geneous on TLC: ir (neat) 2.96 (NH), 5.73 μ (C=O); NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 6, CH_3–), 2.53 (br s, 1, NH), 3.94 (s, 2, –CH_2–N–), 4.17 (s, 1, CH), 4.34 (q, J = 7 Hz, 4, –CH_2O–), 7.54 (s, 5, Ph protons).

Ethyl 1-Substituted 5-Hydantoincarboxylates. General Method A. A solution of **2** (0.01–0.02 mol) in H_2O (30 ml) and a solution of KCNO (0.011–0.022 mol) in a minimum amount of H_2O were mixed, stoppered, vigorously stirred at ambient temperature for 0.5–2 hr, and then heated with stirring on a steam bath for 0.5–2 hr. After cooling, the reaction mixture was extracted with CH_2Cl_2. Drying the extract (Na_2SO_4) followed by evaporating to dryness in vacuo afforded the product as a solid residue, which was recrystallized from an appropriate solvent.

Ethyl 1,3-Disubstituted 5-Hydantoincarboxylates. General Method B. To a solution of **2** (0.01–0.05 mol) in $CHCl_3$ (25–50 ml) were added in turn an isocyanate (0.011–0.053 mol) and Et_3N or pyridine[14] (0.011–0.055 mol). The resulting solution was heated at reflux for 2–3 hr and then evaporated to dryness in vacuo until any excess isocyanate was removed. The residue was redissolved in CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), and evaporated to dryness in vacuo to give the crude product, which was purified by short-path distillation in a Kugelrohr apparatus.

General Method C. An isocyanate (0.011–0.022 mol) was added to a solution of **3b** (0.01–0.02 mol) in C_6H_6 (25–40 ml). The resulting solution was heated at reflux for 2 hr and then evaporated in vacuo until any excess isocyanate was removed. The residue was distilled in a Kugelrohr apparatus to give the product.

General Method D. A mixture of **3a** (0.02–0.03 mol) and an isocyanate (0.022–0.033 mol) was heated at reflux in an oil bath at 90–110° for 2–6 hr. The reaction temperature and duration were varied appropriately according to the boiling point and reactivity of the isocyanate. In the reaction of **3a** and CH_3NCO, the reaction mixture solidified upon cooling and was therefore recrystallized from EtOAc to give pure **1h.**

In the reaction of **3a** and PhNCO, the reaction mixture became an orange-colored syrup, the spectral data of which indicated that it was largely the urea **4f** containing a very small amount of **1i:** ir (neat) 2.95 (m, NH), 5.74 (s, ester C=O), 5.94 μ (s, urea C=O); NMR ($CDCl_3$) δ 1.18 (t, CH_3–), 4.17 (q, –CH_2O–), 5.56 (s, methine proton), 6.35 (br s, NH), 6.8–7.8 (m, Ph protons). The methyl, methylene, and methine protons of **1i** appeared at δ 1.25 (t), 4.25 (q), and 5.24 (s), respectively. Upon heating during short-path distillation at 180–190°, the above material afforded the hydantoincarboxylate **1i,** which no longer showed absorptions at 2.95 and 5.94 μ but exhibited one of the hydantoin characteristic C=O bands at 5.59 μ.

Registry No.—**1a,** 56598-90-4; **1b,** 56598-91-5; **1c,** 56598-92-6; **1d,** 3531-91-7; **1e,** 56598-93-7; **1f,** 56598-94-8; **1g,** 56598-95-9; **1h,** 56598-96-0; **1i,** 56598-97-1; **2a,** 56598-98-2; **2b,** 56598-99-3; **3a,** 6414-58-0; **3b,** 56599-00-9; **4f,** 56599-01-0; **6,** 56599-02-1; isocyanic acid potassium salt, 15586-00-2; methyl isocynate, 624-83-9; benzyl isocyanate, 3173-56-6; phenyl isocyanate, 103-71-9; diethyl bromomalonate, 685-87-0; dibenzylamine, 103-49-1; benzylamine, 100-46-9.

References and Notes

(1) This work was performed under the auspices of the Division of Cancer Treatment, National Cancer Institute, Department of Health, Education and Welfare, Contract No. N01-CM-23706. The opinions expressed in this article are those of the author and not necessarily those of the NCI.
(2) 1-Methyl- and 3-methyl-5-hydantoincarboxylic acid and various 5-hydantoincarboxamides have been obtained as degradation products of nitrogen-substituted purines, mainly uric acids: (a) E. Fischer, *Justus Liebigs Ann. Chem.*, **215,** 253 (1882); (b) H. Biltz, *Ber.*, **43,** 1600, 1618 (1910); *ibid.*, **46,** 3407 (1913); (c) H. Biltz and M. Bergius, *Justus Liebigs Ann. Chem.*, **414,** 54 (1917); (d) H. Biltz and F. Max, *ibid.*, **414,** 68 (1917); (e) H. Biltz and R. Lemberg, *ibid.*, **432,** 137 (1923); H. Biltz and P. Nachtweg, *Ber.*, **64,** 1974 (1931); (g) E. S. Gatewood, *J. Am. Chem. Soc.*, **45,** 3056 (1923); (h) *ibid.*, **47,** 2175 (1925); (i) *ibid.*, **47,** 2181 (1925).
(3) W. Garner and H. Tieckelmann, *J. Org. Chem.*, **29,** 2003 (1964).
(4) F. Perini and H. Tieckelmann, *J. Org. Chem.*, **35,** 812 (1970).
(5) 5-Hydantoincarboxamide was obtained in small yield with hydantoin from (ethoxycarbonylamino)malonamide upon treatment with KOH; see T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36,** 355 (1914).
(6) V. Cerchez, *Bull. Soc. Chim. Fr.*, **47,** 1287 (1930).
(7) T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36,** 345 (1914).
(8) It is of interest that diethyl (*N*-phenylthioureido)malonate cyclizes to ethyl 3-phenyl-2-thio-5-hydantoincarboxylate upon heatng in water (see ref 3).
(9) For a detailed discussion on symmetry criteria in NMR spectroscopy, see K. Mislow and M. Raban, *Top. Stereochem.*, **1,** 1 (1967).
(10) To a solution of **1g** in $CDCl_3$ in an NMR tube was added a solution of CD_3ONa in CD_3OD. The resulting solution was orange-yellow in color.
(11) E. Hardegger and H. Corrodi, *Helv. Chim. Acta*, **39,** 980 (1956).
(12) D. E. O'Brien, F. Baiocchi, R. K. Robbins, and C. C. Cheng, *J. Med Pharm. Chem.*, **5,** 1085 (1962).
(13) R. D. Haworth, A. H. Lamberton, and D. Woodcock, *J. Chem. Soc.*, 182 (1947).
(14) Triethylamine permitted simpler work-up and generally gave better results.

Halogenated Ketenes. XXVIII. Mixed Dimerizations of Halogenated Ketenes and Nonhalogenated Ketenes[1]

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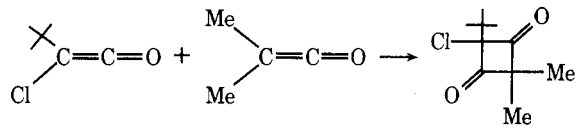
Alkylhaloketenes and dialkylketenes undergo a codimerization to yield the unsymmetrical 1,3-cyclobutanediones. These mixed dimers have been prepared by several different methods. Some of the ketenes employed are methylchloro-, ethylchloro-, *tert*-butylchloro-, dimethyl-, diethyl-, and pentamethyleneketenes. In certain systems some 2-oxetanone mixed dimer was formed.

Most all ketenes are very susceptible to dimerization when heated or when allowed to stand at room temperature for a sufficient length of time.[2] The dimerization produces a 1,3-cyclobutanedione and/or a 2-oxetanone. Mixed dimers of ketenes have rarely been studied, because in addition to the mixed ketene dimers the two homodimers are produced. However, recently England and Krespan have described mixed dimers of bis(trifluoromethyl)ketene.[3] This ketene does not thermally homodimerize and forms mixed dimers with various other ketenes in good yield. Both dimers of the 1,3-cyclobutanedione structure and 2-oxetanones have been observed. The 2-oxetanone dimers were derived only from cycloaddition to the carbon–carbon double bond and not to the carbon–oxygen double bond of the nonfluorinated ketene.

Halogenated ketenes are quite labile but undergo in situ cycloaddition reactions to produce a variety of cycloadducts. We have made numerous attempts to homodimerize halogenated ketenes with no success; only α-halovinyl esters are produced and/or polymeric material. However, we

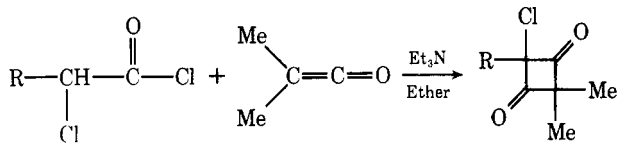
have recently discovered that halogenated ketenes will undergo a mixed dimerization with nonhalogenated ketenes, and the purpose of this paper is to describe these mixed dimerizations. A preliminary report of this work has appeared.[4]

A chloroform solution of *tert*-butylchloroketene was prepared by the triethylamine dehydrochlorination of 2-chloro-3,3-dimethylbutanoyl chloride.[1] An ether solution of dimethylketene was added and a 40% yield of the mixed dimer was obtained in about 3 hr. The 1,3-cyclobutanedione was characterized by elemental analysis, infrared, and NMR spectroscopy. This reaction was accompanied by some polymer from the halogenated ketene and by less than 10% of the homodimer of dimethylketene.[5]



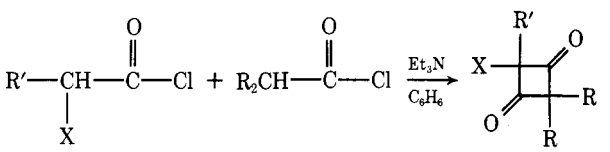
I

Mixed dimerizations involving other alkylhaloketenes were accomplished by generating the alkylhaloketene in the presence of dimethylketene, i.e., an in situ cycloaddition reaction. The alkylchloroketenes were prepared by the triethylamine dehydrochlorination of α-chloro acid chlorides in the presence of dimethylketene in ether solution. The 1,3-cyclobutanedione mixed dimers were produced in 1–2 hr in yields up to 55%. Some halogenated ketene polymer and a small amount of homodimer of dimethylketene was also produced. The attempted mixed dimerizations of diphenylketene and methylchloro- and ethylchloroketene in a similar manner were not successful. Only a small amount of the mixed 1,3-cyclobutanedione dimer was produced as evidenced by NMR.



I, R = *t*-Bu
II, R = Et
III, R = Me

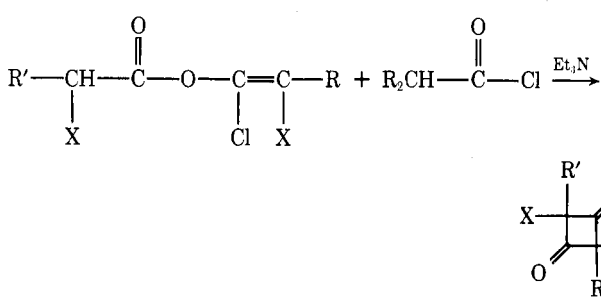
The most successful method for preparing the mixed dimers involves a simultaneous generation of the halogenated ketene and the dialkylketene from the respective acid halides. This method is generally illustrated below.



The unsymmetrical halogenated cyclobutanediones prepared by this method are illustrated in Table I.

The cyclobutanediones were all characterized by a band in the infrared spectrum at 1750–1760 cm^{-1} and NMR and elemental analysis. These reactions were all accompanied by some polymeric material of the halogenated ketenes and some homodimer of the dialkylketenes (<10%). The reaction time is very dependent upon the particular dialkylketene selected. Pentamethyleneketene and diethylketene are formed very slowly from the respective acid halides and thus the reaction time is usually several days to obtain the optimum yield of the mixed dimer. Conversely, dimethylketene is formed very rapidly and the reaction time for the mixed dimerization with this ketene is about 1–3 hr.

It is well known that certain α-halo acid halides react with triethylamine to yield α-halovinyl esters.[6] These vinyl esters were found in some of the reactions described above. The α-halovinyl esters will react with triethylamine to generate halogenated ketenes. An α-halovinyl ester could be used in place of the α-halo acid chloride as a source of the halogenated ketene with those dialkylketenes which formed slowly, i.e., pentamethyleneketene and diethylketene.



The attempted mixed dimerization of methylchloroketene and ethylketene by the generation of these ketenes from the respective acid halides resulted in only the 2-oxetanone homodimer of ethylketene. Efforts to codimerize two different halogenated ketenes were unsuccessful as only polymer resulted. Also, the aldoketene, methylketene, could not be codimerized with methylchloro- or *tert*-butylchloroketene.

Several of the mixed dimerizations described above to produce unsymmetrical cyclobutanediones were accompanied by another type of mixed dimerization which produced a 2-oxetanone. Two such 2-oxetanones are possible depending upon whether cycloaddition occurs across the carbon–oxygen bond of the halogenated ketene or the dialkylketene. The 2-oxetanone exhibited bands in the infrared at 1887, 1828 (C=O), and 1712 cm^{-1} (C=C). Methanolysis was used to determine which of the above 2-oxetanones were produced. The distinction was made on the basis of the α-hydrogen. The β-keto ester produced revealed a proton in the NMR at δ 4.4. We synthesized meth-

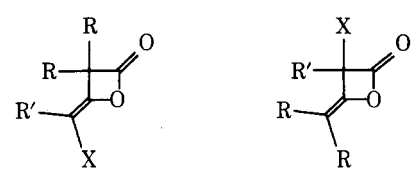
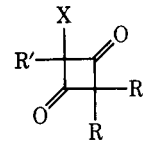
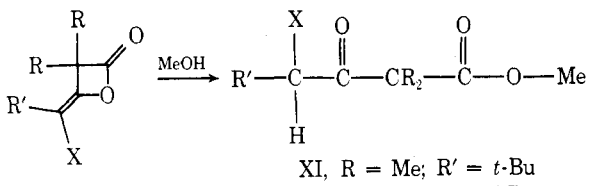


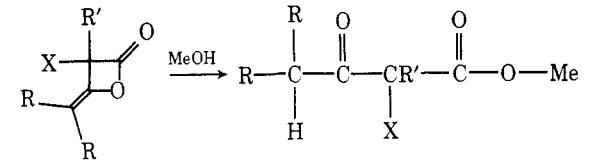
Table I
Unsymmetrical Halogenated Cyclobutanediones



Compd	R	R′	X	Yield, %
III	Me	Me	Cl	34
IV	Et	Me	Cl	63
V	$-(CH_2)_5-$	Me	Cl	62
VI	Et	Et	Cl	51
VII	$-(CH_2)_5-$	Et	Cl	35
II	Me	Et	Cl	41
VIII	Me	*i*-Pr	Cl	40
I	Me	*t*-Bu	Cl	56
IX	Et	*t*-Bu	Cl	43
X	$-(CH_2)_5-$	*t*-Bu	Br	36



XI, R = Me; R′ = *t*-Bu
XII, R = Me; R′ = *i*-Pr
XIII, R = R′ = Et



yl 3-keto-2,2,4-trimethylpentanoate from tetramethylcyclobutanedione for comparison purposes and found that the α hydrogen was revealed in the NMR at δ 2.8.[7] Since the β-keto ester produced had a δ value of 4.4, we conclude that 2-oxetanone was produced whereby cycloaddition occurred only across the carbon–oxygen linkage of the halogenated ketene. This is consistent with what England and Krespan found for bis(trifluoromethyl)ketene.

The mixed dimerizations with pentamethyleneketene did not form any 2-oxetanones. In most of the other cases the 2-oxetanones were produced but in yields of less than 10%.

Since it is known that 1,3-cyclobutanedione dimers of ketenes can isomerize to the 2-oxetanone dimers, it seemed necessary to demonstrate whether isomerization of any kind was occurring in the reaction mixtures.[8] It was found that a mixture of the 1,3-cyclobutanedione mixed dimer of dimethylketene and isopropylchloroketene and the 2-oxetanone mixed dimer upon refluxing in hexane containing triethylamine and triethylammonium chloride for 24 hr underwent no change. Consequently, it is concluded that no isomerization occurred under our reaction conditions and the mixed dimer ratios observed in the reaction mixtures do in fact represent the actual cycloaddition results.

Experimental Section

Proton NMR spectra were recorded on a Jeolco PS-100 NMR spectrometer employing tetramethylsilane as an internal standard and CCl_4 as the solvent. All solvents and triethylamine were dried by distillation from sodium. VPC was performed on an F & M Scientific Model 700 gas chromatograph with 10 ft × 0.25 in. columns packed with 10% SE-30 and Carbowax 20M on an acid-washed Chromosorb W (80/100). Dimethylketene was prepared by the pyrolysis of tetramethylcyclobutanedione.

General Methods for Mixed Dimerizations. Method A. To a stirred solution of 0.05 mol of dimethylketene and 0.05 mol of triethylamine in 50 ml of ether was added to a solution of 0.05 mol of α-chloro acid chloride in 10 ml of ether at room temperature. Stirring was continued for 2 hr and then the amine salt was removed by filtration. The solvent was removed from the filtrate with a rotatory evaporator and the residue vacuum distilled.

Method B. To a refluxing solution of 0.1 mol of α-halo acid chloride and 0.1 mol of isobutyryl chloride, α-ethylbutyryl chloride, or cyclohexanecarboxyl chloride in 150 ml of benzene was added dropwise with stirring 0.25 mol of triethylamine in 15 ml of benzene. The reaction mixture was stirred from 1 hr to 4 days, the salt was removed by filtration, and the filtrate was concentrated with a rotatory evaporator and vacuum distilled. Other solvents which could be used include hexane, acetonitrile, chloroform, and ether.

Method C. To a refluxing solution of 0.05 mol of 1,2-dichloropropenyl 2-chloropropanoate or 1,2-dichlorobutenyl 2-chlorobutanoate and 0.1 mol of triethylamine in 100 ml of benzene was added dropwise 0.05 mol of cyclohexanecarboxyl chloride in 15 ml of benzene. Refluxing was continued for several days as the reaction was monitored by VPC analysis until the reaction was complete. The amine salt was removed by filtration, the solvent was removed by evaporation on a rotatory evaporator, and the mixed dimer was vacuum distilled.

2-Chloro-2-*tert*-butyl-4,4-dimethyl-1,3-cyclobutanedione (I). Method A. A 50% yield of mixed dimer was produced.

Method B. The reaction mixture was stirred for 24 hr and a 56% yield of dione and a 13% yield of 2-oxetanone was produced.

This mixed dimer was also prepared directly from the two ketenes as described below. A solution of 0.05 mol of 2-chloro-3,3-dimethylbutanoyl chloride in 10 ml of chloroform was added dropwise to a stirred solution of 0.05 mol of triethylamine in 100 ml of chloroform at 0–5°. The ketene band in the infrared at 2110 cm^{-1} reached a maximum intensity within about 4 hr. At this time, a solution of 0.07 mol of dimethylketene in 10 ml of ether was added over a period of about 3 hr. The solution was concentrated on a rotatory evaporator and 100 ml of hexane was added to precipitate the amine salt. After removal of the salt by filtration, the filtrate was concentrated and the mixed dimer distilled at 39–40° (0.025 mm) to give a 40% yield: ir 1750 cm^{-1}; NMR δ 1.19 (s, 9 H), 1.28 (s, 3 H), 1.60 (s, 3 H).

Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.41; Cl, 17.53. Found: C, 59.09; H, 7.20; Cl, 17.29.

2-Chloro-2-ethyl-3,3-dimethyl-1,3-cyclobutanedione (II). Method A. A 55% yield was obtained.

Method B. The reaction mixture was refluxed for 3 hr and then stirred for an additional 3 hr to produce a 41% yield of the dione and a 13% yield of the vinyl ester, 1,2-dichlorobutenyl 2-chlorobutanoate. The dione had bp 54–55° (0.25 mm); ir 1755 cm^{-1}; NMR δ 1.14 (t, 3 H), 1.34 (s, 3 H), 1.54 (s, 3 H), and 2.40 (q, 2 H).

Anal. Calcd for $C_8H_{11}ClO_2$: C, 55.01; H, 6.30; Cl, 20.34. Found: C, 55.20; H, 6.39; Cl, 20.06.

2-Chloro-2-methyl-4,4-dimethyl-1,3-cyclobutanedione (III). Method A. A 42% yield was obtained along with a small amount of 1,2-dichloropropenyl 2-chloropropanoate.

Method B. As soon as the addition was completed at reflux, the reaction mixture was cooled over a period of 1 hr. Vacuum distillation afforded the mixed dimer at 70° (0.25 mm) which crystallized from ether giving a 34% yield and a small amount of the vinyl ester. The dione had mp 78–80°; ir 1750 cm^{-1}; NMR δ 1.36 (s, 3 H), 1.52 (s, 3 H), and 1.70 (s, 3 H).

Anal. Calcd for $C_7H_9ClO_2$: C, 52.34; H, 5.61; Cl, 22.12. Found: C, 52.52; H, 5.75; Cl, 21.63.

2-Chloro-2-methyl-4,4-diethyl-1,3-cyclobutanedione (IV). Method B. The reaction mixture was refluxed for 24 hr; a 63% yield was obtained at 43° (0.05 mm); ir 1750 cm^{-1}; NMR δ 1.08 (2 t, 6 H), 1.72 (s, 3 H), 1.96 (m, 4 H).

Anal. Calcd for $C_9H_{13}ClO_2$: C, 57.29; H, 6.90; Cl, 18.83. Found: C, 57.44; H, 7.04; Cl, 18.71.

2-Chloro-2-methylspiro[3.5]nona-1,3-dione (V). Method B. Refluxed for 24 hr; bp 67–70° (0.025 mm), then recrystallized from alcohol, mp 67–69° (62%).

Method C. After 48 hr, the reaction was complete (63%): ir 1750 cm^{-1}; NMR a multiplet centered at δ 1.80 out of which there was a singlet at δ 1.70.

Anal. Calcd for $C_{10}H_{13}ClO_2$: C, 59.85; H, 6.48; Cl, 17.70. Found: C, 59.60; H, 6.65; Cl, 17.45.

2-Chloro-2,4,4-triethyl-1,3-cyclobutanedione (VI). Method B. Refluxed for 4 days, 51% yield of dione and 7% yield of vinyl ester. The dione had bp of 41–43° (0.025 mm); ir 1750 cm^{-1}; NMR δ 1.04 (m, 9 H), 1.84 (m, 6 H).

Anal. Calcd for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.41; Cl, 17.53. Found: C, 59.17; H, 7.46; Cl, 17.29.

2-Chloro-2-ethylspiro[3.5]nona-1,3-dione (VII). Method B and Method C. Refluxed for 2–3 days, 35% yield of dione and 14% yield of vinyl ester. The dione had bp 60–62° (0.1 mm); ir 1750 cm^{-1}; NMR δ 1.16 (t, 3 H) and 1.84 (m, 12 H).

Anal. Calcd for $C_{11}H_{15}ClO_2$: Cl, 16.55. Found: Cl, 16.72.

2-Chloro-2-isopropyl-4,4-dimethyl-1,3-cyclobutanedione (VIII). Method B. Refluxed for 20 hr (40%), bp 40–43° (0.05 mm); ir 1750 cm^{-1}; NMR δ 1.20 (d, 6 H), 1.34 (s, 3 H), 1.52 (s, 3 H), and 2.40 (heptet, 1 H).

Anal. Calcd for $C_9H_{13}ClO_2$: C, 57.29; H, 6.90; Cl, 18.83. Found: C, 57.63; H, 7.03; Cl, 18.36.

2-Chloro-2-*tert*-butyl-4,4-diethyl-1,3-cyclobutanedione (IX). Method B. Stirred for 2 days at room temperature in $CHCl_3$ (43%), bp 52° (0.1 mm) and mp 43–45°; ir 1750 cm^{-1}; NMR δ 1.08 (t, 6 H), 1.16 (s, 9 H), 1.80 and 2.10 (2 q, 4 H).

Anal. Calcd for $C_{12}H_{19}ClO_2$: C, 62.47; H, 8.24. Found: C, 62.10; H, 8.46.

2-Bromo-2-*tert*-butylspiro[3.5]nona-1,3-dione (X). Method B. Refluxed for 2 days (36%); bp 32–34° (0.25 mm); recrystallized

from ethanol, mp 77–78°; ir 1760 cm^{-1}; NMR δ 1.10 (s, 9 H) and 1.60 (m, 10 H).

Anal. Calcd for $C_{13}H_{19}BrO_2$: C, 54.36; H, 6.68; Br, 27.82. Found: C, 54.33; H, 6.82; Br, 27.45.

General Procedure for Methanolysis of 2-Oxetanones. The 2-oxetanones could not be easily separated from the diones but were observable by ir bands at 1887, 1828, and 1712 $cm.^{-1}$ Methanolysis of the mixture of dione and 2-oxetanone was accomplished by refluxing this mixture with methanol for 1.5 hr. The β-keto ester revealed bands in the ir at 1748 and 1718 $cm.^{-1}$ Methanolysis of the 1,3-cyclobutanediones required a much longer (1–3 days) reflux period.

Methyl 4-Chloro-3-keto-2,2,5,5-tetramethylhexanoate (XI): bp 90–92° (0.1 mm); NMR δ 1.12 (s, 9 H), 1.40 (s, 3 H), 1.52 (s, 3 H), 3.74 (s, 3 H), and 4.42 (s, 1 H).

Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10; Cl, 15.14. Found: C, 56.53; H, 8.40; Cl, 15.20.

Methyl 4-Chloro-3-keto-2,2,5-trimethylhexanoate (XIII): bp 57–59° (0.5 mm); NMR δ 1.00 (2 d, 6 H), 1.44 (s, 3 H), 1.52 (s, 3 H), 2.40 (m, 1 H), 3.83 (s, 3 H), and 4.40 (d, 1 H).

Anal. Calcd for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.71; Cl, 16.09. Found: C, 54.65; H, 7.80; Cl, 15.52.

Methyl 4-Chloro-2,2-diethyl-3-ketohexanoate (XIII): bp 52–54° (0.05 mm); NMR δ 0.90 (m, 9 H), 2.00 (m, 6 H), 3.76 (s, 3 H), 4.40 (t, 1 H).

Anal. Calcd for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10; Cl, 15.14. Found: C, 56.64; H, 8.21; Cl, 14.72.

Attempted Isomerization of a 1,3-Cyclobutanedione and a 2-Oxetanone. A 1.0-g portion of a mixture of VIII and the 2-oxetanone obtained from the preparation of VIII was refluxed in hexane for 24 hr. No change in the isomer distribution was observed. The addition of triethylamine and triethylammonium chloride and continued reflux for another 24 hr also caused no change in the isomer distribution.

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Registry No.—I, 56513-91-8; II, 56513-92-9; III, 56513-93-0; IV, 54363-24-5; V, 54363-23-4; VI, 54363-25-6; VII, 56513-94-1; VIII, 56513-95-2; IX, 56513-96-3; X, 56513-97-4; XI, 56513-98-5; XII, 56513-99-6; XIII, 56514-00-2; dimethyl ketene, 598-26-5; 2-chloro-3,3-dimethylbutanoyl chloride, 52920-18-0; 2-chlorobutanoyl chloride, 7623-11-2; 2-chloropropanoyl chloride, 7623-09-8; 2-bromo-3,3-dimethylbutanoyl chloride, 29336-30-9; isobutyryl chloride, 79-30-1; α-ethylbutyryl chloride, 2736-40-5; cyclohexanecarboxyl chloride, 2719-27-9; 1,2-dichloropropenyl 2-chloropropanoate, 52920-13-5; 1,2-dichlorobutenyl 2-chlorobutanoate, 23649-91-4; 4-chloro-3,3-dimethyl-4-*tert*-butyl-2-oxetanone, 56514-01-3; 4-chloro-3,3-dimethyl-4-isopropyl-2-oxetanone, 56514-02-4; 4-chloro-3,3,4-triethyl-2-oxetanone, 56514-03-5.

References and Notes

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An Efficient α-Halogenation of Acyl Chlorides by *N*-Bromosuccinimide, *N*-Chlorosuccinimide, and Molecular Iodine[1]

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An efficient procedure (yields ~75%) for the α-halogenation of acyl halides has been demonstrated using *N*-bromosuccinimide, *N*-chlorosuccinimide, and molecular iodine. Thionyl chloride was found to be the most effective solvent for all halogenation reactions and necessary for α-iodination. Various anomalies and possible mechanisms are discussed.

The halogenation of carboxylic acids can be carried out either by free-radical[2] or acid-catalyzed reactions.[3] The former occurs with random orientation and the latter, via the Hell–Volhard–Zelinsky (HVZ) procedure,[3] gives exclusively α-halogenated products only in the case of bromination, but variable selectivity in chlorination, and no reaction at all in iodination.[4]

In an effort to develop new and efficient methods for preparing α-halo acid chlorides, from which a wide variety of compounds may be obtained by replacing both the halogen on the α carbon and on the acyl function, a study was undertaken of the ability of *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS), and molecular iodine as α-halogenating agents.

Results and Discussion

α-Bromo acids can be prepared by a multistep procedure, involving alkylation, bromination, deacylation, and hydrolysis.[5] In the more direct method (HVZ),[3] carboxylic acids are treated with free bromine in the presence of a catalyst which can be phosphorus trichloride or phosphorus itself. However, the experimental conditions are sometimes strenuous, often involving high temperature and extended reaction times.

Although NBS is well known as a brominating agent,[6a] there appears to be no report of this reagent being employed to directly brominate acyl chlorides.

We have found that NBS α-brominates a variety of acyl chlorides (formed in situ by the reaction of thionyl chloride[6b] with carboxylic acids, Table I) in good yield.[7] NBS is not only easy to handle but also α-brominates more rapidly and efficiently than molecular bromine, as shown by a comparative study. After 2 hr at 54°, the reaction of *n*-hexanoyl chloride (1) with NBS was almost complete, whereas that with free bromine had only occurred to an extent of ca. 60% (Figure 1). Furthermore, bromination reactions with Br_2 often do not proceed past ca. 80% completion. At 85°, the reaction with NBS was complete after 1.5 hr.[8]