ture was stirred at room temperature for 2 hr under nitrogen. The product was filtered under nitrogen, washed (D_2O), and dried (P_2O_5). It had the same melting point as that of diprotio starting material. The nmr spectrum (DMSO-d_6) showed the absence of NH protons in the 9.5–10.5 ppm region.

Kinetics of the Reaction. An approximately 0.1 *M* solution of the sodium salt of the 1-benzenesulfonyl-2-acylhydrazine, obtained either by using the preformed sodium salt (0.002 mol) or from a mixture of the hydrazine (0.002 mol) and anhydrous sodium carbonate (1 equiv) in diethylcarbitol (*ca.* 10 ml), was heated in a constant-temperature bath at 160 ± 0.5°. At the end of the reaction period, the mixture was poured into ice and the aldehyde was extracted with ether. The ether extract was concentrated and treated with *ca.* 50 ml (0.0025 mol) of an 0.05 M solution 2,4-dinitrophenylhydrazine in 0.25 *M* methanolic HCl. The yield of aldehyde was estimated gravimetrically. Results of a typical run are given below: a = per cent of aldehyde formed after time t (seconds). Mean values for k were calculated using the method of least squares. The results recorded in Table I were obtained in the same way.

t	60	120	180	240	300	360
a	12.7	24.2	33.5	43.0	50.1	56.2
$10^4 k$	22.65	23.09	22.67	23.43	23.18	22.91
		Mean	23.10			

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Synthesis of Dioxocarboxylic Acids[1]

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The reaction of ω-halocarboxylates $M^+{}^-OOC(CH_2)_nX$ (II) with disodioacetylacetone (I) was investigated. For II (n = 2; M = Na; X = Cl) and II (n = 5; M = Na; X = Br), no product was isolated. For II (n = 1, 2, 3, 5, 6, and 10; M = Na or Li; X = Cl or Br), except as indicated above, alkylation occurred in 9–92% yields to form the terminal alkylation products (the dioxocarboxylic acids). Overall, lithium salts were superior to sodium salts and ω-bromocarboxylates were better than the chloro compounds.

Plant cuticular lipids contain β-diketones in significant amounts; however, their biosynthesis is poorly understood.[3] One unexplored pathway is the decarboxylation of dioxocarboxylic acids. There is no convenient method for synthesizing acids of this type, although esters of some of these acids have been prepared by a rather cumbersome procedure.[4]

To develop an effective procedure for attaching carboxylic acid chains to β-diketones, we have investigated the reaction of the salts of several ω-halo acids with disodioacetylacetone. In previous work, some alkyl halides have been shown to be highly effective in alkylating dianions of this type selectively at the terminal position[5,6] (eq 1). In

$$\underset{\text{I}}{CH_3C(\overset{Na^+}{\overline{C}}H)C(=O)\overset{Na^+}{\overline{C}}H_2} + RX \longrightarrow \xrightarrow{H^+} CH_3COCH_2COCH_2R \quad R = \text{methyl, ethyl, butyl, etc.} \quad (1)$$

the present investigation it was found that alkylation of the dianion of 2,4-pentanedione (I) at the terminal posi-

Table I
Products of Alkylations of Haloacid Salts $M^{+-}OOC(CH_2)_nX$ with Disodioacetylacetone[a]

Acid	Registry no.	n	M	X	Salt registry no.	Product	Mp, °C	Yield, %	Registry no.
Chloroacetic	79-11-8	1	Na	Cl	3926-62-3	4,6-Dioxoheptanoic acid	67–69	52	51568-18-4
Chloroacetic		1	Li	Cl	19326-51-3	4,6-Dioxoheptanoic acid	67–69	82	
3-Chloropropanoic	107-94-8	2	Na	Cl	16987-03-4	5,7-Dioxooctanoic acid		None	51568-19-5
3-Chloropropanoic		2	Li	Cl	51568-11-7	5,7-Dioxooctanoic acid	44–47	9	
3-Bromopropanoic	590-92-1	2	Na	Br	43165-24-8	5,7-Dioxooctanoic acid	44–47	11	
3-Bromopropanoic		2	Li	Br	51568-12-8	5,7-Dioxooctanoic acid	44–47	58	
4-Chlorobutanoic	627-00-9	3	Na	Cl	51568-13-9	6,8-Dioxononanoic acid	44–46	11	3991-20-6
4-Chlorobutanoic		3	Li	Cl	51568-14-0	6,8-Dioxononanoic acid	44–46	41	
6-Bromohexanoic	4224-70-8	5	Na	Br	50530-06-8	8,10-Dioxoundecanoic acid		None	51568-20-8
6-Bromohexanoic		5	Li	Br	51568-15-1	8,10-Dioxoundecanoic acid	57–58	70	
7-Bromoheptanoic	30515-28-7	6	Li	Br	51568-16-2	9,11-Dioxododecanoic acid	59–60	92	51568-21-9
11-Bromoundecanoic	2834-05-1	10	Li	Br	51568-17-3	13,15-Dioxohexadecanoic acid	77–79	82	51568-22-0

[a] Satisfactory analytical data (±0.3% for C, H) were reported for all new compounds listed in the table. Ed.

tion proceeded reasonably well with salts of ω-halo acids, (II) but the yield depended on both the cation of the acid salt and the halogen (eq 2).

$$\underset{\text{I}}{CH_3\overset{Na^+}{\overline{C}}HCO\overset{Na^+}{\overline{C}}H_2} + \underset{\text{II}}{M^{+-}OOC(CH_2)_nX} \longrightarrow \xrightarrow{H^+} CH_3COCH_2COCH_2(CH_2)_nCOOH \quad (2)$$

M = Na or Li

n = 1, 2, 3, 5, 6, or 10

X = Cl or Br

The essential effects of four combinations of cation and halogen upon the yield in the alkylation reaction can be seen by comparing the 3-halopropanoates. With 3-chloropropanoic acid, the sodium salt gave no isolable product and the lithium salt gave 9%. The sodium salt of 3-bromopropanoic acid gave only 11% but the lithium salt gave 58% alkylation product. These results are consistent with those in other cases, summarized in Table I, in showing that the bromo acid salts (0–92% yields) are more reactive toward the dianion than the corresponding chloro acid salts (0–82%).[7] They also typify our finding that yields obtained using the lithium salts (9–92% yields) are consistently higher than those obtained using the sodium salts (0–52%). The latter generalization may not be true for any given case when the halogen is changed as well, however, since sodium 3-bromopropanoate and lithium 3-chloropropanoate give approximately the same yield of product. We attempted to maximize the yields of 9,11-dioxododecanoic acid and 13,15-dioxohexadecanoic acid by taking advantage of the above findings from the lower molecular weight cases (Br > Cl; Li > Na). The excellent results indicate that these alkylations could be extended to even longer chain lithium ω-bromocarboxylates than studied in the present investigation. Preparation of the halo acid salts by neutralization with aqueous base was found to be inappropriate because of the difficulty encountered in removing the water. Similarly, direct reaction with the metal was found to be rather slow because of the difficulty in maintaining active surface area. The best method was direct reaction with the metal hydride in anhydrous tetrahydrofuran. Potassium salts of a few of the acids were also prepared but not used in alkylation reactions because of their rapid deliquescence, observed even when anhydrous preparations were made. The salts of 4-bromobutanoic acid were not investigated, since the commercially available compound was not of the quality required for our work and was difficult to purify.

As an alternative to adding the isolated halo acid salt to the prepared dianion, we prepared the dianion with an excess of 1 equiv of sodium amide and then added 1 equiv of chloroacetic acid. Unfortunately, the amide apparently reacted rather rapidly with the halogen, since a considerable amount of glycine was formed and only trace amounts of the intended product could be isolated.

The structures of the dioxocarboxylic acids are supported by analogy with previous alkylation reactions of dianions,[5,6] by elemental analysis, and by infrared and nmr spectra which were consistent with our proposed structures (see Experimental Section).

Experimental Section[8]

Preparation of Halo Acid Salts. The Na and Li salts of the halo acids were prepared by reaction of the appropriate hydride with the halo acid in dry tetrahydrofuran (THF). A 500-ml three-necked flask was fitted with an overhead stirrer, an addition funnel, and a condenser with a dry N_2 purge. Either NaH or LiH was placed in the flask; normally 0.25 mol was used. NaH was washed three times with 50 ml of petroleum ether (bp 35–60°) to remove the mineral oil dispersant. THF (150 ml) was added; then 0.26 mol of the halo acid in 100 ml of THF was added dropwise with stirring over about 1 hr. The mixture was stirred at room temperature overnight; after Büchner filtration the solid product was rinsed three times with 25 ml of Et_2O and dried for 6 hr at 20 mm and 25°. The solid was then powdered in a mortar and dried at 10 mm and 60° for 2 days prior to use.

Alkylation of Disodioacetylacetone with Halo Acid Salts. All reactions were carried out using this generalized procedure. A 500-ml three-necked flask (fitted with an overhead stirrer, Dry Ice condenser, and dry N_2 line) containing 0.2 mol of $NaNH_2$[9] in 300 ml of liquid NH_3 was cooled to −78° in a Dry Ice–acetone bath while N_2 was passed over the reaction mixture. A solution of 10 g (0.1 mol) of acetylacetone in 15 ml of dry Et_2O was added with stirring in small portions from a pressure-compensating addition funnel. The cooling bath was removed and the temperature was allowed to return to reflux. After the solution had stirred for 1 hr, 0.1 mol of the halo acid salt (Table I) was added through Gooch tubing over 30 min. The mixture was stirred for 4 hr; then 200 ml of Et_2O was added slowly as the NH_3 was allowed to evaporate (*ca.* 2 hr). The flask was cautiously warmed with hot water until the ether began to reflux. After 5 min, the suspension was cooled with an ice bath for 15 min. A few chips of ice were added cautiously followed by a mixture of 30 ml of concentrated HCl and 40 g of crushed ice. Ethereal and aqueous layers were separated and the latter was extracted three times with 50 ml of Et_2O. The combined Et_2O solution was dried ($MgSO_4$), filtered, and concentrated. The crude product was recrystallized from a mixture of $CHCl_3$ and CCl_4.

Spectral Data. 4,6-Dioxoheptanoic acid: ir 3100 (br), 2940, 1720, 1630, and 1420 cm^{-1}; nmr[10] δ 2.05 (2.25 H, s), 2.25 (0.75 H, s), 3.55 (0.52 H, s), 5.55 (0.75 H, s), and a broad absorption at 12.

5,7-Dioxooctanoic acid: ir 3120 (br), 2940, 2880, 1720, 1640, 1600, and 1410 cm^{-1}; nmr δ 1.8 (2 H, m), 2.05 (*ca.* 3 H, s), 2.4 (*ca.* 4 H, m), 3.6 (0.3 H, s), 5.55 (*ca.* 1 H, s), and a broad absorption at 11.5.

6,8-Dioxononanoic acid: ir 3120 (br), 2940, 2880, 1720, 1690, 1600, and 1410 cm^{-1}; nmr δ 1.7 (4 H, m), 2.05 (*ca.* 3 H, s), 2.35 (*ca.* 4 H, s), 3.6 (0.4 H, s), 5.55 (*ca.* 1 H, s), and a broad absorption at 11.5.

8,10-Dioxoundecanoic acid: ir 3120 (br), 2940, 2860, 1720, 1690, 1650, 1600, and 1420 cm^{-1}; nmr δ 1.4 (8 H, m), 2.05 (*ca.* 3 H, s), 2.25 (*ca.* 4 H, s), 3.55 (0.3 H, s), 5.55 (*ca.* 1 H, s), and a broad absorption at 11.5.

9,11-Dioxododecanoic acid: ir 3100 (br), 2940, 2850, 1710, 1610, and 1410 cm^{-1}; nmr δ 1.4 (10 H, m), 2.05 (*ca.* 3 H, s), 2.25 (*ca.* 4 H, m), 3.55 (0.4 H, s), 5.55 (*ca.* 1 H, s), and a broad absorption at 11.5.

13,15-Dioxohexadecanoic acid: ir 3100 (br), 2930, 1720, 1650, 1600, 1470, and 1420 cm^{-1}; nmr δ 1.4 (18 H, m), 2.05 (*ca.* 3 H, s), 2.25 (*ca.* 4 H, m), 3.55 (0.4 H, s), 5.55 (*ca.* 1 H, s), and a broad absorption at 11.5.

Registry No.—Acetylacetone, 123-54-6.

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Notes

Resolution of Some 3-(3,4-Dihydroxyphenyl)alanine Precursors with α-Chymotrypsin

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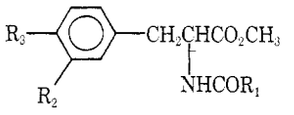
Preferential hydrolysis of aliphatic esters of a variety of L aromatic amino acid esters or their *N*-acyl derivatives by α-chymotrypsin has been exploited to resolve racemic mixtures of these compounds.[1] In an effort to further evaluate the synthetic utility and limitations of this method, we resolved the 3-(3,4-dihydroxyphenyl)alanine (dopa) precursors **1–3** enzymatically and used the enantiomers, plus racemic **4**, to obtain information about the effect of the ring substituents on the rates and stereoselectivities of the reactions.[2]



Compd	R_1	R_2		R_3
1	CH_3	CH_3O		HO
2	C_6H_5	CH_3O		HO
3	CH_3		OCH_2O	
4	CH_3	CH_3O		CH_3O
5	CH_3	H		HO

Erlenmeyer condensation of 3,4-methylenedioxybenzaldehyde or 3,4-dimethoxybenzaldehyde with acetylglycine afforded the corresponding 4-benzylidine-2-methyl-2-oxazolin-5-ones. Methanolysis of the oxazolinone rings produced the ring-substituted methyl *N*-acetyl-α-aminocinnamates. Subsequent catalytic hydrogenation yielded racemic **3** and **4**. A similar procedure was used to synthesize **1** and **2**, except that the starting aldehyde was 4-benzyloxy-3-methoxybenzaldehyde, and with **2**, benzoylglycine replaced acetylglycine. In each case, hydrogenolysis of the benzyl protecting group accompanied reduction of the cinnamate esters.

Stereoselective hydrolysis of DL-**1** and DL-**3** by α-chymotrypsin was accomplished in aqueous suspensions of the esters at pH 7.0. The enzyme was essentially unreactive toward DL-**2** under similar conditions. However, in 15% v/v acetonitrile–water the reaction proceeded at a measurable rate. Results of subsequent kinetics studies in solution indicate that the observed order of reactivity in the heterogeneous mixtures (**1** > **3** > **2**) parallels the solubilities of the esters in water. The time course of production of *N*-acylamino acid was followed by addition of 1 *N* NaOH such that neutral pH was maintained. Uptake of base continued until the amount required to account for hydrolysis of one enantiomer had been added and the reactions stopped. Unreacted ester was isolated by continuous extraction with EtOAc, or with **2**, by filtration. Decreasing the pH of the aqueous layer to 3 followed by continuous extraction produced the *N*-acylamino acids corresponding to **1–3**. HBr-catalyzed hydrolysis of a portion of the isolated unreactive isomers of esters **1–3** gave D-dopa. Thus, the enzyme preferentially hydrolyzes the L esters. The *N*-acyl-L amino acids were reconverted to their methyl esters with thionyl chloride in methanol. A high degree of optical purity of the resolved enantiomers is suggested by their nearly equal and opposite specific rotations and behavior in enzyme kinetics studies. α-Chymotrypsin was