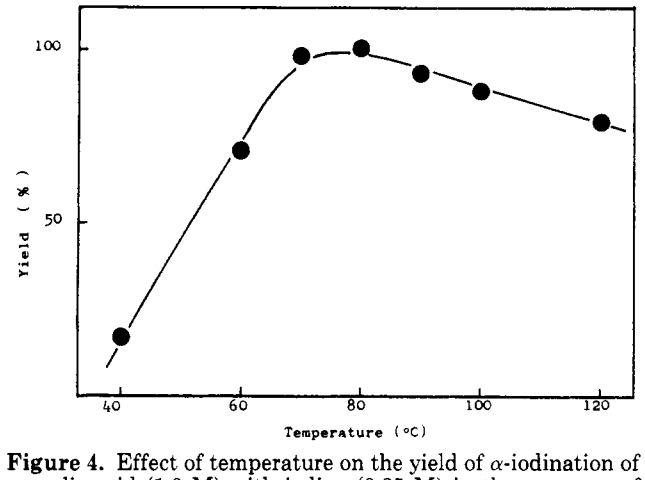

Figure 4. Effect of temperature on the yield of α-iodination of caprylic acid (1.0 M) with iodine (0.25 M) in the presence of chlorosulfonic acid (1.0 M) in 1,2-dichloroethane for 2 h.

Kinetics by Iodometry. A solution of 1,2-dichloroethane (50 mL) containing aliphatic acid (65 mmol) and iodine (6.5 mmol) was thermostated at 80 °C, and a thermostated dichloroethane solution of $ClSO_3H$ (25 mmol) was mixed in, to start the reaction. Each 2-mL sample of the reaction mixture was pipetted out at appropriate intervals of time, poured into water, and then added with excess aqueous KI. Liberated iodine was titrated with 0.02 N $Na_2S_2O_3$ to measure the concentration of iodine. The sec-

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Table IV. Values of 10^3k (in M^{-2} s^{-1}) for Iodination of Butyric and Caprylic Acids

acid	time, min 0	1	2	3	4	5
$CH_3CH_2CH_2CO_2H$	2.96	2.80	2.50	2.34	2.20	2.09
$CH_3(CH_2)_6CO_2H$	2.92	2.39	2.04	1.79	1.61	1.50

ond-order rate constants (k) were calculated by eq 8 according to the stoichiometric eq 1-5.

$$\ln\left(\frac{a-x}{b-(x/2)}\right) = \frac{k}{2}(a-2b)t - \ln\left(\frac{b}{a}\right) \quad (8)$$

Here, a and b are the initial concentrations of the aliphatic acid and iodine, respectively, and $x/2$ is the molar concentrations of consumed iodine at time t.

As typical examples, the $k \times 10^3$ M^{-2} s^{-1} values for the iodination of butyric and caprylic acids are shown in Table IV, where the k values at time 0 are obtained by extrapolation and used in Table III.

Products and Conversion Curves of Products. A 1,2-dichloroethane solution (50 mL) containing a mixture of aliphatic acid (85 mmol) and iodine (6.5 mmol) was thermostated at 80 °C, and a thermostated dichloroethane solution of $ClSO_3H$ (32 mmol) was introduced to start the reaction. Aliquots (2 mL), after treatment with aqueous $Na_2S_2O_3$, were esterified by an ethereal solution of diazomethane. The yields were calculated by GLC as described below. The residual mixture in the flask was esterified by refluxing with methanol (30 mL) for 8 h. The ester solution obtained was successively washed with water and aqueous $Na_2S_2O_3$, dried (Na_2SO_4), and distilled in vacuo after removal of methanol and 1,2-dichloroethane. The resulting methyl esters of α-iodo acids were identified and their amounts estimated by means of GLC with a Yanagimoto GCG-550 gas chromatograph equipped with a hydrogen-flame ion detector and a copper column packed with PEG 20M (10%) on Chromosorb WAW (60-80 mesh), with methyl caprate as an internal standard. The isolated methyl esters of α-iodo acids were identified by GLC and NMR (a 60-MHz Hitachi, R-24B NMR spectrometer) in comparison with the authentic samples. IR spectra were measured with a Perkin-Elmer Model 337 spectrophotometer (Table II). For long-chain aliphatic acids, a solution of 1,2-dichloroethane (50 mL) containing aliphatic acid (50 mmol), iodine (12.5 mmol), and $ClSO_3H$ (50 mmol) was reacted analogously at 80 °C for 2 h. α-Iodo acid produced was esterified as described above and analyzed by means of GLC using PEG 20M and Silicon OV 17 (5%) on Shimalite W 201D (80-100 mesh) and employing methyl caprate and dodecane as internal standards.

The yields estimated by the actual isolation of methyl esters of α-iodo acids were ca. 30-40% lower than those by GLC because of a loss in the esterification with methanol and in the distillation. For example, the yield of methyl α-iodobutyrate [85-86 °C (31 mm)] was ca. 59% (93.6% by GLC), and the yield of methyl α-iodocaprylate [81-83 °C (0.2 mm)] was ca. 62% (100% by GLC). The direct vacuum distillation of prepared α-iodo acids results in a considerable decomposition and gave darkly colored product, the yield being 30% lower, e.g., 63% for α-iodobutyric acid [110-114 °C (3.2 mm)].

Registry No. Acetic acid, 64-19-7; propionic acid, 79-09-4; butyric acid, 107-92-6; isobutyric acid, 79-31-2; isovaleric acid, 503-74-2; diethylacetic acid, 88-09-5; α-methylvaleric acid, 97-61-0; caprylic acid, 124-07-2; capric acid, 334-48-5; lauric acid, 143-07-7; myristic acid, 544-63-8; palmitic acid, 57-10-3; stearic acid, 57-11-4; iodine, 7553-56-2; chlorosulfonic acid, 7790-94-5; methyl α-iodoacetate, 5199-50-8; methyl α-iodopropionate, 56905-18-1; methyl α-iodobutyrate, 73651-35-1; methyl α-iodoisobutyrate, 67194-53-0; methyl α-iodoisovalerate, 73635-60-6; methyl α-iodocaprylate, 73635-61-7; methyl α-iodocaprate, 73635-62-8; methyl α-iodolaurate, 73635-63-9; methyl α-iodomyristate, 73635-64-0; methyl α-iodopalmitate, 73635-65-1; methyl α-iodostearate, 67810-48-4; α-iodobutyric acid, 7435-10-1.

Reaction of Nitroso Aromatics with Glyoxylic Acid. A New Path to Hydroxamic Acids[1]

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In aqueous solution substituted aromatic nitroso compounds react rapidly with glyoxylic acid to produce *N*-hydroxyformanilides and CO_2. The reaction is nearly quantitative for all nitroso aromatics investigated and serves as a convenient synthetic route to *N*-hydroxyformanilides. This reaction follows second-order reaction kinetics overall and is unimolecular in each of the two reactants. The reaction is strongly inhibited by organic cosolvents but is not affected by hydroquinone, H_2O_2, catalase, superoxide dismutase, or O_2. The rate of reaction was found to increase with increasing electron donation by ring substituents. Possible ionic reaction mechanisms are presented in which the nitroso group behaves as a nucleophile.

Hydroxamic acids have received considerable attention in recent years as the result of the discovery of their role in the biochemical toxicology of many drugs and other chemicals. Their production by the microsomal oxidation of amide-containing chemicals explains in large part the mechanism by which the latter exert toxic effects on living systems.[2] Our interest in this structural group arose from earlier studies on a unique family of natural products that contain the hydroxamic acid functionality.[3] More recently we have elucidated a new biochemical pathway for the production of aromatic hydroxamic acids through the interaction of thiamine-dependent enzymes with aromatic nitroso compounds.[4,5] During the course of these investigations we discovered a purely chemical reaction that was totally unexpected. We now describe this novel reaction between nitroso aromatics 1 and glyoxylic acid (2) that

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