room temperature. The reaction mixture, which contained a suspended solid, was diluted with water and acidified with concentrated HCl. The solid was separated by filtration and washed with water. Recrystallization from benzene gave 1.35 g (43.3%) of material, mp 109–112°, which on further recrystallization gave material identical with that obtained from Clemmensen reduction: NMR ($CDCl_3$) δ 1.42–3.55 (m, 10 H), 3.88 (s, 6 H), 6.58–7.40 (m, 6 H).

3,9-Dimethoxybenz[*a*]anthracene (9a). A solution of 200 mg (0.678 mmol) of the hexahydro compound **8** and 930 mg (4.07 mmol) of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in 60 ml of benzene was refluxed for 16 hr. The reaction mixture was cooled to room temperature, filtered through an alumina column, and eluted with benzene. The colorless eluate on concentration gave 190 mg of white crystals, fluorescent in ultraviolet light, mp 175–176°. Recrystallization from benzene–hexane afforded the analytical sample of **9a** as colorless needles: mp 190–192°; ir (KBr) Ar, 1625, 1590; $-OCH_3$, 1025 cm^{-1}; NMR ($CDCl_3$) δ 3.98 (s,6 H), 7.24–8.94 (m, 10 H). Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.05; H, 5.67.

3,9-Dihydroxybenz[*a*]anthracene (9b). To a heated, stirred solution of 394 mg (1.36 mmol) of 3,9-dimethoxybenz[*a*]anthracene (**9a**) in 30 ml of benzene was added a solution of 3 ml of BBr_3 in 10 ml of benzene. Initially, during the dropwise addition of the latter, a precipitate was formed which redissolved on further heating. The solution was refluxed for 3 hr protected from moisture with a Drierite tube, then cooled to room temperature, poured onto crushed ice, and extracted with ether. The organic solution was washed with water and extracted with 10% NaOH (3 × 35 ml). The fluorescent yellow base solution was cooled to 0°, acidified with concentrated HCl, and extracted with ethyl acetate. The organic extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 370 mg of brown solid, mp >250° dec. High vacuum sublimation of this material at 255° afforded analytically pure diol **9b** as a yellow solid: mp 265–270° dec; ir (KBr) –OH, 3100; Ar, 1620, 1595 cm^{-1}. Anal. Calcd for $C_{18}H_{12}O_{12}$: C, 83.06; H, 4.65. Found: C, 82.89; H, 4.68.

3,9-Diacetoxybenz[*a*]anthracene (9c). A 125-mg sample of the dihydroxy compound **9b** was dissolved in 5 ml each of acetic anhydride and pyridine, and left overnight at room temperature. The usual work-up afforded analytically pure diacetate **9c** as white platelets: mp 200–201°; ir (KBr) C=O, 1760; Ar, 1620, 1590 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 6 H), 7.18–9.10 (m, 10 H). Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68. Found: C, 76.56; H, 4.70.

Acknowledgment. We would like to thank Mr. Norman Angelino, of Dr. Walter Korytnyk's laboratory in this institute, for help in NMR spectral determinations on the Varian XL100 spectrometer, and Dr. Alan J. Solo, Department of Medicinal Chemistry, State University of New York at Buffalo, for helpful discussion on spectral data.

Registry No.—**1**, 120-44-5; **2**, 56554-10-0; **3**, 56554-11-1; **4**, 56554-12-2; **5**, 56554-13-3; **6**, 56554-14-4; **6b**, 56554-15-5; **7**, 56554-16-6; **8**, 56554-17-7; **9a**, 56554-18-8; **9b**, 56614-97-2; **9c**, 56554-19-9; dimethyl succinate, 196-65-0.

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Synthesis of 1-Substituted and 1,3-Disubstituted 5-Hydantoincarboxylates[1]

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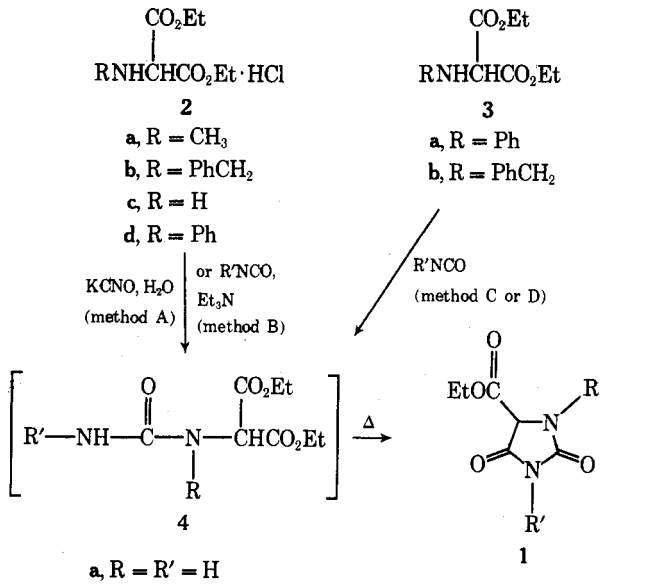
N-Substituted aminomalonates react with KCNO or isocyanates to give directly 1-substituted or 1,3-disubstituted 5-hydantoincarboxylates. The initial products, i.e., the hitherto unknown N-substituted or N,N′-disubstituted ureidomalonates, cyclize spontaneously on heating under the experimental conditions. This behavior is in contrast to that of ureidomalonate and N′-substituted ureidomalonates, which require base catalysis for cyclization. The benzylic protons of 1-benzyl-5-hydantoincarboxylates display chemical shift nonequivalence.

In a synthetic program for 8-hydroxypurines, it was necessary to prepare ethyl 1-substituted 5-hydantoincarboxylates. A literature search has not revealed a description of any 1-substituted or 1,3-disubstituted 5-hydantoincarboxylates,[2] although 3-substituted 5-hydantoincarboxylates[3,4] are known. We wish to report a facile general synthesis of the title 5-hydantoincarboxylates by the cyclization of N-substituted and N,N′-disubstituted ureidomalonates.

5-Hydantoincarboxylate (**1k**) and many 3-substituted 5-hydantoincarboxylates are known and can be prepared by base-catalyzed cyclization of ureidomalonate (**4a**) and N′-substituted ureidomalonates.[3-5] However, under no circumstances can the cyclization be effected simply by heating. Gatewood[2h] reported that **4b** failed to cyclize to **1j** under various conditions, including heating at its melting point for varying lengths of time. We noted that **4a** behaved similarly. Heating **4a** beyond its melting point, e.g., at 200°, caused gas evolution and numerous products were formed, as indicated by the TLC of the residue. An apparent route to 1-substituted 5-hydantoincarboxylates would be, therefore, the base-catalyzed cyclization of N-substituted ureidomalonates.

1-Substituted 5-Hydantoincarboxylates. Heating *N*-methyl- (**2a**) and *N*-benzylaminomalonate hydrochloride (**2b**) with KCNO in water produced directly 1-methyl- (**1a**) and 1-benzyl-5-hydantoincarboxylate (**1e**), respectively (method A). The initial products, i.e., the N-substituted ureidomalonates **4c** and **4d**, apparently cyclized spontaneously under the experimental conditions. This result is surprising in view of the fact that the reaction of amino-



2
a, R = CH_3
b, R = $PhCH_2$
c, R = H
d, R = Ph

3
a, R = Ph
b, R = $PhCH_2$

KCNO, H_2O (method A); or R'NCO, Et_3N (method B); R'NCO (method C or D)

4
a, R = R' = H
b, R = H; R' = Ph
c, R = CH_3; R' = H
d, R = $PhCH_2$; R' = H
e, R = Ph; R' = H
f, R = R' = Ph

1
a, R = CH_3; R' = H
b, R = R' = CH_3
c, R = CH_3; R' = $PhCH_2$
d, R = CH_3; R' = Ph
e, R = $PhCH_2$; R' = H
f, R = $PhCH_2$; R' = CH_3
g, R = $PhCH_2$; R' = Ph
h, R = Ph; R' = CH_3
i, R = R' = Ph
j, R = H; R' = Ph
k, R = R' = H

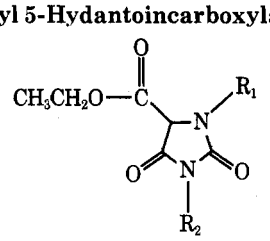
malonate hydrochloride (**2c**) and KCNO is known to afford the urea **4a**.[3,4,6,7] Anilinomalonate hydrochloride (**2d**) failed to form the ureidomalonate **4e** by reacting with KCNO under the same conditions and the free amine **3a** was recovered quantitatively.

1,3-Disubstituted 5-Hydantoincarboxylates. Heating an N-substituted aminomalonate hydrochloride **2** or the corresponding free amine **3** and an isocyanate, such as methyl, benzyl, or phenyl isocyanate, with or without a solvent produced 1,3-disubstituted 5-hydantoincarboxylates with equal success (methods B–D, see Table I). Owing to the ease of formation of the desired hydantoins **1**, no attempt was made to isolate the urea intermediates **4** except in one case. In the reaction of **3a** and PhNCO, the product was shown to be the urea **4f** by ir and NMR spectroscopy. The urea **4f** did cyclize to the hydantoin **1i** just by heating, although much higher temperatures were needed. The urea **4f** is the first known N,N'-disubstituted ureidomalonate. Although the reaction of aminomalonate hydrochloride (**2c**) with isocyanates to form N'-substituted ureidomalonates is well documented,[2h,3,4,6] there is no description of any N-substituted or N,N'-disubstituted ureidomalonates in the literature.

Whereas N'-substituted ureidomalonates, **4** (R = H; R' = H, alkyl, aryl), are quite resistant to heat[8] and are readily cyclized to hydantoins upon base catalysis,[3,4] the results of this work clearly show that the presence of a substituent at the ureido nitrogen drastically changes the chemical properties of the ureidomalonates, **4** (R = alkyl or aryl; R' = H, alkyl, aryl). These N-substituted and N,N'-disubstituted ureidomalonates cyclize spontaneously to hydantoins simply on heating without the need of base catalysis.

The two benzylic protons of the 1-benzyl-5-hydantoin-

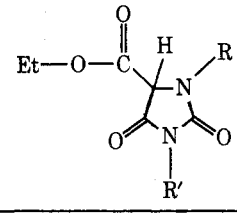
Table I
Ethyl 5-Hydantoincarboxylates



Compd	R_1	R_2	Formula	Method	Yield,[a] %	Mp, °C (recrystn solvent)	Bp,[b] °C (mm)	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1a	CH_3	H	$C_7H_{10}N_2O_4$	A	80.6	85–87 (Et_2O)		45.16	45.03	5.41	5.50	15.05	15.07
1b	CH_3	CH_3	$C_8H_{12}N_2O_4$	B	88		75–78 (5×10^{-3})	47.99	47.75	6.04	5.96	13.99	13.72
1c	CH_3	$PhCH_2$	$C_{14}H_{16}N_2O_4$	B	97	67–70[c]	114–115 (3×10^{-4})	60.86	61.05	5.84	5.80	10.14	10.07
1d	CH_3	Ph	$C_{13}H_{14}N_2O_4$	B	90		118 (6×10^{-4})	59.54	59.54	5.38	5.36	10.68	10.57
1e	$PhCH_2$	H	$C_{13}H_{14}N_2O_4$	A	42	137.5–138.5 (EtOAc)		59.54	59.50	5.38	5.31	10.68	10.79
1f	$PhCH_2$	CH_3	$C_{14}H_{16}N_2O_4$	C	90		120–125 (5×10^{-4})	60.86	61.11	5.84	5.81	10.14	10.27
1g	$PhCH_2$	Ph	$C_{19}H_{18}N_2O_4$	B C	47 80	63–68[c]	160–165 (7×10^{-4})	67.45	67.55	5.36	5.29	8.28	8.48
1h	Ph	CH_3	$C_{13}H_{14}N_2O_4$	D	50	120–121 (EtOAc)		59.54	59.57	5.38	5.32	10.68	10.77
1i	Ph	Ph	$C_{18}H_{16}N_2O_4$	D	73.4	131–132.5 (EtOH)	180–190 (8×10^{-4})	66.66	66.88	4.97	5.00	8.64	8.73

[a] Yield of purified product. Some of the reactions were conducted only once and the yields of products were not optimized. [b] These are not real boiling points. The given temperatures are the air-bath temperatures at which the compounds were collected during short-path distillation. [c] Melting point of solidified material.

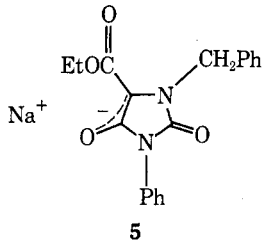
Table II
Ir and NMR[a] Spectral Data of Ethyl 5-Hydantoincarboxylates



Compd	Ir, μ ($\nu_{C=O}$)	NMR, δ Solvent	H	R	R'
1a	(Nujol) 3.16 (NH), 5.61, 5.75, 5.84	$CDCl_3$	4.67	CH_3, 3.0 (s)	H, 9.5 (br s)
1b	(Neat) 5.61, 5.81 (br)	CCl_4	4.54	CH_3, 2.94 (s)	CH_3, 2.94 (s)
1c	(Neat or Nujol) 5.6, 5.8 (br)	$CDCl_3$	4.58	CH_3, 2.97 (s)	CH_2, 4.67 (s); Ph, 7.2–7.58 (m)
1d	(Neat) 5.59, 5.79 (br)	$CDCl_3$	4.65	CH_3, 2.95 (s)	Ph, 7.37 (s)
1e	(Nujol) 3.14 (NH), 5.61, 5.72, 5.86	Me_2SO-d_6[b]	4.66	CH_2, 4.34 and 4.54 (AB q, J_{AB} = 14.3 Hz),[d] Ph, 7.27 (s)	H, 11.36 (br s)
1f	(Neat) 5.6, 5.8 (br)	$CDCl_3$[c]	4.35	CH_2, 4.21 and 4.93 (AB q, J_{AB} = 14.5 Hz),[d] Ph, 7.24 (s)	CH_3, 3.0 (s)
1g	(Neat) 5.6, 5.79 (br)	$CDCl_3$[c]	4.48	CH_2, 4.28 and 5.0 (AB q, J_{AB} = 14.6 Hz),[d] Ph, 7.28 (s)	Ph, 7.4 (s)
1h	(Nujol) 5.66, 5.73, 5.86	$CDCl_3$	5.11	Ph, 7.02–7.6 (m)	CH_3, 3.11 (s)
1i	(Neat or Nujol) 5.59, 5.79 (br)	$CDCl_3$	5.23	Ph, 6.95–7.65 (m)	Ph, 7.41 (s)

[a] Spectra were recorded on a Perkin-Elmer Hitachi Model R-24 60-MHz NMR spectrometer at probe temperature 40°. [b] Concentration 15% w/v. [c] Concentration 25% w/v. [d] ν_A, ν_B, $|\nu_A - \nu_B|$, and $|J_{AB}|$ are calculated on the basis of the observed four absorption lines of the AB quartets.

carboxylates **1e–g** are diastereotopic[9] and hence show chemical shift nonequivalence. They appear as AB quartets (Table II). Under the given experimental conditions, the magnitude of the difference in chemical shift of the two benzylic protons in **1f** and **1g** is considerably large (0.72 ppm). Destroying the asymmetric center at carbon 5 by converting **1g** to the enolate salt **5**[10] leads to the expected



5

coalescence of the signals of the benzylic protons. However, the two benzylic protons in the 3-benzyl-5-hydantoincarboxylate **1c** show a singlet.

Experimental Section

Materials. The ethanol used throughout this work was denatured alcohol formula 12A. Diethyl *N*-methylaminomalonate was synthesized after Hardegger and Corrodi[11] and isolated as the hydrochloride **2a**, mp 118–119°. Diethyl anilinomalonate (**3a**) and benzyl isocyanate were prepared according to O'Brien et al.[12] and Haworth et al.,[13] respectively.

Diethyl *N,N*-Dibenzylaminomalonate Hydrochloride (6). Diethyl bromomalonate (technical grade, 95.6 g, 0.4 mol) was added slowly into dibenzylamine (158 g, 0.8 mol) with stirring. The mixture was heated on a steam bath with occasional swirling for 2 hr, cooled, and extracted with Et_2O. The white crystals of $(PhCH_2)_2NH$·HBr were removed by filtration, and the ethereal filtrate was washed with water, dried (Na_2SO_4), cooled in ice, and saturated with HCl gas. The crystals of **6** were collected, washed well with Et_2O, and air dried, mp 95–98° dec, yield 103.6 g (66%).

The free amine could readily be purified on a silica gel column, using CH_2Cl_2–EtOAc (8:2 v/v) as eluting solvent. An analytical specimen of **6** prepared from a chromatographically purified amine had the following physical data: mp 103–104° (EtOH); ir (Nujol) 3.6–4.45 ($^+$NH), 5.7 μ (C=O).

Anal. Calcd for $C_{21}H_{25}NO_4$·HCl: C, 64.36; H, 6.69; N, 3.57; Cl, 9.05. Found: C, 64.32; H, 6.54; N, 3.65; Cl, 8.89.

Diethyl *N*-Benzylaminomalonate Hydrochloride (2b). Compound **6** (3.9 g, 0.01 mol) was dissolved in EtOH (20 ml) and hydrogenated in the presence of 10% Pd/C catalyst (0.2 g) at 22° and atmospheric pressure. The hydrogenolysis was stopped after 1 molar equiv of H_2 was taken up. Removal of the catalyst and the solvent in vacuo afforded a pale syrup which crystallized upon standing. Triturating the crystalline residue with Et_2O and collecting the solid gave **2b** (2.7 g, 90% yield), mp 142–143° dec.

A portion of the above material was recrystallized from EtOH–Et_2O to give an analytical specimen as white granules: mp 153° dec; ir (Nujol) 5.69, 5.75 μ; NMR ($CDCl_3$) δ 1.3 (t, J = 7 Hz, 6, CH_3–), 4.26 (q, J = 7 Hz, 4, $-CH_2O-$), 4.43 (s, 1, CH), 4.56 (s, 2, $-CH_2N^+-$), 7.26–7.84 (m, 5, Ph protons), 10.92 (br s, 2, $^+NH_2$).

Anal. Calcd for $C_{14}H_{19}NO_4$·HCl: C, 55.72; H, 6.68; N, 4.64; Cl, 11.75. Found: C, 55.86; H, 6.61; N, 4.66; Cl, 11.75.

Compound **2b** was also obtained by direct alkylation of benzylamine with diethyl bromomalonate with or without using EtOH as solvent, followed by treatment with HCl gas. However, the yield of **2b** was about 9% (isolated and purified product). The reaction appeared to be complicated by aminolysis of the malonate, especially when no solvent was used. The product in this case showed an amide absorption at 5.94 μ.

Diethyl *N*-Benzylaminomalonate (3b). The amine **3b** was readily obtainable by washing a solution of the hydrochloride **2b** in CH_2Cl_2 with dilute NaOH and then with water, drying (Na_2SO_4), and evaporating to dryness in vacuo, as a pale oil which was homo-

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).
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(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).
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(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