dried, affording 0.97 g. (57%) of the hydrochloride salt of the starting material. The filtrate was washed with water until neutral, dried over magnesium sulfate, and concentrated on a steam bath. The residue, which weighed 0.40 g. (27%), was dissolved in 8 ml. of pyridine, treated with 12 ml. of acetic anhydride, and left overnight at room temperature. The solution was poured into dilute hydrochloric acid, and the precipitate was collected by filtration, dried in air, and chromatographed on Florisil. Elution with 5% ether in benzene afforded 0.23 g. of a mixture of the 3-acetates of 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-one and 3β,17aβ-dihydroxy-17aα-methyl-D-homoandrost-5-en-17-one. The compounds were identified by thin layer chromatography. Repeated fractional crystallization of the mixture from ether afforded 52 mg. of the 3-acetate of **17**, m.p. 269–271° (lit.[33] m.p. 277–279°), and 75 mg. of the 3-acetate of **11b**, m.p. 179–180° (lit.[33] m.p. 176–178°). Saponification of each acetate with sodium hydroxide in methanol at room temperature for 1 hr. afforded the corresponding 3-alcohols, m.p. 298–300° (**17**) and 182–184° (**11b**), respectively, which were identical with authentic samples of these two compounds.

17α-Amino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (16a).—A suspension of 2.8 g. of 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one (**3a**) in 40 ml. of Dowtherm A was covered with an atmosphere of nitrogen and heated at 200° for 10 hr. The solution then was cooled to room temperature, diluted with 1 l. of cold ether, and filtered, affording 0.95 g. (34%) of 17α-amino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one. A sample was recrystallized from methanol for analysis, m.p. 227–229°, $[\alpha]^{24}D$ −47°.

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.20; H, 9.97; N, 4.24. Found: C, 76.30; H, 10.12; N, 4.28.

The ether filtrate was treated with anhydrous hydrogen chloride. The precipitate was collected and recrystallized from methanol to give 0.34 g. (11%) of the **hydrochloride salt** of **16a** with 0.5 mole of methanol of crystallization, m.p. 272–282° dec.

Anal. Calcd. for $C_{21}H_{34}ClNO_2 \cdot 0.5CH_3OH$: C, 67.34; H, 9.45; Cl, 9.24; N, 3.65. Found: C, 67.48; H, 9.48; Cl, 9.27; N, 3.83.

17α-Methylamino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (16b).—A suspension of 708 mg. of 17β-methylamino-3β-hydroxy-17α-pregn-5-en-20-one (**3e**) in 10 ml. of Dowtherm A was covered with an atmosphere of nitrogen and heated at 200° for 10 hr. The cooled solution was diluted with ether and treated with anhydrous hydrogen chloride. The brown gum which deposited was crystallized from methanol–ethyl acetate, affording 217 mg. (28%) of the hydrochloride salt of 17α-methylamino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one. The infrared spectrum of the salt was identical with that of an authentic sample prepared earlier.[35] The salt was converted in the usual manner to the free base, m.p. 205–207°, which exhibited no depression in melting point when mixed with an authentic sample prepared earlier.[35]

17α-Acetamino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (16d).—A solution of 288 mg. of 17α-amino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (**16a**) in 35 ml. of methanol was treated with 4 ml. of acetic anhydride and left overnight at room temperature. The solution was concentrated to dryness under reduced pressure, and the residue was recrystallized from methanol, affording 137 mg. (42%) of 17α-acetamino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (**16d**), m.p. 305–307°, $[\alpha]^{24}D$ −55°.

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 74.00; H, 9.50; N, 3.74.

(3β-Hydroxy-17β-methyl-D-homoandrost-5-en-17a-on-17α-yl)-trimethylammonium Iodide (16c).—A solution of 133 mg. of the hydrochloride salt of 17α-amino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (**16a**) in 12 ml. of acetonitrile was treated with 200 mg. of potassium carbonate and 2.5 ml. of methyl iodide and stirred and refluxed overnight. The mixture was concentrated under reduced pressure to a small volume, diluted with water, and filtered. The precipitate was air dried, affording 147 mg. (80%) of (3β-hydroxy-17β-methyl-D-homoandrost-5-en-17a-on-17α-yl)trimethylammonium iodide (**16c**), m.p. 235–237°. The infrared spectrum of the salt was identical with the spectrum of the salt (m.p. 240–242°) prepared previously from **16b** in similar manner.[35]

Hydrolysis of 2-(3β-Hydroxypregn-5-en-20-ylidine)-1,1,1-trimethylhydrazonium Iodide.—A suspension of 500 mg. of **2** in 50 ml. of water was refluxed for 24 hr., cooled, and extracted with ether. The ether solution was dried over magnesium sulfate and concentrated to dryness, affording 125 mg. (40%) of pregnenolone, m.p. 190–191°, $[\alpha]^{24}D$ +25° (*c* 1.0, EtOH). The reported rotation in ethanol of pregnenolone is +28°,[42] whereas that of 17-isopregnenolone is −140°.[42] When the reaction was repeated with the addition of 200 mg. of sodium bicarbonate, 255 mg. (81%) of pregnenolone, $[\alpha]^{24}D$ +24° (*c* 1.0, EtOH), was isolated.

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(42) J. P. Mathieu and A. Petit, "Pouvoir Rotatoire Naturel I. Steroides," Masson and Co., Paris, 1956, p. 46.

Cupric Halide Halogenations

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Cupric bromide and cupric chloride in refluxing methanol and higher alcohols effect the following transformations: β-alkoxylation α-halogenation of carbonyl-conjugated vinyl groups, halogenation of isolated double bonds, *trans* halogenation of internal acetylenes, and trihalogenation of terminal acetylenes. In a reaction of undefined scope, ethanol is oxidatively halogenated with cupric bromide to dibromoacetaldehydediethyl acetal. Kinetics of some representative transformations have been examined. Cupric bromide but not cupric chloride functions as a source of low concentrations of halogen. Mechanisms for some of the conversions are suggested.

The high-temperature gas phase halogenation of aromatic,[1a] unsaturated aliphatic,[1b] and alicyclic compounds[1c] with solid cupric halides has been industrially employed. Recently, the gas phase chlorination of olefins with cupric chloride supported on pumice has been described[2] to proceed with *trans* addition of halogen.

The relatively low temperature liquid phase reduction of copper salts by organic molecules has not received early attention. Thus, although the reduction of cupric chloride by acetone in aqueous media was noted[3] at the turn of the century, the synthetic and

(1) (a) N. N. Vorozhtov, I. S. Travkin, and I. I. Ioffe, *J. Appl. Chem. USSR*, **11**, 271 (1938); (b) G. W. Hearne, British Patent 558,888 (1944); (c) M. DeSimo, British Patent 559,080 (1944).

(2) R. P. Arganbright and W. F. Yates, *J. Org. Chem.*, **27**, 1205 (1962).

(3) V. Kohlschutter, *Ber.*, **27**, 1170 (1904).

TABLE I

PRODUCTS OF HALOGENATION WITH CUPRIC HALIDES

Reactant	CuX_2	Reflux time, hr.	Solvent	% conversion (% CuX)	Product	% yield[a]
$CH{\equiv}CH_2OH$	$CuBr_2$	0.5	MeOH	100	$Br_2C{=}CBr{=}CH_2OH$[e]	93
$CH{\equiv}CH_2OH$	$CuBr_2$[b]	0.5	MeOH	100	$BrCH{=}CHBrCH_2OH$ (*trans*)	30
					$Br_2C{=}CBrCH_2OH$	18
$CH{\equiv}CH_2OH$	$CuCl_2$	22	MeOH	76	$Cl_2C{=}CClCH_2OH$	31
$CH{\equiv}CCHO$	$CuBr_2$	16	MeOH	90	$Br_2C{=}CBrCH(OMe)_2$[e]	57
$CH{\equiv}CCHO$	$CuCl_2$	6.5	MeOH	55	$Cl_2C{=}CClCH(OMe)_2$[e]	57
$CH_2{=}CHCHO$	$CuBr_2$	3	MeOH	64	$MeOCH_2CHBrCH(OMe)_2$[e]	61
$CH_2{=}CHCHO$	$CuCl_2$	43	MeOH	11.4	$MeOCH_2CHClCH(OMe)_2$	102
					$MeOCH_2CH_2CH(OMe)_2$	25[c]
$CH_3CH_2CH_2CHO$	$CuBr_2$	9	MeOH	60	$CH_3CH_2CHBr{=}CH(OMe)_2$	66
$CH_3CH_2CH_2CHO$	$CuCl_2$	24	MeOH	19.2	$CH_3CH_2CHClCH(OMe)_2$	80
$CH_3CH_2CH_2CHO$		2 (85°)	DMF[g]	62	$CH_3CH_2CHClCHO$	97[f]
$CH_3CH_2CH_2CH(OMe)_2$	$CuBr_2$	12	MeOH	66	$CH_3CH_2CHBrCH(OMe)_2$	68
$CH{\equiv}CCO_2Me$	$CuBr_2$	11	MeOH	66	$Br_2C{=}CBrCO_2Me$[e]	50
					$BrCH{=}CHBrCOMe$ (*trans*)	47
	$CuCl_2$	25	MeOH	35	$ClCH{=}CHClCO_2Me$ (*trans*)	68
$PhC{\equiv}CH$	$CuBr_2$	15	MeOH	100	$Br_2C{=}CBr{=}Ph$[e]	67
$CH_2{=}CHCH_2OH$	$CuBr_2$	24	MeOH	99	$BrCH_2CHBrCH_2OH$	99
$PhC{\equiv}CCO_2H$	$CuBr_2$	23	MeOH	51	$PhCBr{=}CBrCO_2H$ (*trans*)	64
$PhC{\equiv}CPh$	$CuBr_2$	25	MeOH	23	$PhCBr{=}CBrPh$ (*trans*)	81
CH_3CH_2OH	$CuBr_2$	49	Neat	72	$Br_2CHCH(OEt)_2$	90
$CH_2{=}CHCN$	$CuBr_2$	82	EtOH	70	$Br_2CHCH(OEt)_2$	*d*
					$BrCH_2CHBrCO_2Et$	*d*
					$EtOCH_2CHBr{=}CO_2Et$	12
$CH_2{=}CHCO_2Et$	$CuBr_2$	96	EtOH	70	$Br_2CHCH(OEt)_2$	*d*
					$BrCH_2CHBrCO_2Et$	*d*
					$EtOCH_2CHBrCO_2Et$	8

[a] 200[moles of product/moles of Cu(I)X]. [b] Run with 10-mole excess of alcohol. [c] 100(moles of product/moles of substrate changed). [d] From 0.1 mole of substrate there was obtained a mixture of dibromo acetal and dibromo ester in the amount of 5.9 g. starting with the nitrile and 14.3 g. starting with the ester. [e] Not previously described. [f] The product aldehyde was converted to the dimethyl acetal for comparison with an authentic sample. [g] Dimethylformamide containing LiCl; conditions F, Table II.

mechanistic consequences of this chlorination were not intimated until 1955.[4] Subsequently, some isolated cases of the α-halogenation of ketones in the steroid,[5a,d] acetophenone,[5b] and cyclohexanone[5c] series with cupric halides in methanol or dioxane have been reported. Similarly, the α-halogenation of saturated ketones with cupric halides in dimethylformamide and the conversion of α,β-unsaturated ketones to the corresponding α-halo olefins by this reagent has been noted.[6a,b] Moreover, the preparation of β-alkoxy-α-halo aldehydes or their acetals by the action of cupric bromide or chloride upon the corresponding unsaturated aldehyde in refluxing alcohol has been described.[7] Several descriptions of the nuclear[8a,b,c] and side-chain[8c,d] halogenation of polynuclear aromatic compounds with these salts have appeared as have reports of the halogenation of phenols.[5c,6a,9]

The relevance of Cu(II) halogenations to many biological transformations[10] is emphasized by the recently reported Cu(II)-catalyzed *trans* aminations[11] and more directly by the enzymatic halogenation of ketones.[12]

This study was undertaken to delineate the scope of the alcohol addition halogenation reaction previously reported.[7] In addition to providing a route to potential nematocides,[13] the reaction offered the possibility of a mechanistic counterpoint to the reduction of alkyl halides[14a] and multiple bonds[14b] by Cr(II).

Results

The products of the reaction of a variety of carbonyl-conjugated and isolated multiple bonds with cupric halides in alcohol are depicted in Table I. Initial concentrations of substrate and cupric halide were usually in the range of 0.2–0.3 *M* and 0.8–1.0 *M*, respectively. The substrates are listed in a decreasing order of reactivity toward cupric bromide. Both methyl acrylate and *n*-propyl alcohol[15] were inert to cupric bromide in refluxing methanol. Similarly a refluxing solution of

(4) J. K. Kochi, *J. Am. Chem. Soc.*, **77**, 5274 (1955).

(5) (a) E. R. Glazier, *J. Org. Chem.*, **27**, 2937, 4397 (1962); (b) K. B. Doifode and M. G. Marathey, *ibid.*, **29**, 2025 (1964); (c) A. W. Fort, *ibid.*, **26**, 765 (1961); (d) P. B. Sollman and R. M. Dodson, *ibid.*, **26**, 4180 (1961)

(6) (a) E. M. Kosower, W. J. Cole, G. S. Wu, D. E. Cardy, and G. Meisters, *ibid.*, **28**, 630 (1963); (b) E. M. Kosower and G. S. Wu, *ibid.*, **28**, 633 (1963).

(7) C. E. Castro, *ibid.*, **26**, 4183 (1961).

(8) (a) D. C. Nonhebel, *J. Chem. Soc.*, 1216 (1963); (b) J. C. Ware and E. F. Borchert, *J. Org. Chem.*, **26**, 2263, 2267 (1961); (c) P. Kovacic and K. E. Davis, *J. Am. Chem. Soc.*, **86**, 427 (1964); (d) D. C. Nonhebel, *Proc. Chem. Soc.*, 307 (1961).

(9) W. W. Kaeding and R. O. Lindblom, U. S. Patent 2,805,263 (1957).

(10) E. M. Kosower, "Molecular Biochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 157; V. S. Butt and M. Hallaway, *Arch. Biochem. Biophys.*, **92**, 24 (1961); F. L. Crane and H. Beinert, *J. Biol. Chem.*, **218**, 717 (1956); B. L. Vallee, "The Enzymes," Vol. III, P. D. Boyer, H. Lardy and K. Myrback, Ed., Academic Press Inc., New York, N. Y., 1960, p. 256; T. Yonetani, *ibid.*, Vol. VIII, 1963, pp. 50–52.

(11) H. Mix, *Z. Physiol. Chem.*, **323**, 173 (1961); **325**, 106 (1961).

(12) J. R. Beckwith and L. P. Hager, *J. Biol. Chem.*, **238**, 3086, 3091 (1963), and references therein.

(13) The nematocidal properties of these substances will be reported elsewhere.

(14) (a) C. E. Castro and W. C. Kray, Jr., *J. Am. Chem. Soc.*, **85**, 2768 (1963). (b) C. E. Castro and R. D. Stephens, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1962, p. 23Q; *J. Am. Chem. Soc.*, **86**, 4358 (1964).

(15) However, the alcohol was oxidized when refluxed neat with cupric bromide—presumably to the bromo acetal.

cupric chloride in methanol did not react with *n*-butyraldehyde dimethyl acetal.

Coupled with the results of previous work,[7] the data of Table I portray four general transformations exemplified by the following specific cases.

β-alkoxylation α-halogenation of carbonyl-conjugated vinyl groups

$$CH_2{=}CHCHO + 2CuBr_2 + 3MeOH \longrightarrow MeOCH_2CHBrCH(OMe)_2 + 2CuBr + HBr + H_2O \quad (1)$$

halogenation of isolated double bonds

$$CH_2{=}CHCH_2OH + 2CuBr_2 \xrightarrow{MeOH} BrCH_2CHBrCH_2OH + 2CuBr \quad (2)$$

trans halogenation of internal acetylenes

$$Ph{\equiv}CPh + 2CuBr_2 \xrightarrow{MeOH} \begin{matrix} Ph & & Br \\ & C{=}C & \\ Br & & Ph \end{matrix} + 2CuBr \quad (3)$$

trihalogenation of terminal acetylenes

$$CH{\equiv}CCH_2OH + 4CuBr_2 \xrightarrow{MeOH} Br_2C{=}CBrCH_2OH + 4CuBr + HBr \quad (4)$$

Although of undefined scope, the clean oxidative halogenation of ethanol (eq. 5) is suggestive of the

$$3CH_3CH_2OH + 6CuBr_2 \longrightarrow Br_2CHCH(OEt)_2 + 6CuBr + 4HBr + H_2O \quad (5)$$

complications encountered with higher alcoholic solvents. Indeed the distilled product previously obtained from the action of cupric bromide on acrylonitrile in refluxing ethanol is *not* the reported[7] ethyl α,α-dibromo-β-ethoxypropionate but rather a mixture of the corresponding monobromide, the α,β-dibromo ester, and (predominantly) dibromoacetaldehyde diethyl acetal.[16]

Kinetics.—Because of the relative ease of the cupric bromide reactions and the quantitative halogenation of both allyl alcohol and propargyl alcohol, the kinetics of those transformations were examined. Both reactions obeyed over-all second-order kinetics. For allyl alcohol a rate expression *independent* of olefin was obtained (eq. 6); in contrast, eq. 7 was valid for the

$$\text{rate} = k_2(CuBr_2)^2 \quad (6)$$

$$\text{rate} = k_2(CuBr_2)(HC{\equiv}CCH_2OH) \quad (7)$$

acetylenic alcohol over a wide range of initial concentrations of reactants. The rate constants are presented in Table II. It should be noted that the reactant concentrations employed for propargyl alcohol correspond (C) to its conversion to a mixture of the dibromo olefin (predominantly) and the tribromide (Table I) and (D) to the production of tribromoallyl alcohol exclusively.

The kinetics of the chlorination of *n*-butyraldehyde with cupric chloride in dimethylformamide with added lithium chloride was examined as a simple case of reaction (eq. 1) uncomplicated by alcoholysis and acetal formation.[17] The reaction showed over-all second-order kinetics with a rate expression of this form.

$$\text{rate} = k_2(CuCl_2)(n\text{-BuCHO}) \quad (8)$$

(16) The above mixture does give an elemental analysis and infrared spectrum corresponding to the previously reported ethyl α,α-dibromo-β-ethoxypropionate.

TABLE II

RATE CONSTANTS FOR THE HALOGENATION OF ALLYL ALCOHOL, PROPARGYL ALCOHOL, AND *n*-BUTYRALDEHYDE

Initial concn.			k_2 (M^{-1} min.$^{-1}$)	Temp., °C.
Allyl alcohol	$CuBr_2$			
A, 0.0716	0.0716		0.37	64
B, 0.1432	0.00716		0.30	64
Propargyl alcohol				
C, 0.0716	0.00716		0.92	64
D, 0.00179	0.00716		0.88	64
Butyraldehyde	$CuCl_2$	LiCl		
E, 0.0358	0.0634	0.0716	0.012	82.5
F, 0.358	0.0088	0.0104	0.014	83.5

Discussion

Halogenation with Cupric Bromide.—Despite the low temperatures employed (64°), it is clear from the kinetics of the allyl alcohol bromination that refluxing solutions of cupric bromide contain a brominating agent other than the copper salt. We attribute the rate expression to the reversible dissociation of cupric bromide[18] to molecular bromine. This interpretation

$$2CuBr_2 \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} 2CuBr + Br_2 \quad (9)$$

is in accord with the observation that bromine could be distilled from a boiling solution of cupric bromide in acetonitrile.[19] Thus, although cupric bromide does not readily decompose in refluxing methanol nor oxidize this alcohol,[20] the presence of an olefinic substrate capable of rapidly consuming trace concentrations of bromine drives the autodecomposition (eq. 9) to completion. Thus, except for propargyl alcohol and presumably other terminal acetylenes, it is not known whether cupric bromide, bromine, or both are the entities responsible for halogenation in this work.[21]

In our hands, the trihalogenation of terminal acetylenes could not be effected with bromine in methanol under a variety of conditions. This transformation (eq. 4) must proceed through the dihalo olefin—most reasonably *via* the following sequence.

$$HC{\equiv}C{-}R \xrightarrow[\text{slow}]{CuBr_2} \begin{matrix} Br & & R \\ & C{=}C & \\ H & & Br \end{matrix} \longrightarrow \begin{matrix} Br & Br \\ | & | \\ H{-}C & C{-}R \\ | & | \\ Br & Br \end{matrix} \longrightarrow HBr + RCBr{=}CBr_2$$

A plausible mechanism for the initial step might entail a halogen transfer from copper to carbon within

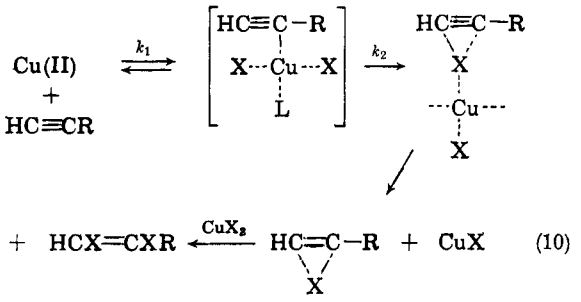
(17) The consumption of $CuCl_2$ by butyraldehyde in methanol slowed greatly after a few minutes. Large amounts of unhalogenated acetal were produced. In dimethylformamide the reaction was slower in the absence of lithium chloride. The chloroaldehyde was obtained in good yield under condition F, Table II.

(18) P. Barret and N. Guenebaut-Thévenot, *Compt. rend.*, **242**, 119 (1956).

(19) J. C. Barnes and D. N. Hume, *Inorg. Chem.*, **2**, 444 (1963).

(20) A 0.1 *M* solution refluxed for 12 hr. afforded at most a 2.1% yield of Cu(I) by titration.

(21) All halogenations with $CuBr_2$ noted in the introduction were carried out in methanol or in higher boiling media; moreover, the products obtained could be explained to result from attack by Br_2.



$$CuX + HCX{=}CXR \xleftarrow{CuX_2} HC{\equiv}C{-}R + CuX \qquad (10)$$

a 1:1 complex[22] (eq. 10). Depicted in this fashion the transition state resembles that advocated for the dehalogenation of vicinal dihalides by Cr(II).[23]

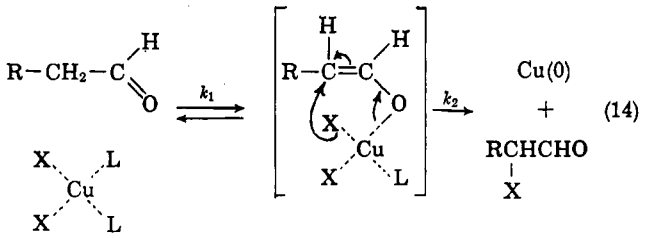
The Cupric Chloride Reactions.—Cupric chloride is not prone to decomposition at low temperatures in solution[24] and none of our data suggests the intermediacy of chlorine. Isolation of large amounts of nonhalogenated β-methoxypropionaldehyde dimethyl acetal from the reaction of cupric chloride with acrolein in methanol (Table I) confirms the suggested[7] sequence (eq. 11, 12, and 13) for these transformations. Thus,

$$MeOH + CH_2{=}CHCHO \xrightarrow{Cu(II)} MeOCH_2CH_2CHO \qquad (11)$$

$$MeOCH_2CH_2CHO + 2CuCl_2 \xrightarrow[\text{rate detg.}]{k_3} MeOCH_2CHClCHO + 2CuCl + HCl \qquad (12)$$

$$MeOCH_2CHClCHO + MeOCH_2CH_2CHO \xrightarrow{MeOH\text{-}HCl} MeOCH_2CHClCH(OMe)_2 + MeOCH_2CH_2CH(OMe)_2 \qquad (13)$$

the β-alkoxyaldehyde may acetalyze before reaction with cupric chloride. In this event, the halogenation ceases since, unlike the cupric bromide reagent,[25] cupric chloride will not halogenate the acetal. The kinetics of the chlorination of *n*-butyraldehyde are consistent with this view. Our data can be rationalized by a mechanism involving a rapid Cu(II)-catalyzed enolization[6b,26] followed by α-halogenation within the enol complex (eq. 14).



$$Cu(0) + Cu(II) \longrightarrow 2Cu(I) \qquad (15)$$

This path accords with that implied to be operative in the aqueous chlorination of acetone.[4] An alternate mechanism that would entail two concomitant one-electron transfers[6b] would not be consonant with the kinetics of this case unless a copper-catalyzed enolization were rate determining.

It should be noted that in addition to those normal biological processes to which this work is relevant,[10] the efficiency of cupric halides to function as wide-range biocides may in part be described to the ability of these salts to halogenate biologically important sites.

Experimental

Materials.—Baker and Adamson reagent grade cupric bromide and cupric chloride were used directly. Drying these substances or running the reactions in the absence of light or in a nitrogen atmosphere had no influence on the course of these reactions. Organic substrates and solvents were freshly distilled or recrystallized before use. The physical constants checked with those of the literature. Propargaldehyde was prepared by the chromic acid oxidation of propargyl alcohol.[27] Butyraldehyde dimethyl acetal was obtained from the aldehyde by treatment with methanolic $CaCl_2$.[28]

Kinetics.—All runs were made in methanol and were at reflux. Samples were withdrawn with a hypodermic syringe and the concentration of Cu(I) was followed by the titrimetric procedure previously described for Cr(II).[14] Runs with allyl alcohol were carried out in a large excess of substrate. Plots of $1/(CuBr_2)$ were linear to 80% completion. Varying initial concentrates of allyl alcohol had no influence on the slope of those plots. The fractional life method applied to $(CuBr_2)$ *vs.* time plots with stoichiometric ratios of halide and propargyl alcohol indicated an over-all order of two for this reaction. At high propargyl alcohol concentrations, pseudo-first-order plots of $\log(CuBr_2)$ *vs.* time were linear. Similarly stoichiometric ratios of reactants (4:1) gave good linear plots of $1/(CuBr_2)$ *vs.* time. The cupric chloride chlorination of *n*-butyraldehyde in dimethylformamide was followed in similar fashion at 83°. Both pseudo-first-order and typical second-order plots were linear.

The Cupric Halide Halogenations.—Some typical transformations are described in detail. In general the purity of all products was assayed by v.p.c. on an Aerograph A-90P fitted with a DC-710 column. Structure was established by elemental analyses, n.m.r. and infrared spectra. Known compounds checked the physical constants reported in the literature. The salient data for other products are reported in Table III.

Acrolein with Cupric Bromide.—In a 1-l. three-neck flask equipped with a mechanical stirrer and a reflux condensor fitted with a calcium chloride tube was placed 89.4 g. (0.4 mole) of cupric bromide in 500 ml. of anhydrous methanol. To this solution was added 6.72 g. (0.12 mole) of freshly distilled acrolein. The mixture was stirred and refluxed for 3 hr. After cooling, cuprous bromide was filtered off and the filtrate was concentrated to a volume of *ca.* 100 ml. *in vacuo*. The residue was taken up in 500 ml. of petroleum ether (b.p. 60–71°) and shaken with 500 ml. of water. Additional cuprous bromide was removed. The total amount of air-dried cuprous bromide was 22.1 g. (64%). The aqueous layer was extracted twice with petroleum ether and the combined extracts were washed successively with 5% $NaHCO_3$ and water and dried over $MgSO_4$. The dried extracts were concentrated and the residue was distilled under argon through a small vacuum-jacketed Vigreux column to yield 10.0 g. of 2-bromo-1,3,3-trimethoxypropane having b.p. 43–45° (0.8 mm.), lit.[7] b.p. 60° (2 mm.). The infrared spectrum showed the acetal doublet at 1070–1185 cm.$^{-1}$. The substance showed one peak on gas chromatography.

Anal. Calcd. for $C_6H_{13}BrO_3$: C, 33.9; H, 6.15; Br, 37.5.; mol. wt., 213.08. Found: C, 33.5; H, 6.1; Br, 37.8; mol. wt., 211.

With Cupric Chloride.—In similar fashion 13.4 g. (0.24 mole) of acrolein and 107.6 g. (0.8 mole) of $CuCl_2$ in 500 ml. of methanol refluxed for 43 hr. provided no precipitate of cuprous chloride. Titrimetric analyses of the solution indicated 3.42 g. of CuCl had been produced. Diethyl ether and petroleum ether were

(22) The consumption of free radicals by cupric halides is rapid: H. E. DeLaMare, J. K. Kochi, and F. F. Rust, *J. Am. Chem. Soc.*, **85**, 1437 (1963), and references therein.

(23) W. C. Kray, Jr., and C. E. Castro, *ibid.*, **86**, 4603 (1964). However, the halogen movement might also be formulated as a $2e^-(Br^+)$ transfer followed by Cu(0) + Cu(II) → Cu(I). We prefer an atom transfer because of the relative lethargy of acetylenes toward electrophiles.

(24) Prolonged refluxing of cupric chloride in *t*-butyl alcohol or methanol afforded no Cu(I)Cl.

(25) Ketals can be halogenated with bromine: A. Marquet, *et al.*, *Bull. soc. chim. France*, 1822 (1961).

(26) As noted earlier, *cf.* ref. 7, crotonaldehyde which does not readily add alcohol and therefore cannot form an enol reacted at best only very slowly.

(27) F. Von Wille and L. Saffer, *Ann.*, **568**, 34 (1950).

(28) L. F. Chelpanova and V. D. Nemirovskii, *Chem. Abstr.*, **54**, 24358a (1960).

TABLE III

ANALYSES AND PHYSICAL PROPERTIES OF PRODUCTS

Product	M.p., °C. (recrystn. solvent)	B.p., °C. (mm.)	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% halogen Calcd.	% halogen Found	N.m.r., p.p.m.[a]	Infrared, cm.$^{-1}$	Comment
$Br_2C{=}CBrCH_2OH$	69.2–69.5 (benzene)		$C_3H_3Br_3O$[b] (295)	12.20	12.51	1.02	1.19	81.4	81.5			
$BrCH{=}CHBrCH_2OH$		60–62 (0.3)										Infrared identical with lit.[c]
$Cl_2C{=}CClCH_2OH$		93 (25)										Infrared and n_D identical with lit.[d]
$CH_3CH_2CHBrCH(OMe)_2$		58 (10)		36.55	36.57	6.60	6.48	40.60	40.34		1060–1150 acetal	
$CH_3CH_2CHClCH(OMe)_2$		48–51 (12)	$C_6H_{13}ClO_2$					23.25	23.33	4.35 d, 3.8 m 3.4 d,[e] 1.83 m 1.05 t	1060–1150 acetal	
$Br_2C{=}CBrCO_2Me$		60 (0.8)	$C_4H_3Br_3O_2$	14.88	15.32	0.93	1.05	74.27	74.22	3.58 s	C=O 1750, C=C 1600, C—O 1250	
$BrCH{=}CHBrCO_2Me$		43 (0.5)	$C_4H_4Br_2O_2$	19.68	19.80	1.64	1.81	65.57	65.46	7.25 s, 3.86 s (ratio 1:3)	C=O 1745, C=C 1590, C—O 1290, 1215	N.m.r. and infrared identical with authentic *trans* olefin[f]
$ClCH{=}CHClCO_2Me$		78 (33)	$C_4H_4Cl_2O_2$	30.98	30.89	2.58	2.55	45.75	45.25	6.79 s, 3.86 s (ratio 1:3)	C=O 1745, C=C 1585, C—O 1320, 1225	
$BrCH_2CHBrCH_2OH$		74–75 (0.6)										Infrared identical with authentic sample
$Br_2C{=}CBrPh$		102 (0.3)	$C_8H_5Br_3$					70.35	70.63	7.19 s	C=C 1595, Ph 755	
$PhCBr{=}CBrPh$	209–210 (CCl_4)											M.m.p. identical with *trans* olefin
$PhCBr{=}CBrCO_2H$	136–136.5 (hexane)											M.m.p. identical with authentic *trans* acid[g]

[a] TMS = 0; s = singlet, d = doublet, t = triplet, m = multiplet. [b] Prepared *via* R. Stoermer and H. Kirchner, *Ber.*, **53**, 1289 (1920). [c] L. F. Hatch, W. E. Blankenstein, and S. H. Chu, *J. Org. Chem.*, **23**, 397 (1958). [d] L. F. Hatch and D. W. McDonald, *J. Am. Chem. Soc.*, **74**, 3328 (1952). [e] Very finely split (OCH_3). [f] Prepared by brominating the ester at room temperature in CCl_4. [g] Found: mol. wt., 297.

employed as extractants in the work-up that was analogous to that for the cupric bromide reaction. Distillation of the concentrated organic residue provided 8.08 g. of 1,1,3-trimethoxypropane, b.p. 53–54° (24 mm.), 149° (760 mm.), $n^{23.5}$D 1.3993 (lit.[29] b.p. 148°, n^{25}D 1.4000). The infrared spectrum showed characteristic acetal and ether linkage in the 1050–1175-cm.$^{-1}$ region. A second fraction, 4.69 g. (104%), of 2-chloro-1,3,3-trimethoxypropane, b.p. 41–43° (0.8 mm.), was obtained. The substance showed one peak on gas chromatography. The infrared spectrum was very similar to that of the corresponding bromide.

Anal. Calcd. for $C_6H_{13}ClO_3$: C, 42.76; H, 7.71; Cl, 21.04. Found: C, 42.98; H, 7.84; Cl, 20.63.

Propargaldehyde with Cupric Bromide.—A mixture of 4.10 g. (0.076 mole) of propargaldehyde and 89.3 g. (0.40 mole) of $CuBr_2$ in 400 ml. of methanol stirred and refluxed for 16 hr. afforded upon work-up 39.2 g. (90%) of cuprous bromide and 14.7 g. (63%) of tribromoacrolein dimethyl acetal having b.p. 89–91° (2 mm.). The infrared spectrum showed C=C at 1580 cm.$^{-1}$ and acetal at 1140–1070 cm.$^{-1}$. The n.m.r. spectrum consisted of two singlets at 5.08 (acetal H) and 3.38 p.p.m. (OCH_3) (tetramethylsilane reference) having peak areas in the approximate ratio of 1:6.

Anal. Calcd. for $C_5H_7Br_3O_2$: C, 17.67; H, 2.06; Br, 70.65. Found: C, 17.96; H, 2.25; Br, 70.30.

A 2,4-dinitrophenylhydrazone had m.p. 235–237°.

With Cupric Chloride.—In similar fashion, 5.40 g. (0.10 mole) of propargaldehyde and 53.8 g. (0.40 mole) of $CuCl_2$ in 175 ml. of methanol yielded, after 6.5 hr. at reflux, 21.9 g. (55%) of cuprous chloride and 5.53 g. (49%) of trichloroacrolein dimethyl acetal having b.p. 58–60° (2.8 mm.). The infrared spectrum showed C=C at 1595 cm.$^{-1}$ and acetal bands at 1150–1060 cm.$^{-1}$. The n.m.r. spectrum consisted of two singlets at 5.26 and 3.35 p.p.m. with peak areas in the ratio of 1:6.

Anal. Calcd. for $C_5H_7Cl_3O_2$: Cl, 51.76. Found: Cl, 51.86.

A 2,4-dinitrophenylhydrazone had m.p. 228.5–229° (lit.[30] m.p. 229–230°).

Anal. Calcd. for $C_9H_5Cl_3N_4O_4$: C, 32.13; H, 1.49. Found: C, 32.23; H, 1.73.

The Oxidative Bromination of Ethanol.—A solution of 44.7 g. (0.2 mole) of cupric bromide in 250 ml. of absolute ethanol refluxed for 49 hr. yielded 20.64 g. (72.4%) of cuprous bromide and 5.9 g. (90%) of 1,1-dibromo-2,2-diethoxyethane having b.p. 71–74° (2.5 mm.), n^{25}D 1.4808 (lit.[31] n_D 1.4802). A small amount of lower boiling material was not investigated. The dibromo acetal emerged as one peak when gas chromatographed and its infrared spectrum exhibited the characteristic acetal 1060–1150-cm.$^{-1}$ bands. The n.m.r. spectrum consisted of doublets at 5.60 and 4.60, a quartet at 3.65, and a triplet at 1.20 p.p.m.

Anal. Calcd. for $C_7H_{12}Br_2O_2$: C, 26.10; H, 4.35. Found: C, 26.07; H, 4.68, 4.52.

Acrylonitrile with Cupric Bromide in Ethanol.—A solution of 5.3 g. (0.10 mole) of acrylonitrile and 89.4 g. (0.4 mole) of cupric bromide in 500 ml. of absolute ethanol stirred and refluxed for 89 hr. yielded 40.1 g. (70%) of cuprous bromide. Distillation of the organic product afforded 7.81 g. of a fraction having b.p. 52–57.5° (0.85 mm.). A very small higher boiling fraction (57–68° at 0.6 mm.) was not investigated. Gas chromatography (10-ft. column, DC-710, 152°) of the major fraction indicated the presence of three constituents. The first peak (19.8 min.) accounted for 24% (1.9 g.) of the mixture. This substance was trapped from the column and found to have an identical infrared spectrum and emergence time with authentic ethyl α-bromo-β-ethoxypropionate. The latter was prepared by treating ethyl α,β-dibromopropionate with 2 moles of sodium ethoxide.[32]

The other, later emerging constituents were not well resolved. The shouldered peaks were trapped and their infrared spectrum accorded with a mixture of 1,1-dibromo-2,2-diethoxyethane and ethyl α,β-dibromopropionate. Gas chromatography of the authentic mixture closely resembled the unknown chromatogram, and spiking the unknown with either constituent shifted the shoulder. The n.m.r. spectrum of the unknown mixture exhibited bands characteristic of the authentic mixture. When ethyl acrylate was the substrate the yield of dibromo ester was greatly increased.

Cupric Bromide with Methanol.—A solution of 22.35 g. (0.10 mole) of cupric bromide in 200 ml. of absolute methanol refluxed for 12 hr. afforded upon titration 0.41 g. of cuprous bromide (2.1%).

Cupric Chloride with Ethanol.—A solution of 53.8 g. (0.40 mole) of cupric chloride in 250 ml. of absolute ethanol refluxed for 25 hr. provided no detectable cuprous chloride by titration.

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A New Synthetic Route to Substituted Mercaptoethylamines. Hydroxyl Displacement by Thiols[1a]

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A catalytic displacement reaction of the hydroxyl group of ethynyl carbinols (I) by thiols has been discovered. The displacement is accompanied by internal hydration of the acetylenic function of I. These developments have made possible a new synthetic approach to substituted mercaptoethylamines (V). The β-keto sulfide II is converted to an oxime III. The protecting benzyl group of III is then removed by reaction with sodium in liquid ammonia to give an α-thiol oxime (IV). This intermediate is reduced with lithium aluminum hydride to yield a substituted mercaptoethylamine V, wherein the thiol group is located on a tertiary carbon atom and the amino group, on a secondary carbon atom.

The synthesis of substituted mercaptoethylamines has been of value in the correlation of structure with the activity of prospective antiradiation agents.[2] Until recently[3] few mercaptoethylamines containing a tertiary thiol group had been synthesized. We now wish to report a new synthetic approach for substituted mercaptoethylamines (V) which contain a tertiary thiol group and an amino group on an adjacent secondary carbon atom. This synthesis involves a novel displacement of a hydroxyl group of an ethynylcarbinol (I) with concomitant transformation of the acetylenic linkage to a methyl ketone function (II). Additional

(1) (a) Presented on sabbatical leave (G. W. S.) at various universities in Australia and New Zealand, 1963, and before the Division of Organic Chemistry at the 148th Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964. (b) In part from the Ph.D. Thesis of B. F. Barnett, Washington State University, June 1963. (c) National Defense Education Act Fellow, 1961–1964.

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(3) F. I. Carroll, J. D. White, and M. E. Wall, *J. Org. Chem.*, **28**, 1236, 1240 (1963).