

Synthetic Reactions by Complex Catalysts. XXX.
Synthesis of Cyclic Compounds by Means of Copper-Isonitrile Complex.
Copper(I) Carbenoid Intermediate

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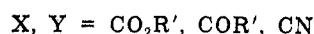
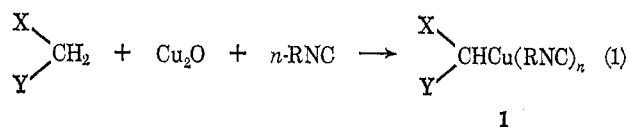
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In the reaction of α -monohalo carbonyl and nitrile compounds such as chloroacetate, chloroacetonitrile, and chloroacetone with α,β -unsaturated carbonyl and nitrile compounds in the presence of cuprous oxide-isonitrile complex, cyclopropane derivatives (3) were produced. This reaction may be explained by the stepwise process involving the addition of α -halomethylcopper(I)-isonitrile intermediate (2), a new class of copper carbenoid, to the electron-deficient olefin which leads to the formation of the corresponding γ -haloorganocopper(I)-isonitrile (11), followed by the intramolecular ring closure. The cyclopropane synthesis by means of the cuprous oxide-isonitrile complex could be applied also to the reactions of α,α -dihaloacetate and of α,α -dihaloacetonitrile with an electron-deficient olefin leading to the corresponding monohalocyclopropane derivatives (6). In addition, the reaction of trichloromethyl compound, Cl_3CY ($\text{Y} = \text{Ph}, \text{CN}, \text{CO}_2\text{R}$), with electron-deficient olefin in the presence of metallic copper and isonitrile produces monochlorocyclopropane derivative. The key intermediate of this reaction is assumed to be an α,α -dichloromethylcopper-isonitrile complex (5), $\text{Cl}_2\text{C}(\text{Y})\text{Cu}(\text{RNC})_n$, a copper carbenoid which may be formed *via* an oxidative addition of the C-Cl bond to the copper(0)-isonitrile complex. The reaction of the so-called active methylene compound with α -haloacrylonitrile or α -haloacrylate was caused by the cuprous oxide-isonitrile complex, producing cyclopropane (18) and/or dihydrofuran (19) in moderate yields. These products were also explained in terms of γ -haloalkylcopper(I)-isonitrile (16) and δ -haloalkoxy-copper(I)-isonitrile (17) intermediate.

Much attention has been centered on the chemistry of metal carbenoids in the last decade. Especially, zinc¹ and mercury carbenoids² have been intensively studied with the view of their synthetic utilities in the preparation of cyclopropane derivatives. Here, we wish to describe the three-membered ring synthesis, which involves a halomethylcopper(I)-isonitrile as a key intermediate, a new class of copper carbenoid.

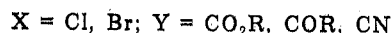
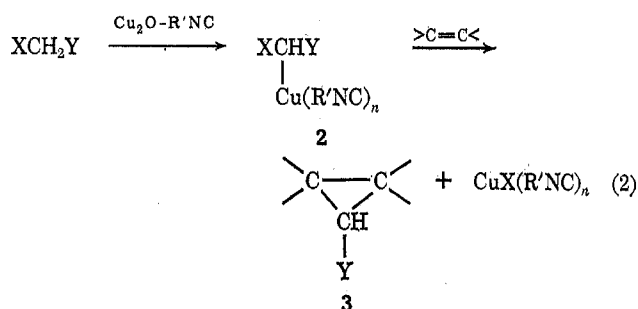
In the continuation of studies³ on copper(I)-isonitrile-catalyzed reactions, it has been established that the so-called active hydrogen compounds such as malonate and acetylacetone react with the cuprous oxide-isonitrile complex to produce the organocopper(I)-isonitrile complexes (1). The formation of 1 has



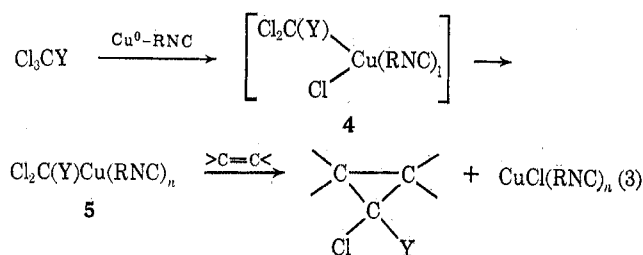
been demonstrated by trapping experiments. For instance, the treatment of diethyl malonate with cuprous oxide-*tert*-butyl isocyanide in the presence of ethyl bromide produced diethyl ethylmalonate in 45% yield. Moreover, in the reaction of cyclopentadiene with the cuprous oxide-*tert*-butyl isocyanide complex, *penta-haptocyclopentadienylcopper(I) tert*-butyl isocyanide^{3c} was successfully isolated as a stable crystalline solid.

In our preliminary paper,⁴ we reported a new cyclopropane synthesis from an α -halo compound, olefin, and

the cuprous oxide-isonitrile complex. In the scheme of this reaction, it has been assumed that α -halomethylcopper (2) is first formed by the reaction of the cuprous oxide-isonitrile complex with the α -halo compound, which then reacts with an electron-deficient olefin to yield the corresponding cyclopropane derivative (3) as shown in eq 2. We found another cyclopropane syn-



thesis by means of a α,α -dihalomethylcopper-isonitrile complex 4 and/or 5 which may be formed by an



oxidative addition of a carbon-chlorine bond of trichloromethyl compounds onto a soluble complex of copper(0)-isonitrile. The intermediates 2 and 4 or 5 constitute a new class of copper carbenoids.

In the present paper, we wish to report some details of reaction 2 and reaction 3 as well as the related cyclic compound syntheses by means of copper-isonitrile complex.

(1) H. E. Simmons and D. J. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(2) D. Seyferth, M. A. Eisert, and L. J. Todd, *J. Amer. Chem. Soc.*, **86**, 121 (1964).

(3) (a) T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, *J. Org. Chem.*, **35**, 870 (1970); (b) T. Saegusa, Y. Ito, H. Kinoshita, and S. Tomita, *Bull. Chem. Soc. Jap.*, **43**, 877 (1970); (c) T. Saegusa, Y. Ito, and S. Tomita, *J. Amer. Chem. Soc.*, **93**, 5658 (1971); (d) T. Saegusa, Y. Ito, H. Kinoshita, and S. Tomita, *J. Org. Chem.*, **36**, 3316 (1971); (e) T. Saegusa, I. Murase, and Y. Ito, *ibid.*, **36**, 2876 (1971); (f) T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, *Bull. Chem. Soc. Jap.*, **45**, 496 (1972).

(4) T. Saegusa, Y. Ito, K. Yonezawa, Y. Inubushi, and S. Tomita, *J. Amer. Chem. Soc.*, **93**, 4049 (1971).

TABLE I

CYCLOPROPANE SYNTHESIS FROM α -MONOHALO COMPOUND, OLEFIN, AND CUPROUS OXIDE-ISONITRILE^a

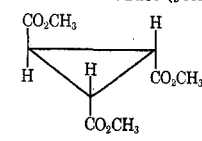
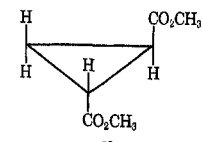
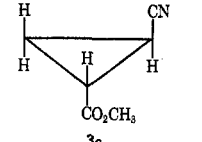
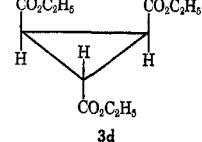
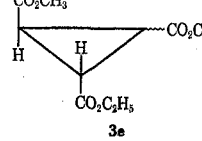
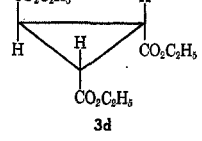
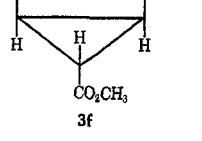
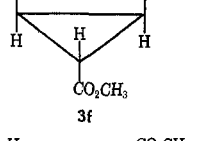
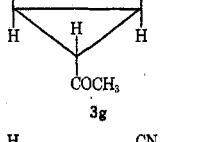
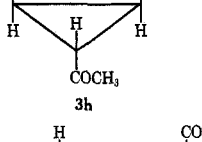
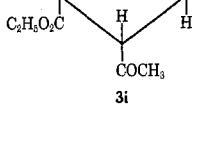
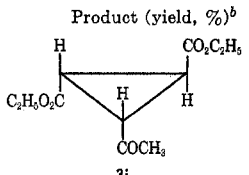
Registry no.	α -Monohalo compd	Registry no.	Olefin	Product (yield, %)
96-34-4	$\text{ClCH}_2\text{CO}_2\text{CH}_3$	None		 3a (34)
	$\text{ClCH}_2\text{CO}_2\text{CH}_3$	96-33-3	$\text{CH}_2=\text{CHCO}_2\text{CH}_3$	 3b (22)
	$\text{ClCH}_2\text{CO}_2\text{CH}_3$	107-13-1	$\text{CH}_2=\text{CHCN}$	 3c (31)
105-39-5	$\text{ClCH}_2\text{CO}_2\text{C}_2\text{H}_5$	141-05-9	<i>cis</i> - $\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CHCO}_2\text{C}_2\text{H}_5$	 3d (29)
	$\text{ClCH}_2\text{CO}_2\text{C}_2\text{H}_5$	624-48-6	<i>cis</i> - $\text{CH}_3\text{O}_2\text{CCH}=\text{CHCO}_2\text{CH}_3$	 3e (29)
	$\text{ClCH}_2\text{CO}_2\text{C}_2\text{H}_5$	623-91-6	<i>trans</i> - $\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CHCO}_2\text{C}_2\text{H}_5$	 3d (53)
96-32-2	$\text{BrCH}_2\text{CO}_2\text{CH}_3$		$\text{CH}_2=\text{CHCN}$	 3f (4)
107-14-2	ClCH_2CN		$\text{CH}_2=\text{CHCO}_2\text{CH}_3$	 3f (10)
78-95-5	$\text{ClCH}_2\text{COCH}_3$		$\text{CH}_2=\text{CHCO}_2\text{CH}_3$	 3g (21)
	$\text{ClCH}_2\text{COCH}_3$		$\text{CH}_2=\text{CHCN}$	 3h (16)
	$\text{ClCH}_2\text{COCH}_3$		<i>trans</i> - $\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CHCO}_2\text{C}_2\text{H}_5$	 3i (33)

TABLE I (Continued)

Registry no.	α -Monohalo compd	Olefin	Product (yield, %) ^b
	$\text{ClCH}_2\text{COCH}_3$	$\text{cis-C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CHCO}_2\text{C}_2\text{H}_5$	 (15)

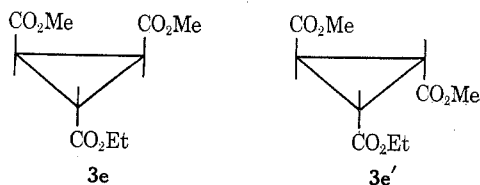
^a Reaction conditions: A mixture of 20 mmol of an α -halo compound, 30 mmol of an olefin, 10 mmol of Cu_2O , and 60 mmol of *tert*-butyl isocyanide was stirred at 80° for 3 hr. ^b Cis and trans mixture.

Results and Discussion

Reaction of α -Halocarbonyl and α -Halonitrile Compounds with Olefin by Cuprous Oxide-Isonitrile Complex.—On heating, cuprous oxide was dissolved in methyl monochloroacetate in the presence of *tert*-butyl isocyanide. From the reaction mixture, trimethyl cyclopropane-1,*cis*-2,*trans*-3-tricarboxylate was isolated in a yield of 34%. When this reaction was carried out in the presence of an electron-deficient olefin such as acrylate and acrylonitrile, the corresponding cyclopropane derivative in eq 2 was formed without being accompanied by the formation of trimethyl cyclopropanetricarboxylate. In the same way, monochloroacetone and monochloroacetonitrile react with electron-deficient olefins to produce the corresponding cyclopropane derivatives. This reaction is applied to electron-deficient olefins. However, no reaction occurred with electron-rich olefins such as cyclohexene and vinyl ethers.

Some representative results are shown in Table I. Spectral data and elemental analyses support the assigned structures of the products. The stereochemistry of the cyclopropanes produced is interesting. In all the reactions except for maleate and fumarate, only one of the stereoisomers, in which two polar substituents on the cyclopropane ring are oriented trans to each other, is selectively produced. A finding that cyclopropane-*cis*-dicarboxylic ester is readily isomerized to the more stable trans isomer under the reaction conditions suggests that the product stereochemistry is thermodynamically controlled.

The reaction of ethyl chloroacetate with methyl acrylate in the presence of sodium methoxide affords a *cis*-*trans* mixture of cyclopropanedicarboxylic acid ester in yields of 26 (*cis*) and 22% (*trans*), respectively.⁵ On the other hand, when this reaction with a strong base was carried out in dimethylformamide or in hexamethylphosphoramide-benzene mixture, the *trans* isomer predominated.⁵ In the reactions of ethyl chloroacetate with methyl maleate and with methyl fumarate in the presence of the cuprous oxide-isonitrile system, about a 1:1 mixture of the two stereoisomers, **3e** and **3e'**, was formed. This result may be

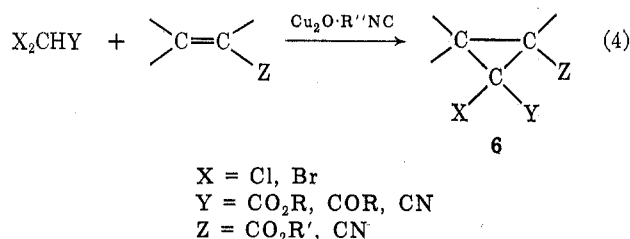


rationalized on the basis of the thermodynamic stabilities of the products; *i.e.*, the carbomethoxy group

(5) L. L. McCoy, *J. Amer. Chem. Soc.*, **80**, 6568 (1958); **82**, 6416 (1960); **84**, 2246 (1962).

and carbethoxy group are almost equivalent in steric bulk. In the reaction with methyl maleate, the isomerization of maleate to fumarate may have occurred prior to the formation of the cyclopropanetricarboxylate. In fact, both maleate and fumarate were recovered from the reaction mixture. However, the rapid equilibration between the isomers of the cyclopropane products seems to be the most important for the control of the **3e** to **3e'** ratio, because cyclopropane-*cis*-1,2-dicarboxylic acid ester was found to be isomerized rapidly into the *trans* isomer under the present reaction conditions.

Reaction of α,α -Dihalocarbonyl and α,α -Dihalonitrile Compounds with Olefin by Cuprous Oxide-Isonitrile Complex.—Cyclopropane synthesis by means of a cuprous oxide-isonitrile complex can be applied to the reactions of α,α -dihaloacetate and of α,α -dihaloacetonitrile with an electron-deficient olefin, leading to the corresponding monohalocyclopropane derivative **6** (eq 4). The results are summarized in Table II.

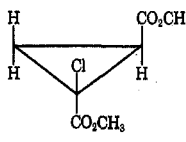
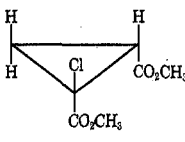
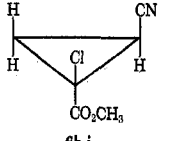
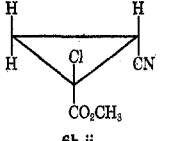
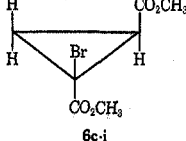
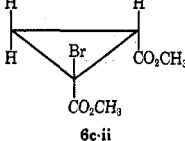
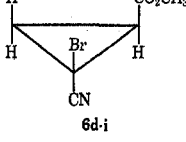
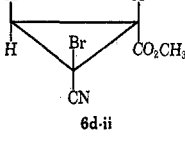
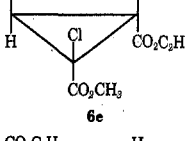
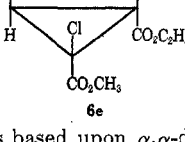


In the cases of acrylate ($\text{Z} = \text{CO}_2\text{R}$) and acrylonitrile ($\text{Z} = \text{CN}$) as the olefin component, the cyclopropane product consisted of the two stereoisomers in which Y and Z are either *trans* or *cis*. The combinations of methyl dichloroacetate with ethyl maleate and with ethyl fumarate gave a single product of 1-chloro-1-methoxycarbonyl-2,3-di(ethoxycarbonyl)cyclopropane in which the two ethoxycarbonyl groups from maleate and fumarate were oriented *trans*.

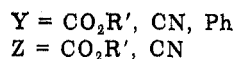
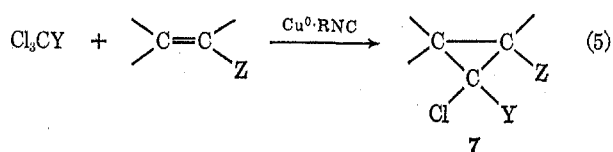
Reactions of Trichloroacetonitrile, Trichloroacetate, and Benzotrichloride with Olefins by Metallic Copper-Isonitrile Complex.—A solution freshly prepared by dissolving metallic copper in cyclohexyl isocyanide under nitrogen showed electron spin resonance (g value = 2.0041) which may be assigned to a zero-valent copper-isonitrile complex. Recently, electron spin resonance of $\text{Cu}(0)$ species has been reported by Kochi, *et al.*⁶ The mixture of metallic copper and isonitrile under nitrogen was treated at 80° with a mixture of a trichloromethyl compound and an electron-deficient olefin to produce chlorocyclopropane derivative (**7**) in a fair yield. This reaction was not catalyzed by the

(6) K. Wada, M. Tamura, and J. K. Kochi, *J. Amer. Chem. Soc.*, **92**, 6656 (1970).

TABLE II.—CYCLOPROPANE SYNTHESIS FROM α,α -DIHALO COMPOUND, OLEFIN, AND CUPROUS OXIDE-ISONITRILE^a

Registry no.	α,α -Dihalo compd	Olefin	Product (yield, %) ^b	
116-54-1	$\text{Cl}_2\text{CHCO}_2\text{CH}_3$	$\text{CH}_2=\text{CHCO}_2\text{CH}_3$	 (11)	 (36)
			 (14)	 (15)
6482-26-4	$\text{Br}_2\text{CHCO}_2\text{CH}_3$	$\text{CH}_2=\text{CHCO}_2\text{CH}_3$	 (20)	 (12)
			 (9)	 (11)
3252-43-5	Br_2CHCN	$\text{CH}=\text{CHCO}_2\text{CH}_3$	 (30)	
			 (28)	
	$\text{Cl}_2\text{CHCO}_2\text{CH}_3$	<i>trans</i> - $\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CHCO}_2\text{C}_2\text{H}_5$		
	$\text{Cl}_2\text{CHCO}_2\text{CH}_3$	<i>cis</i> - $\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CHCO}_2\text{C}_2\text{H}_5$		

^a Reaction conditions: Cu_2O , 5 mmol; α,α -dihalo compound, 10 mmol; olefin, 30 mmol. ^b Yield is based upon α,α -dihalo compound.

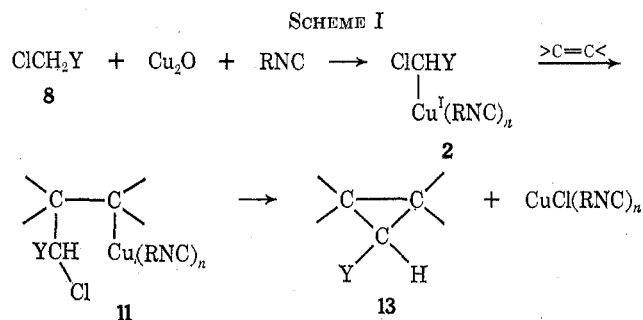


cuprous oxide-isonitrile complex. Results are summarized in Table III.

Products and their stereochemistry are almost the same as those of the reaction of α,α -dihalocarbonyl and α,α -dihalonitrile compounds with olefin by the cuprous oxide-isonitrile complex. These findings may suggest that both reactions involve a similar reaction intermediate.

Reaction Scheme.—These cyclopropane syntheses using cuprous oxide-isonitrile and copper(0)-isonitrile complexes may be explained by a stepwise process (Scheme I) involving the addition of α -halomethylcopper(I)-isonitrile intermediate 2 and 5, a new class of copper carbenoid, to an electron-deficient olefin.

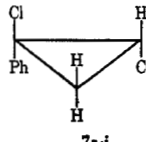
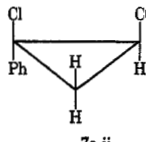
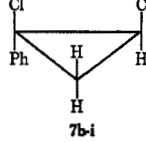
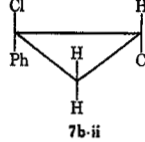
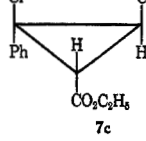
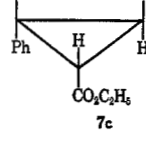
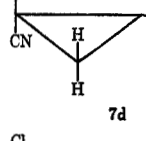
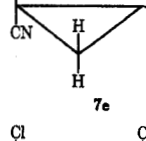
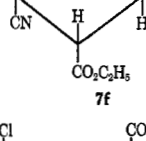
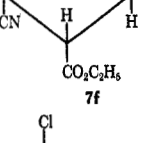
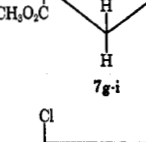
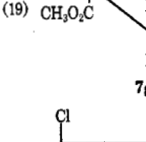
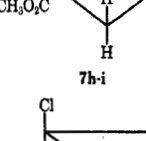
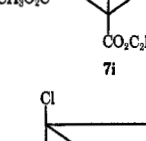
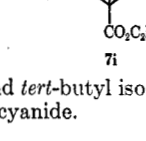
The copper carbenoid complexes are derived from the abstraction of the α hydrogen of 8 and 9 by the cuprous oxide-isonitrile complex and from the abstraction of the α chlorine of 10 by the copper(0)-isonitrile com-



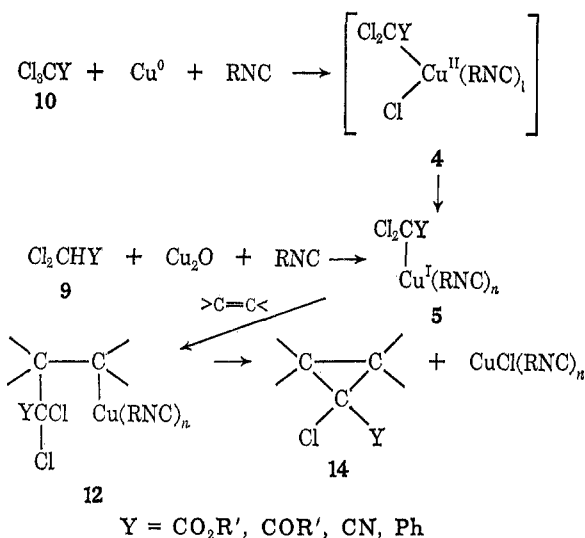
plex. The latter process may involve an oxidative addition of a carbon-chlorine bond of trichloromethyl compounds 10 to the copper(0)-isonitrile complex leading to copper(II) carbenoid-isonitrile complexes 4, which are known⁷ to be readily converted into copper(I)-isonitrile complexes 5. The addition of α -halomethylcopper(I)-isonitrile intermediates 2 and 5 to an electron-deficient olefin leads to the formation of the corresponding γ -chloro-organocopper(I) complexes 11 and 12, respectively, whose intramolecular ring closure brings about the cyclopropane product 13 and 14.

(7) R. W. Stephany and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **89**, 305 (1970).

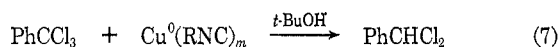
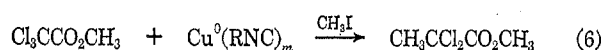
TABLE III.—CHLOROCYCLOPROPANE SYNTHESIS FROM TRICHLOROMETHYL COMPOUNDS, OLEFIN, AND COPPER(0)-ISONITRILE^a

Registry no.	Trichloromethyl compd	Olefin	Product (yield, %)
98-07-7	PhCCl ₃	CH ₂ =CHCO ₂ CH ₃	 (36)
			 (18)
	PhCCl ₃	CH ₂ =CHCN	 (17)
			 (12)
	PhCCl ₃	<i>trans</i> -C ₂ H ₅ O ₂ CCH=CHCO ₂ C ₂ H ₅	 (35)
	PhCCl ₃	<i>cis</i> -C ₂ H ₅ O ₂ CCH=CHCO ₂ C ₂ H ₅	 (36)
545-06-2	Cl ₃ CN	CH ₂ =CHCO ₂ CH ₃	 (66) (1:1.7) ^c
			 (20) (1:1.4) ^c
	Cl ₃ CCN	<i>trans</i> -C ₂ H ₅ O ₂ CCH=CHCO ₂ C ₂ H ₅	 (38)
	Cl ₃ CCN	<i>cis</i> -C ₂ H ₅ O ₂ CCH=CHCO ₂ C ₂ H ₅	 (27)
598-99-2	Cl ₃ CCO ₂ CH ₃	CH ₂ =CHCO ₂ CH ₃	 (19)
			 (42)
	Cl ₃ CCO ₂ CH ₃	CH ₂ =CHCN	 (17)
	Cl ₃ CCO ₂ CH ₃	<i>trans</i> -C ₂ H ₅ O ₂ CH=CHCO ₂ C ₂ H ₅	 (71)
	Cl ₃ CCO ₂ CH ₃	<i>cis</i> -C ₂ H ₅ O ₂ CCH=CHCO ₂ C ₂ H ₅	 (28)

^a Trichloromethyl compound, 10 mmol; olefin, 30 mmol; Cu, 20 mg-atoms; and *tert*-butyl isocyanide, 40 mmol. ^b Cis and trans mixture. ^c Isomer ratio. ^d Cyclohexyl isocyanide was used instead of *tert*-butyl isocyanide.

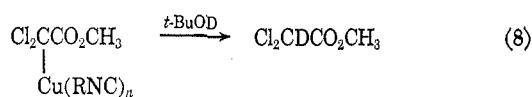


The intermediates, α -halomethylcopper(I)-isonitriles, have not been isolated. However, the following findings support the assumption of copper carbenoid intermediates 2 and 5. When methyl trichloroacetate was treated with the copper(0)-isonitrile system in the presence of methyl iodide, methyl α,α -dichloropropionate was produced (eq 6). In addition,

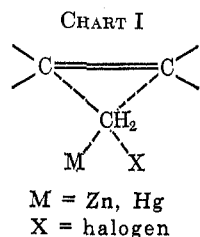


benzal chloride was formed when benzotrichloride was treated with the copper(0)-isonitrile complex in *tert*-butyl alcohol solvent (eq 7). These findings are taken to support the transient formation of 5.

Hydrogen-deuterium exchange in the system of dichloroacetate and cuprous oxide-isonitrile may also support a transient copper carbenoid intermediate 2. Deuterium was rapidly incorporated into dichloroacetate recovered from a short time reaction of dichloroacetate with the cuprous oxide-isonitrile complex in the presence of *tert*-butyl alcohol-*d*₁.



For the reaction of 2 and 5 with olefin, the one-step addition mechanism (Chart I) as in the cyclopropane

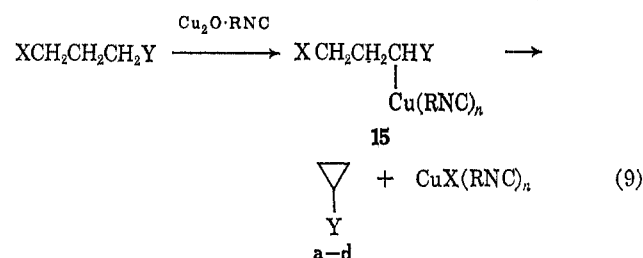


synthesis by means of zinc carbenoid¹ and mercury carbenoid² does not seem to be operating in the present reaction, because zinc and mercury carbenoids prefer to react with electron-rich olefins rather than with electron-poor olefins.

The stepwise reaction mechanism seems to be supported by the following findings. According to Scheme

I, γ -halocarboxylic acid esters and nitriles having α -acidic hydrogen may undergo the cyclization reaction in the presence of the cuprous oxide-isonitrile complex, because they form a γ -haloorganocopper(I)-isonitrile complex resembling complexes 11 and 12. In fact, methyl 4-chlorobutanoate, 5-chloropentan-2-one, and 4-chlorobutyronitrile were cyclized to the corresponding cyclopropane derivatives by the cuprous oxide-isonitrile complex in fairly good yields. This reaction is a good synthetic method.

A γ -haloorganocopper(I)-isonitrile complex (15) intermediate in the cyclization reaction (eq 9) is sup-

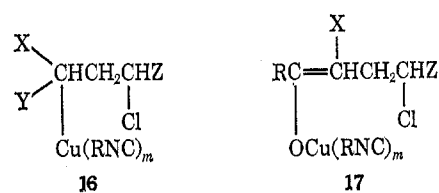


Yield, %	a	b	c	d
	58	57	61	55

- a, X = Cl; Y = CO₂C₂H₅
 b, X = Cl; Y = COCH₃
 c, X = Cl; Y = CN
 d, X = Br; Y = CN

ported by deuterium incorporation in the 4-chlorobutyronitrile recovered after a short time reaction of 4-chlorobutyronitrile with the cuprous oxide-isonitrile complex in the presence of *tert*-butyl alcohol-*d*₁.

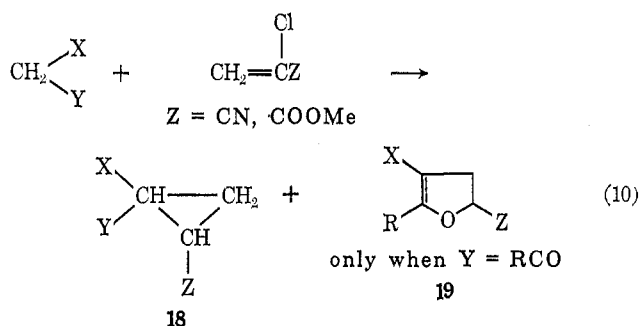
Reaction of α -Chloroacrylonitrile and α -Chloroacrylate with Active Methylene Compound by Cuprous Oxide-Isonitrile Complex.—We have hitherto mentioned a couple of cyclization reactions which involve the copper carbenoid isonitrile complexes as the key intermediates. These cyclization reactions are based upon a common elementary process of the intramolecular elimination of copper(I) halide-isonitrile complex from γ -haloalkylcopper(I)-isonitrile intermediates 11 and 12 formed by addition reaction of the copper carbenoid isonitrile complexes 2 and 5 to olefin. Now another combination leading to γ -haloalkylcopper(I)-isonitrile intermediate 16 and δ -haloalkoxycopper(I)-isonitrile intermediate 17 is presented, which gives



cyclopropane (18) and dihydrofuran (19) derivatives, respectively (eq 10). The reactions of α -chloroacrylonitrile and α -chloroacrylate with active methylene compounds such as dimethyl malonate and methyl cyanoacetate were carried out in benzene at 80° for 6 hr in the presence of Cu₂O and *tert*-butyl isocyanide. As the reaction proceeds, Cu₂O was dissolved progressively to form a homogeneous solution. The product was a mixture of *cis* and *trans* 1,1,2-trisubstituted cyclopropane (18) (eq 10). These reactions with malonate and cyanoacetate as the active methylene

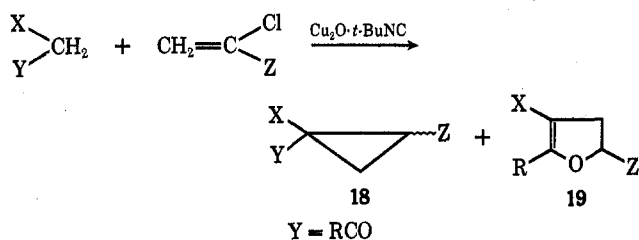
component gave a single product of the cyclopropane derivative.

On the other hand, the reaction with active methylene compounds such as acetylacetone and phenylacetone, which have at least one acyl substituent, afforded dihydrofuran derivative (19) together with cyclopropane products (18) (eq 10).



Results are shown in Table IV. The structures of all the products were established by nmr, mass, and ir

TABLE IV
REACTIONS OF α -CHLOROACRYLATE AND α -CHLOROACRYLONITRILE WITH ACTIVE METHYLENE COMPOUNDS BY MEANS OF CUPROUS OXIDE-*tert*-BUTYL ISOCYANIDE^a



Registry no.	Run	X	Y	Z	Products yield, %	
					18 (isomer ratio) ^b	19
105-34-0	a	CN	CO ₂ Me	CO ₂ Me ^c	61 (100:0)	
108-59-8	b	CO ₂ Me	CO ₂ Me	CO ₂ Me	54 (100:0)	
140-29-4	c	CN	Ph	CO ₂ Me	55 (73:27)	
101-41-7	d	CO ₂ Me	Ph	CO ₂ Me	9 (86:34)	
109-77-3	e	CN	CN	CO ₂ Me	23	
105-53-3	f	CO ₂ Et	CO ₂ Et	CN ^d	29	
123-54-6	g	COMe	COMe	CO ₂ Me	8	68
141-97-9	h	COMe	CO ₂ Et	CO ₂ Me	10 (89:11)	53
103-79-7	i	COMe	Ph	CO ₂ Me	42 (95:5)	9
122-78-1	j	CHO	Ph	CO ₂ Me	62 (87:13)	9
	k	COMe	COMe	CN	33	5
	l	COMe	CO ₂ Et	CN	42 (88:12)	1
	m	COMe	Ph	CN	Trace	

^a Reaction conditions: active methylene compound, 15 mmol; α -chloro olefin, 15 mmol; Cu₂O, 7.7 mmol; *tert*-butyl isocyanide, 24 mmol; benzene, 20 ml; 80°, 6 hr. ^b The stereoisomers ratio was determined by glpc. ^c Registry no., 80-63-7. ^d Registry no., 920-37-6.

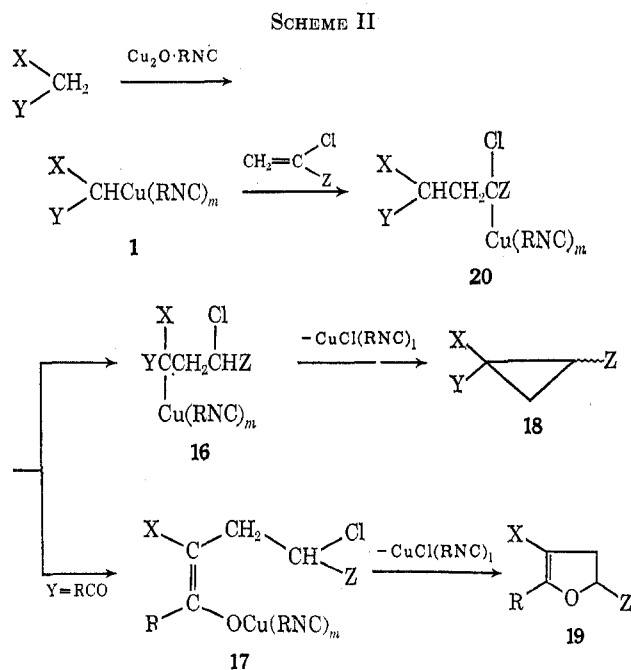
spectra as well as elementary analyses. However, the stereochemistry of cyclopropane derivatives (18) remained unknown except for those of phenylcyclopropane derivatives (18c, 18d, 18i, and 18j), of which the two isomers were differentiated from each other by nmr spectrum on the basis of a characteristic upfield shift of the proton cis to phenyl group on the cyclopropane ring.⁸ In the products of phenylcyclopropanes, an isomer in which two polar substituents are oriented trans to each other is always predominating.

(8) G. A. Closs, R. A. Moss, and J. J. Coyle, *J. Amer. Chem. Soc.*, **84**, 4985 (1962).

The nmr spectra of 2,3,5-trisubstituted dihydrofurans exhibited a diagnostic long-range coupling⁹ between 2 substituent and 4 protons. For example, 2-methyl-3-acetyl-5-methoxycarbonyldihydrofuran showed a strong triplet splitting ($J_{\text{CH}_2\text{CH}_3} = 1.5$ Hz) on the 2-methyl absorption band owing to spin coupling with the 4-methylene protons.

As is seen in Table IV, the products ratio of dihydrofuran (19) to cyclopropane (18) formed in the reaction of the chloro olefin with the acyl-substituted methylene compound increases with the increasing acidity of the active methylene compound. The reaction of α -chloroacrylonitrile afforded lower yields of the products than the corresponding reactions of α -chloroacrylate, because α -chloroacrylonitrile was readily polymerized under these reaction conditions.

The present reaction may be explained by Scheme II, involving several organocopper(I)-isonitrile complexes



as the intermediates. The addition of organocopper(I)-isonitrile (1) to an electron-deficient olefin leads to the formation of α -chloroalkylcopper(I)-isonitrile (20), which is converted intramolecularly or intermolecularly into γ -chloroalkylcopper(I)-isonitrile (16) and/or δ -chloroalkenyloxy copper(I)-isonitrile (17). The intramolecular eliminations of copper(I)chloride-isonitrile complex from 16 and 17 bring the products of 18 and 19, respectively.

The following observation is consistent with the above mechanism (Scheme II). In the reaction of α -chloroacrylate with diethyl ethylmalonate, an addition product of 22 was given in a yield of 46%. No cyclization occurred in this case, because the α -chloroalkylcopper(I)-isonitrile (21) had no active hydrogen at the γ -carbon atom.

Finally, an alternative mechanism involving α elimination of copper(I) chloride-isonitrile from 20 producing an intermediate of carbene might be considered. The carbene mechanism, however, seems less probable from the fact that olefinic product (23)

(9) K. Ichikawa and S. Uemura, *J. Org. Chem.*, **32**, 493 (1967).

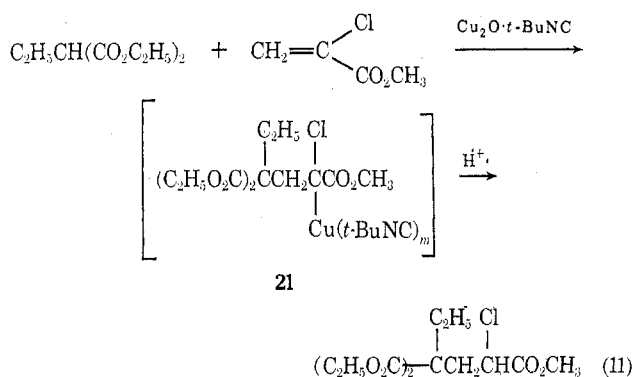
TABLE V
 IDENTIFICATION DATA OF CYCLOPROPANE 3

Compd	Ir, cm ⁻¹	Nmr, τ			
3a	3050, 1725	6.27 (3 H, s)	6.30 (6 H, s)	7.52 (3 H, m)	
3b	3050, 1725	6.30 (6 H, s)	7.90-8.62 (4 H, m)		
3c	3090, 3040 2225, 1730	6.23 (3 H, s)	7.72 (1 H, m)	8.08 (1 H, m)	8.50 (2 H, m)
3d	3050, 1730	5.82 (6 H, q)	7.42 (3 H, m)	8.73 (9 H, t)	
3e	3055, 1730	5.91 (2 H, q)	6.36 (6 H, s)	7.53 (3 H, m)	8.74 (3 H, t)
3g	3050, 1730 1710	6.33 (3 H, s)	7.73 (3 H, s)	7.43-8.10 (2 H, m)	8.63-8.80 (2 H, m)
3h	3100, 3030 2230, 1710	7.63 (3 H, s)	7.27-7.53 (1 H, m)	7.90-8.20 (1 H, m)	8.37-8.67 (2 H, m)
3i	3050, 1730 1715	5.83 (2 H, q)	5.87 (2 H, q)	7.07-7.40 (3 H, m)	7.80 (3 H, s)
		8.68 (3 H, t)	8.73 (3 H, t)		

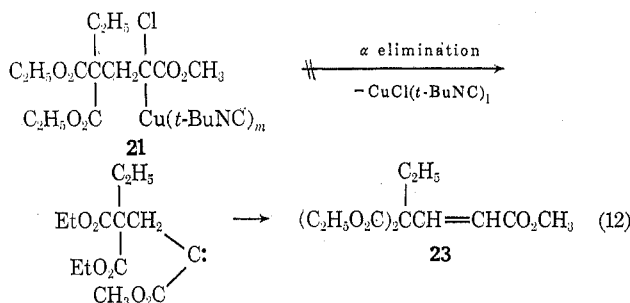
 TABLE VI
 IDENTIFICATION DATA OF HALOCYCLOPROPANE 6

Compd	Ir, cm ⁻¹	Nmr, τ			
6a-i	3100, 1735	6.27 (3 H, s)	6.33 (3 H, s)	7.53-8.05 (2 H, m)	8.30-8.53 (1 H, m)
6a-ii	3100, 1735	6.18 (3 H, s)	6.25 (3 H, s)	7.27-7.55 (1 H, m)	8.07-8.20 (2 H, m)
6b-i	3100, 2230, 1740	6.17 (3 H, s)	7.33-8.33 (3 H, m)		
6b-ii	3100, 2230, 1740	6.09 (3 H, s)	7.47-8.33 (3 H, m)		
6c-i	3080, 1740	6.27 (3 H, s)	6.30 (3 H, s)	7.50-8.52 (3 H, m)	
6c-ii	3090, 1740	6.24 (3 H, s)	6.29 (3 H, s)	7.36-7.65 (1 H, m)	8.00-8.24 (2 H, m)
6d-i	3100, 3050, 2230, 1745	6.16 (3 H, s)	7.34-8.32 (3 H, m)		
6d-ii	3090, 3050, 2225, 1740	6.14 (3 H, s)	7.24-8.08 (3 H, m)		
6e	3050, 1740	5.73 (2 H, q)	5.80 (2 H, q)	6.18 (3 H, s)	6.98 (1 H, d)
		7.18 (1 H, d)	8.65 (3 H, t)	8.70 (3 H, t)	

has not been detected in the reaction of α -chloroacrylate with ethyl malonate (eq 11). It has been known



that carbene, if it is formed as an intermediate, would have been rearranged into the olefinic compound (eq 12) according to the known behavior of carbene.¹⁰



Experimental Section

Reagents.—Cuprous oxide was a commercial reagent and was used without further purification. Copper was prepared by

(10) W. Kirmse and G. Wächtershäuser, *Tetrahedron*, **22**, 73 (1966).

reducing¹¹ CuSO₄ with zinc powder and dried under nitrogen. *tert*-Butyl and cyclohexyl isocyanides were prepared by Ugi's procedure.¹² Methyl α -chloroacrylate¹³ and α -chloroacrylonitrile¹⁴ were synthesized according to the literature procedures and were distilled under nitrogen. All other commercially available reagents were distilled under nitrogen prior to use.

A. Reaction of Methyl α -Chloroacetate with Acrylonitrile Caused by the Cuprous Oxide-*tert*-Butyl Isocyanide Complex.—A mixture of 1.4 g (10 mmol) of Cu₂O, 5.0 g (60 mmol) of *tert*-butyl isocyanide, 2.2 g (20 mmol) of methyl chloroacetate, and 1.6 g (30 mmol) of acrylonitrile was stirred at 80° for 3 hr under nitrogen. As the reaction proceeded, Cu₂O gradually dissolved in the mixture to form a homogeneous system. The reaction mixture was treated with ether to remove the copper(I) chloride-*tert*-butyl isocyanide complex, and the ether solution was concentrated and distilled under 30 mm. *trans*-1-Cyano-2-methoxycarbonylcyclopropane was isolated from the distillate by preparative glpc. The stereochemistry of this product was determined by converting it by treatment with HCl-CH₃OH¹⁵ into *trans*-1,2-dimethoxycarbonylcyclopropane, which exhibits a symmetrical A₂B₂ pattern in the region between τ 7.7 and 8.7. Spectral data are summarized in Table V. The other combinations of an α -monohalo compound and an olefin in Table I were treated similarly.

B. Reaction of Methyl Dichloroacetate with Methyl Acrylate Caused by Cuprous Oxide-*tert*-Butyl Isocyanide Complex.—To a stirred mixture of 0.7 g (5 mmol) of Cu₂O and 2.5 g (30 mmol) of *tert*-butyl isocyanide maintained at about 60°, a mixture of 1.4 g (10 mmol) of methyl dichloroacetate and 2.6 g (30 mmol) of methyl acrylate was added dropwise over 30 min. After the addition was complete, the reaction mixture was heated at 80° for 5 hr. The reaction mixture was treated with ether to remove the copper(I) chloride-*tert*-butyl isocyanide complex. The ether solution was concentrated, and the residue was distilled under reduced pressure. The distillate was analyzed by glpc, and two

(11) "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 320.

(12) I. Ugi and R. Meyer, *Chem. Ber.*, **93**, 239 (1960).

(13) C. S. Marvel, H. G. Cooke, and J. C. Cowan, *J. Amer. Chem. Soc.*, **62**, 3496 (1940).

(14) H. Brintzinger, K. Pfannstiel, and H. Koddebusch, *Angew. Chem.*, **60**, 311 (1948).

(15) M. M. Rising and Tsoh-Wu Zee, *J. Amer. Chem. Soc.*, **50**, 1210 (1928).

stereoisomers of 1-chloro-1,2-dimethoxycarbonylcyclopropane were isolated separately by preparative glpc. The structures of 1-chloro-1,2-dimethoxycarbonylcyclopropanes were confirmed by reducing them with Zn-HCl to 1,2-dimethoxycyclopropanes, and comparing their nmr spectra with those of authentic samples. Spectral data are summarized in Table VI. The reaction of dichloroacetate with acrylonitrile was carried out in the same way.

C. Reaction of Methyl Dichloroacetate with Diethyl Fumarate Caused by Cuprous Oxide-*tert*-Butyl Isocyanide Complex.—To a stirred mixture of 0.7 g (5 mmol) of Cu_2O , 2.5 g (30 mmol) of *tert*-butyl isocyanide, and 5.2 g (30 mmol) of diethyl fumarate, 1.4 g (10 mmol) of methyl dichloroacetate was added dropwise over 30 min, and the reaction mixture was heated at 80° for 5 hr. Work-up was carried out in a similar way to that described in B.

D. Reaction of Benzotrichloride with Methyl Acrylate in the Presence of Metallic Copper and Isonitrile.—Under nitrogen, a mixture of 2.6 g (30 mmol) of methyl acrylate and 2.0 g (10 mmol) of benzotrichloride in 3 ml of benzene was added dropwise over 30 min to a preheated mixture of 1.3 g (20 mg-atom) of copper metal and 3.3 g (40 mmol) of *tert*-butyl isocyanide in 5 ml of benzene at 80°. Then the reaction mixture was heated with stirring for an additional 7 hr. Finally, the reaction mixture was extracted with ether to remove copper(I) chloride-*tert*-butyl isocyanide complex, and the extract was concentrated and subjected to glpc analysis. About a 1:2 mixture of *cis* (7a-ii) and *trans* (7a-i) isomers of methyl 2-chloro-2-phenylcyclopropanecarboxylate was produced in a total yield of 54%. (The geometrical isomerism is referred to the positions of a chlorine atom and a methoxycarbonyl group.) Each isomer was isolated by preparative glpc and their structures were convincingly confirmed by elementary analysis and spectra data (see Tables VII and VIII).

TABLE VII
IDENTIFICATION OF 7

	Ir, cm^{-1} (neat)	Nmr (in CCl_4), τ
7a-i	>3000, 1735 750, 696	2.47-2.90 (5 H, m), 6.60 (3 H, s) 7.27-7.63 (1 H, m), 7.73-8.46 (2 H, m)
7a-ii	>3000, 1735 745, 696	2.43-2.93 (5 H, m), 6.23 (3 H, s) 7.57-8.43 (3 H, m)
7b-i	>3000, 2215 755, 696	2.50-2.80 (5 H, m) 7.70-8.20 (3 H, m)
7b-ii	>3000, 2215 755, 695	2.37-2.73 (5 H, m) 7.60-8.20 (3 H, m)
7c	>3000, 1732 745, 692	2.50-2.83 (5 H, m), 5.73 (2 H, q), 6.10 (2 H, q) 6.97 (2 H, s), 8.67 (3 H, t), 8.92 (3 H, t)
7d	>3000, 2230 1738	6.20 (3 H, s) 7.20-8.30 (3 H, m)
7e	>3000, 2245 745, 692	7.23-8.23 (m)
7f	>3000, 2230 1735	5.73 (4 H, q), 7.70 (2 H, m) 8.67 (6 H, t)

The reaction of the other combinations in Table III was carried out by a procedure similar to that mentioned above.

E. Reaction of Methyl Trichloroacetate with Copper Metal and *tert*-Butyl Isocyanide in the Presence of Methyl Iodide.—Under nitrogen, a mixture of 0.32 g (5 mg-atoms) of copper metal, 1.3 g (15 mmol) of *tert*-butyl isocyanide, and 1 ml of benzene was heated at 80° for 1 hr with stirring and then cooled to room temperature. To the stirred mixture, 0.9 g (5 mmol) of methyl trichloroacetate was added dropwise, and, after 1 hr, 4.26 g (30 mmol) of methyl iodide was added, and the solution was stirred for 1 hr at room temperature. The reaction mixture was treated with ether to remove copper(I)-*tert*-butyl isocyanide complex, the ether solution was concentrated, and the residue was analyzed by glpc. Methyl α,α -dichloropropionate was isolated in 30% yield by preparative glpc and identified by comparison with an authentic sample.

F. Cyclization of Methyl 4-Chlorobutanoate by Cuprous Oxide-Cyclohexyl Isocyanide Complex.—To a mixture of 0.7 g (5 mmol) of Cu_2O and 3.3 g (30 mmol) of cyclohexyl isocyanide, 1.4 g of methyl 4-chlorobutanoate was added dropwise with stirring at 80° and then the mixture was heated at 80° for 7 hr. The reaction mixture was treated with ether to remove the copper(I) chloride-cyclohexyl isocyanide complex, the ether solution was concentrated, and the residue was distilled under slightly reduced pressure. Methyl cyclopropanecarboxylate was isolated in 58% yield.

TABLE VIII

Compd	Mass, M ⁺	Ir (neat), cm^{-1}	IDENTIFICATION OF 18 AND 19	
			Nmr (in CDCl_3), τ	
18a	183	3100, 2230, 1735	6.10, 6.15 (s, 6 H, COOCH_3), 7.25 (q, 1 H), 7.90 (m, 2 H)	
18b	216	3100, 1740, 1380	6.25, 6.29 (s, 9 H), 7.40 (q, 1 H), 8.20 (m, 2 H)	
18c ^a	201	3080, 2218, 1740, 1225, 1250, 938 3080, 2220, 1735 1050, 941	2.69 (5 H), 6.58 (s, COOCH_3), 7.25 (q, 1 H), ~7.90 (m, 2 H) 2.65 (5 H), 6.18 (s, COOCH_3), 7.70 (q, 1 H), ~8.00 (m, 2 H)	
18d ^a	234	1738, 1435, 1095	2.70 (5 H), 6.30 (s, 3 H), 6.38 (s, 3 H), 5.7 (q, 1 H), ~7.3-7.4 (m, 2 H)	
		1725, 1435, 1380, 1100, 925	2.71 (5 H), 6.21 (s, 3 H), 6.37 (s, 3 H), 7.25 (q, 1 H), 8.05 (m, 2 H)	
18e	150	3100, 2243, 1740, 1442, 1388, 1018	6.15 (s, COOCH_3), 7.16 (q, 1 H), ~7.8 (m, 2 H)	
18f	211	3098, 2225, 1735, 1375, 1015	5.70 (4 H), 7.51 (q, 1 H), ~8.2 (m, 2 H), 8.70 (6 H)	
18g	184	3100, 1740, 1700	6.30 (s, 3 H, COOCH_3), 7.40 (q, 1 H), 7.68 (s, 3 H), 7.79 (s, 3 H), ~8.20 (m, 2 H)	
	214	3080, 1740, 1710	5.73 (q, 2 H), 6.30 (s, 3 H, COOCH_3), ~7.40 (m, 1 H), 7.66 (s, 3 H, COCH_3), ~8.25 (m, 2 H), 8.68 (t, 3 H)	
18h ^a		3080, 1735, 1710	5.75 (q, 2 H), 6.30 (s, 3 H, COOCH_3), ~7.40 (m, 1 H), 7.69 (s, 3 H, COCH_3), ~8.25 (m, 2 H), 8.7 (t, 3 H)	
	218	3020, 1735, 1700, 1608, 980, 928	2.66 (5 H), 6.55 (s, 3 H, COOCH_3), 7.15 (q, 1 H), 8.00 (s, 3 H), 8.16 (m, 2 H)	
18i ^a		3020, 1730, 1705, 1595, 975, 920	2.71 (5 H), 6.30 (s, 3 H, COOCH_3), 7.80 (q, 1 H), 7.94 (s, 3 H), 8.45 (m, 2 H)	
18j ^a	204	3080, 1725, 1715, 1500, 1270, 1100, 1025, 950 3080, 1728, 1701, 1195, 1170	1.49 (1 H, CHO), 2.7 (5 H), 6.60 (3 H, COOCH_3), 7.35 (q, 1 H), ~8.00 (m, 2 H) 1.45 (1 H, CHO), 2.75 (5 H), 6.23 (3 H, COOCH_3), 7.65 (q, 2 H), ~8.30 (m, 2 H)	
18k ^a		3085, 2242, 1700, 1420, 1362, 920, 965	7.59, 7.72 (s, 6 H, COCH_3), 7.43 (q, 1 H), 7.87 (q, 1 H) 8.35 (q, 1 H)	
18l ^a	181	3098, 2228, 1720, 1370, 1310, 1250	5.62 (2 H), 7.54 (3 H, COCH_3), 7.48 (q, 1 H), 7.93 (q, 1 H), 8.40 (q, 1 H)	
		3100, 2230, 1720, 1370, 1310, 1270	5.73 (2 H), 7.50 (3 H, COCH_3), 7.52 (q, 1 H), 7.85 (q, 1 H), 8.35 (q, 1 H)	
19g	184	1755, 1675, 1630, 1200, 945, 920	4.95 (q, 1 H), 6.19 (s, 3 H), 6.85 (m, 2 H), 7.72 (t, 3 H), 7.79 (s, 3 H)	
19h	214	1760, 1700, 1660, 1215, 1035, 965, 925	4.96 (q, 1 H), 5.84 (q, 2 H), 6.21 (s, 3 H, COOCH_3), 6.85 (m, 2 H), 7.75 (t, 3 H), 8.72 (t, 3 H)	
19i	218	1750, 1660, 1595, 1510, 1195, 975, 955, 912	2.75 (5 H), 5.00 (q, 1 H), 6.20 (s, COOCH_3), ~6.70 (m, 2 H), 7.91 (t, 3 H)	
19j	204	1750, 1640, 1601, 1495, 1440, 1100, 930, 910	2.0 (t, 1 H), 2.6 (5 H), 4.85 (q, 1 H), 6.19 (s, COOCH_3), 6.7 (m, 2 H)	
19k	151	1700, 1680, 1630, 1420, 1380, 1360, 1205	4.72 (q, 1 H), 6.70 (m, 2 H), 7.75 (6 H, CH_3)	

^a Consisted of two isomers.

G. Deuterium Incorporation in 4-Chlorobutyronitrile.—A mixture of 0.7 g (5 mmol) of Cu_2O , 3.3 g (30 mmol) of cyclohexyl isocyanide, 1.0 g of 4-chlorobutyronitrile, and 1.5 g (20 mmol) of *tert*-butyl alcohol- d_4 was heated at 70° with stirring. After 1 hr, the reaction mixture was distilled under reduced pressure, and the recovered 4-chlorobutyronitrile was subjected to spectroscopic analyses. Nmr showed deuterium incorporation at the carbon α to the cyano group and the ir spectrum exhibited a new band at 2120 cm^{-1} which was assigned to $\nu_{\text{C-D}}$.

H. Reaction of α -Chloroacrylonitrile with Active Methylene Compound Caused by Cuprous Oxide-*tert*-Butyl Isocyanide. General Procedure.—To a mixture of 7.7 mmol of Cu_2O , 15.0 mmol of an active methylene compound, and 20 ml of benzene, 15.0 mmol of α -chloroacrylate or α -chloroacrylonitrile was added, and then 24.0 mmol of *tert*-butyl isocyanide was added dropwise at room temperature with stirring under nitrogen. After

the mixture was heated at 80° for 6 hr, 30 ml of a mixture of petroleum ether (bp 30–60°) and diethyl ether (2:1) was poured into the cooled reaction mixture. The precipitated copper(I) chloride-*tert*-butyl isocyanide and some unreacted Cu₂O were removed by filtration. The filtrate was subjected to distillation and the residue was distilled *in vacuo*. Each fraction was analyzed by glpc. An analytical sample was purified by preparative glpc.

I. Reaction of Methyl α -Chloroacrylate with Diethyl Ethylmalonate Caused by Cuprous Oxide-*tert*-Butyl Isocyanides.—Reaction was carried out according to the procedure mentioned above. A main product of **22** [bp 123° (4 mm Hg); yield 46%] was accompanied by several minor by-products, whose nmr spectra exhibited no signal in the olefinic region. **22** (Anal. Calcd for C₁₃H₂₁O₆Cl: C, 50.57; H, 6.86; Cl, 11.48. Found: C, 50.85; H, 6.90; Cl, 11.30.) had nmr (CDCl₃) τ 5.2 (1 H, ClCH \leq), 5.75 (4 H, 2 \times OCH₂CH₃), 6.21 (3 H, OCH₃), ~7.4 (2 H, \gt CCH₂CHCl), 8.01 (2 H, CH₃CH₂C \leq), 8.78 (6 H, 2 \times OCH₂CH₃), 9.16 (3 H, CH₃CH₂C \leq).

Registry No.—**3a**, 717-69-1; **3b**, 826-35-7; **3c**, 34185-94-9; **3d**, 13949-99-0; (1 α ,2 β ,3 β)-**3e**, 34185-95-0; (1 α ,2 α ,3 β)-**3e'**, 34185-96-1; **3g**, 34185-98-3;

3h, 39821-99-3; **3i**, 34185-99-4; **6a-i**, 39822-01-0; **6a-ii**, 39822-02-1; **6b-i**, 39822-03-2; **6b-ii**, 39822-04-3; **6c-i**, 30630-39-8; **6c-ii**, 30630-38-7; **6d-i**, 39822-06-5; **6d-ii**, 39822-07-6; **6e**, 39822-08-7; **7a-i**, 39822-09-8; **7a-ii**, 39822-10-1; **7b-i**, 39822-11-2; **7b-ii**, 39822-12-3; **7c**, 39822-13-4; *trans*-**7d**, 39822-14-5; *cis*-**7d**, 39822-15-6; *cis*-**7e**, 39822-16-7; *trans*-**7e**, 39822-17-8; **7f**, 39822-18-9; **18a**, 39822-24-7; **18b**, 22650-26-6; *cis*-**18c**, 39822-26-9; *trans*-**18c**, 39822-27-0; *cis*-**18d**, 39822-28-1; *trans*-**18d**, 39822-29-2; **18e**, 39822-30-5; **18f**, 714-92-1; **18g**, 39822-32-7; *cis*-**18h**, 39822-33-8; *trans*-**18h**, 39822-34-9; *cis*-**18i**, 39822-35-0; *trans*-**18i**, 39822-36-1; *cis*-**18j**, 39822-37-2; *trans*-**18j**, 39822-38-3; **18k**, 19930-90-6; *cis*-**18l**, 39822-41-8; *trans*-**18l**, 39822-42-9; **19g** (X = Ac; R = Me), 39822-40-7; **19h** (X = EtO₂C; R = Me), 39822-43-0; **19i** (X = Ph; R = Me), 39822-44-1; **19j** (X = Ph; R = H), 39822-45-2; **19k** (X = Ac; R = Me), 39822-46-3; **22**, 39822-47-4; cuprous oxide-*tert*-butylisocyanide complex, 39822-48-5; cuprous oxide-cyclohexylisocyanide complex 39822-49-6.

Reaction of α -Ketols and Other 21-Hydroxy Steroids with Phosgene. II. Structural Requirements in the Formation of 20-Chloro-20,21-cyclic Carbonates from 11-Deoxycorticosterone and 11-Dehydrocorticosterone¹

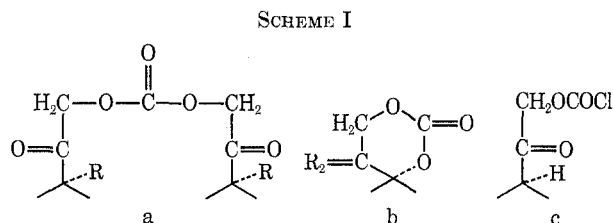
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Reaction of 11-deoxycorticosterone (**1**) in pyridine with excess phosgene in benzene (condition B) affords the novel-20-chloro-20,21-cyclic carbonates **3a,b** as major products and the 21-chloride **2** as a minor product. In contrast, phosgenation of 11-dehydrocorticosterone (**9**) under condition B gives the 21-chloride **10** as a major product and the 20-chloro-20,21-cyclic carbonates **11a** and **11b** as minor products. Reduction of the 11-deoxy-cyclic chlorocarbonates **3a,b** with zinc in acetic acid furnishes both progesterone (**7**) and the epimeric 20-acetoxy-20,21-cyclic carbonates **8a** and **8b**, whereas similar reduction of **11a** and **11b** gives 11-ketoprogesterone (**12**) as the only significant product. Those structural features which are essential for cyclic chlorocarbonate formation have been determined by phosgenating under condition B a number of 17-deoxy-21-ols with various substituents at C-20. These include 11,20-dideoxycorticosterone (**16**) and the 3,20-bisethylene ketals of **1** and **9** as well as the analogous Δ^{16} -20-ketones and Δ^{16} -20-ethylene ketals. It was concluded from these studies that, although all steroidal 21-ols form 21-chlorocarbonates under condition B, hydrolysis to starting material occurs during the work-up in the absence of a carbonyl group at C-20 and a saturated D ring.

In the first paper of this series² we described the preparation of symmetrical and mixed 21,21'-bisteroidal carbonates (partial formula a, R = H or OH, Scheme I)



by the slow addition of phosgene to excess α -ketols in pyridine (condition A). It was also reported that addition of cortisone (but not 11-deoxycortisol) and a number of nonketolic 17,21-diols to excess phosgene (condition B) affords 17,21-cyclic carbonates (partial formula

b). This study has been extended to the phosgenation of 17-deoxy- α -ketols under condition B in the expectation that, in the absence of a hydroxyl group at C-17, 21-chlorocarbonates (partial formula c) would be major products. The results of this investigation, as well as a detailed examination of the influence of neighboring functional groups on reactions at C-21, are reported in the present paper.

Treatment of 11-deoxycorticosterone (**1**, Scheme II) under condition B and tlc analysis of the reaction mixture showed that, in addition to small amounts of the bisteroidal carbonate and a component with the same mobility as 21-chloroprogesterone (**2**),³ a major product with intermediate mobility is formed. The ketolic nature of the latter substance was evident from its rapid reduction of alkaline blue tetrazolium (BT). Column chromatography on silica gel gave the 21-chloride **2** in 14% yield, but resulted in nearly total destruction of the major product. It was found subsequently that repeated crystallizations from methylene chloride permitted direct isolation of this compound in 53% yield.

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(3) H. Reich and T. Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939).