APPROVAL SHEET

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Studies in Pyran Chemistry: Synthesis of 3-Bromohexatriene-1,3,5

Thesis and abstract approved:

G. Kenneth Hoad
Professor in charge of thesis

Date: May 11, 1949.

STUDIES IN FURAN CHEMISTRY: SYNTHESIS OF 3-BROMOHEXATRIENE-1,3,5

By

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Thesis submitted to the Faculty of the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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The author wishes to express his deep appreciation for the suggestion of this problem and for the valuable guidance offered by Dr. C. Forrest Woods who directed this research.

The author also wishes to express his thanks to Mrs. Mary Aldridge for cheerfully devoting so much effort in analysing the various compounds encountered in this investigation.

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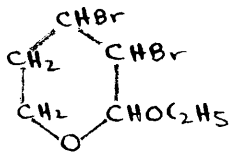
INTRODUCTION

The investigation which is reported in this thesis involved the preparation and reactions of 3,4-dibromo-2-ethoxy tetrahydropyran, (I) and substances derived from it.



I

It was from these reactions that 3-bromohexatriene, $CH_2=CHCBr=CHCH=CH_2$, the open chain analog of bromobenzene was subsequently obtained.

HISTORICAL

The historical portion of this thesis contains a review of the preparation of organic bromides in which there are bromine atoms located α and β to an activating functional group such as the carbonyl or carboxyl and their derivatives; a review of the preparation of vicinal cyclopentane and cyclohexane dibromides and their derivatives; a review of the reactions of these dibromides in which dehydrohalogenation, displacement of bromine or a combination of both occurs, particularly with alkaline reagents; and a review of compounds containing one or more bromine atoms in a highly unsaturated, conjugated system but excluding the aryl bromides which might be considered as related to 3-bromohexatriene.

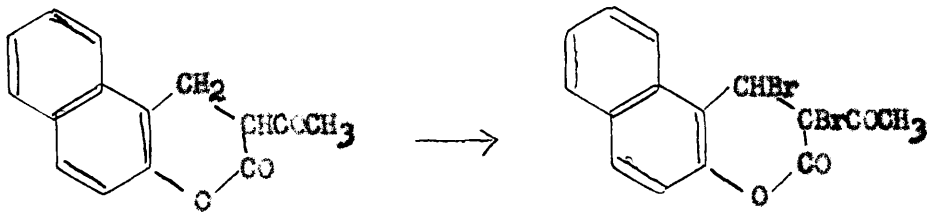
PREPARATIONS

Compounds of the type $-\overset{Br}{\overset{|}{C}}-\overset{Br}{\overset{|}{C}}-A$ where A is considered to be an activating group such as the aldehydo, acetal, keto, carboxyl, ester, etc., have been synthesized in great numbers both for study of themselves and also for purposes of identification. Vicinal dibromo five-member and six-membered non-aromatic ring compounds have also been extensively reported.

In general, the preparation of α,β-dibromides of the types given above consists of the addition of bromine to the corresponding unsaturated compound with variation only in solvent, temperature, concentration, and mode of isolation. Even here the variations are not extreme. The solvents most commonly employed are acetic acid, chloroform, carbon tetrachloride, diethyl ether, carbon disulfide, petroleum ether, etc. On occasion liquid bromine or bromine vapor was used in the absence of any solvent. The reported temperatures were generally room temperature or lower although sometimes the reaction was conducted in boiling solvents. Concentrations of the reactants are not critical and frequently the valwe chosen was for the convenience of temperature control. The mode of isolation depends primarily on whether the product is crystalline or liquid.

Variations from this general procedure include:

(1) Bromination of a saturated precursor. Bartsch [1] prepared an α,β-dibromo derivative (III) from 3-acetyl-5, 6-benzocoumarin (II) with bromine in acetic acid at 100° C.



II III

Franchimont[2] brominated succinic acid to obtain dibromo-succinic acid.

(2) Bromination of an unsaturated compound using N-bromo-succinimide or similar reagent[3]. Howton[4] prepared 1,2-dibromocyclohexane as a by-product through the action of N-bromosuccinimide on cyclohexene.

(3) Oxidation of an alcohol to an acid or ketone, or of an aldehyde to an acid. In this manner α,β-dibromo-propionic acid[5,6,7,8,9] α,β-dibromodiethyl ketone,[10] α,β-dibromobensal acetone,[11] ethyl β,γ-dibromo-α-keto butyrate[12] and α-chloro,α,β-dibromo butyric acid[13] have been prepared. By chromic oxide oxidation α,β-dibromoadipic acid was obtained from 3,4-dibromo-2,2-dihydroxycyclohexane.[14]

(4) Treatment of a diamine with nitrosyl bromide. α,β-Dibromo propionic acid was obtained this way from α,β-diamino propionic acid.[15]

(5) Action of diazo methane on an aldehyde. This unusual method was employed to yield α,β-dibromo ethyl methyl ketone from α,β-dibromoprionaldehyde.[16]

(6) Use of hydrobromic acid. The preparation of α,β-dibromo-

butyric acid is claimed by shaking $CH_3C{\equiv}CCOOH$ with aqueous hydrogen bromide[17].

The α,β-dibromo compounds reviewed in this thesis have been divided according to activating group and presented in tables. Within each table, where a large number of compounds were reported, a further subdivision into type has been made for the sake of clarity. Often only one reference has been selected for each compound where several were available.

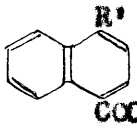
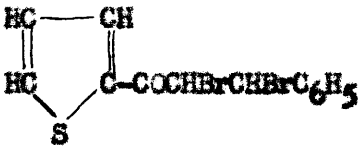
Table I is a general compilation of α,β-dibromoaldehydes and acetals, containing no other activating functional group in the molecule, which have been reported in the literature.

TABLE I

Compound	Properties	Reference
$CH_2BrCHBrCHO$	$b_{0.3}$ 45	16
$CH_2BrCHBrCH(OC_2H_5)_2$	b_{22} -127-129°	18
$CH_2BrCHBrCH(OCH_3)_2$	b_{15} 108°	18
$CH_2BrCClBrCHO$	b_{55} 105° d^{20} 2.17	19
$CH_3CHBrCHBrCHO$	liquid b_{14} 75-82°	20
$CH_2BrCBr(CH_3)CH(OC_2H_5)_2$	b_{35} 137°	21
$CH_3CHBrCHBrCH(OC_2H_5)_2$	b_{13} 113-114 (sl. decompn.)	20
$CH_3CHBrCClBrCHO$	oil not distillable; hydrate m 45-50°	13,22
$CH_2ClCHBrCClBrCHO$	oil	23
$CH_2BrCHBrCBr_2CHO$ (falsely reported) or $CH_2BrCHBrCCHBrCH_2Br$	m 63-4° b_{13} 145-7° according to	24 25
$CH_3CH_2CHBrC(CH_3)BrCHO$	unstable liquid	26
$CH_3CHBrCHBrC(CH_3)BrCH(OH)OC_2H_5$	b_{2-3} 130°	27
$CH_3CHBrCBr_2CHO$	patent for prep.	13,28,29,30
$CH_2BrCHBrCHBrCH(OC_2H_5)_2$	b 92-3° at very low pressure	31
$C_6H_5CHBrCHBrCHO$	m 45-48°	32
$C_6H_5CHBrCClBrCHO$	non-dist. oil	33

Table II is a general compilation of types of α,β-dibromo-ketones reported in the literature. Where only one of its type was reported, it has been listed separately. Cyclic ketones or those in which another functional group is immediately involved have been incorporated in a subsequent table.

TABLE II

Compound	Reference
RCOCHBrCHBrR' (Where R' is H or an alkyl group and R is an alkyl group)	34,35,36,37
RCOCBrXCBrR'R'' (Where X is halogen and R' and R'' are alkyl groups)	38,39
ArCOCR'BrCR''BrR (Where Ar is phenyl or substituted phenyl and R, R', and R'' are H or alkyl)	8, 40-51 inclusive
ArCR'BrCR''BrCOR (Where Ar is phenyl or substituted phenyl, R is alkyl and R' and R'' are alkyl or hydrogen)	8,40, 52-68 inclusive
ArCR'BrCR''BrCOAr' (Where Ar and Ar' are phenyl or substituted phenyl groups and R' and R'' are hydrogen or alkyl groups)	74*,75*, 69-119 inclusive
NapCOCHBrCHBrAr (Where Nap is naphthyl or substituted naphthyl and Ar is phenyl or substituted phenyl)	120-126 inclusive
$(ArCHBrCHBr)_2CO$ (Where Ar is phenyl or substituted phenyl)	127-134 inclusive
ArCOCBr(Ar')CHBr(Ar'') (Where Ar, Ar', and Ar'' are phenyl or substituted phenyl groups)	135
 COCHBrCHBrR (Where R is H or CH_3 and R' is H, CH_3, or halogen)	136
	137

* -∝-alkyl

TABLE II (Continued)

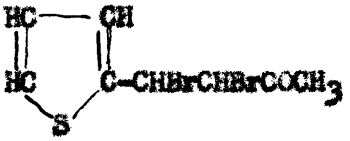
Compound	Reference
$C_6H_5COCHBrCHBrCCl_3$	138
$CH_3COCHBrC(CH_3)BrCH_3$	139
$CH_2BrCHBrCOCH_2Br$	140
	141
o-(HO)C_6H_4COCHBrCHBr(1)$C_{10}H_6OCH_3$(2)	142
2,4,6$(CH_3)_3C_6H_2COCBr(CH_2Br)OCH_3$	143
$C_6H_5CHBrCHBrCHBrCHBrCOCH_3$	144
3:4$CH_2O_2C_6H_3CHBrCBr(CH_3)COCHBrCHBrC_6H_3CH_2O_2$(3:4)	145
$C_6H_5CHBrCHBrCOCCl$(=NOH)	146
$C_6H_5CHBrCHBrCOCH_2COCOOC_2H_5$	147
$CH_3C(NH_2)$=CH(CN)COCHBrCHBrC_6H_5	148
$C_6H_5CHBrCHBrCOCH_2CH(C_6H_5)PO_3H_2$	149
p-$CH_3OC_6H_4CHBrCHBrCOCH$=CHCH=CHC_6H_5	150
C_6H_5CH=CBrCOCBr$_2$CHBrC_6H_5	151
C_6H_5CH=CBrCOCHBrCHBrC_6H_5	151
$C_6H_5CHBrCBr_2COCHBrCHBrC_6H_5$	151
$(CH_3)_2CBrCHBrCOCHBrCBr(CH_3)_2$	139
$(CH_3)_2CBrCHBrCOCHBrCHBrCH(CH_3)_2$	152
C_6H_5CH=CHCOCHBrCHBrC_6H_5	153

TABLE II (Continued)

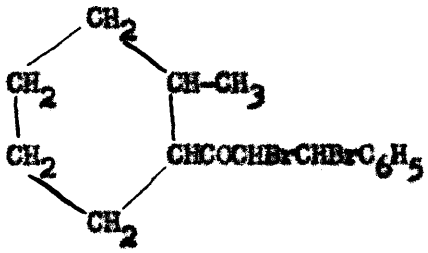
Compound	Reference
$C_6H_4(CHBr)_4COCHBrCBr(CH_3)_2$	152
$C_6H_5CHBrCHBrCHBrCHBrCOC_6H_5$	154
$(C_6H_5)_2CHCBr(CH_2Br)COC_6H_5$	155
$(ArCHBrCHBrCO)_2CBr_2$) Where Ar is phenyl or $(ArCHBrCHBrCO)_2CHBr$) substituted phenyl.	156
$ArCHBrCHBrCOCHBrCHBrAr'$ (Where Ar and Ar' are phenyl or substituted phenyl)	157
	158

Table III is a general compilation of types of simple monobasic α,β-dibromoacids and esters. The arrangement of this table is similar to that of Table II in that unique compounds are listed separately. Compounds in which the bromine atoms are activated by an additional functional group are excluded.

TABLE III

Compound	Reference
RCHBrCHBrCOOR' (Where R and R' are H or an alkyl group)	5,8,9 159-183 inclusive
RCBrXCHBrCOOR' (Where X is halogen and R and R' are H or alkyl groups)	184,185
RCHBrCBrXCOOR' (Where X is halogen and R and R' are H or alkyl groups)	186,187,188
RCBrXCBrX'COOR' (Where X and X' are halogen and R and R' are H or an alkyl group)	169,189
$RCHBrCHBrCONH_2$ (R is H or an alkyl group)	173,190,191
RCHBrCBrR'COOR'' (Where R and R'' are H or alkyl groups and R' is an alkyl group)	171, 192-201 inclusive
RR'CBrCHBrCOOR'' (Where R and R' are alkyl groups and R'' is H or an alkyl group.)	202,203
RCR'BrCR''BrCONHAr (Where R,R', and R'' are H or alkyl and Ar is phenyl or substituted phenyl group)	116,204,205,206,207
RR'CBrCBrR''COOR''' (Where R,R', and R'' are alkyl groups and R''' is H or an alkyl group)	9
ArCHBrCHBrCOOR (Where Ar is phenyl or a substituted phenyl group and R is H or an alkyl group)	208-279 inclusive
ArCHBrCBrXCOOR (Where Ar is phenyl or substituted phenyl, X is halogen, and R is H or an alkyl group)	280,281,282,283,284

TABLE III (Continued)

Compound	Reference
ArCBrICHBrCOOR (Where Ar is phenyl or substituted phenyl group, X is halogen, and R is H or an alkyl group)	284,285
ArCBrCBr(Ar')COOR (Where Ar and Ar' are phenyl or substituted phenyl and R is H or alkyl)	286
ArCHBrCBrRCOOR' (Where Ar is phenyl or substituted phenyl, R is alkyl, and R' is H or an alkyl group)	287,288,289,290
$ArCHBrCHBrCON(R)_2$ (Where Ar is phenyl or substituted phenyl and R is alkyl group)	291,292
NapCHBrCHBrCOOH (Where Nap is a napthyl or substituted naphthyl group)	293,294,295,296,297
$CHBr_2C(CH_3)BrCOOH$	298
$(CH_3)_2CBrCBr(C_6H_5)COOH$	299
$CH_2BrCBr(2,5\text{-}Me_2C_6H_3)COOH$	300
$(CH_3)_2CBrCHBrCOCl$	301
$CH_3CHBrCHBrCHBrCHBrCOOH$	302
$CH_3CHBrCBr(C_2H_5)CONHCONH_2$	303
$CH_3CHBrCHBrCONHCONH_2$	304
$CH_3CHBrCBr(C_2H_5)CONH_2$	305
$(NO_2CBr_2)_2CBrCBr(NO_2)COOH$	306
$C_2H_5OCHBrCBr(CH_3)COOH$	307
$p\text{-}CH_3OC_6H_4CHBrCHBrCONHC_6H_5$	308

TABLE III (Continued)

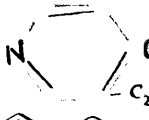
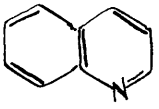
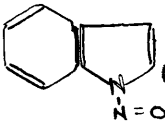
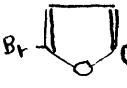
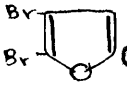
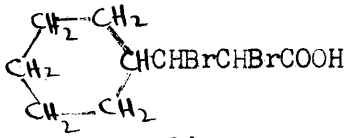
Compound	Reference
$C_6H_5CHBrCHBrCONHCONH_2$	304
$C_6H_5CHBrCHBrCOCl$	309
$C_6H_5CHBrCHBrCHBrCOOR$	302,310,311,312,313,314
$C_6H_5CH{=}CBrCHBrCHBrCOOH(CH_3)$	311,315
$C_6H_5CH{=}CHCHBrCHBrCOOCH_3$	311,316
$C_6H_5CH(OH)CHBrCHBrCOOH(?)$	317
$C_6H_5CHBrCBr(OH)COOC_2H_5$	318
 CHBrCHBrCOOH	319
 CHCHBrCHBrCOOH	320
 CHBrCHBrCOOH	319,321
 CHBrCHBrCOOH	322
 CHBrCHBrCOOH	323
 $CHBrCHBrCOOC_2H_5$	324
 $CHBrCHBrCOOC_2H_5$	324

TABLE III (Continued)

Compound	Reference
	325
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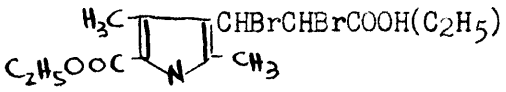
	327

Table IV lists α,β-dibromocarbonyl compounds and acids which because of their complex structure or the presence of more than one functional group in the molecule could not be included in previous tables.

TABLE IV

Compound	Reference
RCHBrCHBrCN (Where R is H, alkyl, phenyl or phenyl substituted group)	173,328,329,330
p-$CH_3OC_6H_4CHBrCBr(p\text{-}ClC_6H_4)CN$	331
ROOCCHBrCHBrCOOR' (Where R and R' are H or alkyl groups)	332-342 inclusive
$ROOCCBr(CBrR')CH_2COOR$ (Where R and R' are H or alkyl groups)	343,344,345,346,347
$ROOCCHBrCHBr(CR'R'')_nCOOR$ (Where R, R' and R'' are H or alkyl groups and n=1 to 3)	14, 348-354 inclusive
Substituted α,β -dibromoglutaric acids and esters)	349, 355-363 inclusive
ROOCCHBrCBrR'COOR	364,365,366,367
ArCOCHBrCHBrCOOR (Where Ar is phenyl or substituted phenyl and R is H or alkyl)	368-377 inclusive
ArCHBrCHBrCOCOOH (Where Ar is phenyl or substituted phenyl)	233, 378-383 inclusive
$ArCHBrCBr(COOH)_2$ (Where Ar is phenyl or substituted phenyl)	384
ArNHCOCHBrCHBrCOOH (Where Ar is phenyl or substituted phenyl)	385,386
α-NapCHBrCHBrCOCOOH	387
ArNHCOCHBrCHBrCONHAr (Where Ar is phenyl or substituted phenyl)	388-394 inclusive
$C_6H_5N(CH_3)COCHBrCHBrCON(CH_3)C_6H_5$	395

TABLE IV (Continued)

Compound	Reference
$C_6H_5COCHBrCHBrCOC_6H_5$	392
$CH_3OOCCHBrCBr(C_6H_5)COOC_2H_5$	396
$CH_3COCHBrCHBrCOOH$	397
$(CH_3OOCCHBrCHBr)_2CO$	398
HOOCCHBrCBrXCOOH	399,400
CHOCHBrCHBrCHO	401
$(CH_3O)_2CHCHBrCHBrCH(OCH_3)_2$	401
ClOCCClBrCHBrCOCl	400
HOOCCHBrCHBrCOCl	402
$HOOCCHBrCHBrCONH_2$	333
$CH_2BrCBr(COOH)CH_2COOH$	366,403
$COOHCH_2(CHBr)_3COOH$	404
$(CHBrCHBrCHBrCOOH)_2$	405
$ROOC(CHBr)_4COOR$	406,407,408
$COORCBr(CH_2Br)CH_2CHBrCOOR$	409
$CH_3CHBrCBr(COOH)CH_2CH_2COOH$	410
$(CH_3)_2CHCH_2CHBrCBr(COOH)CH_2CH_2COOH$	360
$C_2H_5OOCCHBrCBr(COOC_2H_5)CH_2COOC_2H_5$	411
$C_2H_5OOCCHBrCHBrCHOHCHOHCOOC_2H_5$	412
$(C_2H_5OOC)_2CBrCHBrCH(COOC_2H_5)_2$	413
$(CH_3)C_2H_5OOCCHBrCHBrCH{=}CHCOC_2H_5(CH_3)$	412,414

TABLE IV (Continued)

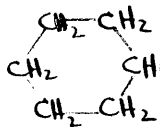
Compound	Reference
$COOHCH_2CBr(COOH)CHBrCOOH$(plus triethyl ester)	349,415
$CCl_3COCHBrCHBrCOOH$	416
$C_6H_5CHBrCBr(COOH)CH_2CH_2COOH$	417
$C_6H_5CHBrCHBrCHBrCBr(COOH)_2$	316
$CH_3COCBr(CHBrC_6H_5)COOC_2H_5$	418
$C_6H_5CHBrCBr(COC_6H_5)CH_2COOH$	419
$[C_6H_5(CHBr)_6]_2CO$	420
$HOOCCBr{=}CBrCHBrCOOH$	421
4,6(m-$OCH_3C_6H_4CHBrCHBrCO)_2$-m-resorcinol dimethyl ether	422
$[(p\text{-}C_6H_5CHBrCHBrCO)C_6H_4]_2O$	423
$[4\text{-}(p\text{-}OCH_3C_6H_4CHBrCHBrCO)C_6H_4]_2O$	423
$[p\text{-}(C_6H_5CHBrCHBrCO)C_6H_4]_2S$	423
$p\text{-}C_6H_5CHBrCHBrCOC_6H_4SC_6H_5$	423
2,4,6-$(CH_3)_3C_6H_2COCBr_2CBr(CH_3)COC_6H_2(CH_3)_3$-2,4,6	424
$p\text{-}CH_3OC_6H_4CBr(CH_2COOH)CHBrCOOH$	425
2,4,6-$(CH_3)_3C_6H_2COCBr(CH_3)CHBrCOC_6H_2(CH_3)_3$2,4,6	426
$CH_2BrCHBrCOCOOC_2H_5$	12
 $CHBrC(C_6H_5)BrCN$	427
 $CHCBrCHBrCOOH$	428

Table V is a compilation of α,β-dibromides of simple cyclopentane and cyclohexane derivatives which have been reported. Compounds with atoms other than carbon in the ring have been incorporated in Table VI.

TABLE V

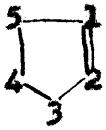
Compound	Reference
Derivatives of Cyclopentane:	
1,2-dibromo	429
1,2,3,4-tetrabromo	430
1,2-dibromo-1,2-dimethyl	431
2,3-dibrom-1,1,2-trimethyl	432,433
2,3-dibromo-1-phenyl	434
1,2-dibromo, carboxylic acid-(1)	435
1,2,2-tribromo-carboxylic acid-(1)	436
2,3-dibromo-1,1,2-trimethyl-carboxylic acid(3)	437
2,3-dibromo-dicarboxylic acid-(1,2)	351
1,2-dibromo,2,6-dimethyl carboxylic acid-(1)	438
Derivatives of Cyclopentenes:	
	
3,4-dibromo	439
3,4,5-dibromo	440
3,4-dibrom-1,2-diphenyl	441

TABLE V (Continued)

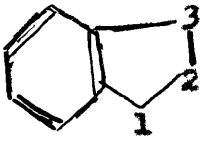
Compound	Reference
Derivatives of Hydrindanes:	
	
1,2-dibromo	442
1,2-dibromo-1,3-dibenzyl	443
2,3-dibromo-1-benzhydryl	444
1,2-dibromo-1-methyl-2-carboxylic acid	445
2,3-dibromo-1-methyl-3-carboxylic acid	446
1,2-dibromo-5-hydroxy	447
2,3-dibromo-3-phenyl	448
1,2,3-tribromo	449
Derivatives of Cyclohexanes:	
1,2-dibromo	450,451
1,1,2-tribromo	452,453
1,2,4-tribromo	454
1,1,2,2-tetrabromo	455
1,2,3,4-tetrabromo	456
1,2,4,5-tetrabromo	457
1,2,3,4,5,6-hexabromo	458,459
1-chloro-1,2-dibromo	460
1,2,3,4,5,6-hexabromo-1-chloro	461
1,1',2,3,4,5,6-heptabromo	461
1,2-dibromo-1-nitro	462

TABLE V (Continued)

Compound	Reference
Derivatives of Cyclohexanes: (cont'd)	
1,2-dibromo-1-benzyl	463,464
1,2-dibromo-1-methyl	465
2,3-dibromo-1-methyl	466
3,4-dibromo-1-methyl	467
1,2,4-tribromo-1-methyl	468
1,2,3,4,5,6-hexabromo-1-methyl	469
1,2-dibromo-1,2-dimethyl	470,471
4,5-dibromo-1,3-dimethyl	472
2,3,5,6-tetrabromo-1,1-dimethyl	473
1,2-dibromo-1,4-dimethyl	465
3,4-dibromo-1,1,4-trimethyl	474,475
1,2-dibromo-3-methyl	476
1,2-dibromo-3-phenyl	476
3,4-dibromo-1-propyl	477
1,2-dibromo-4,5-dibenzoyl	478
4-chloro-3,4-dibromo-1-methyl	479
1,2-dibromo-4,5-di-p-chlorobenzoyl	480
1,2-dibromo-1,2-dimethyl-4,5-di-p-chlorobenzoyl	480
1,2-dibromo-1,2-dimethyl-4,5-di-p-tolyl	480
1,2-dibromo-4,5-di-p-tolyl	480
2,3-dibromo-1-methyl-1-carbethoxy-3-isopropyl	481

TABLE V (Continued)

Compound	Reference
Derivatives of Cyclohexanes: (cont'd)	
1,2-dibromo-carboxylic acid-(1)	482
1,2,3,4-tetrabromo-carboxylic acid-(1)	483
1,2-dibromo-2-methyl-carboxylic acid-(1)	484
1,2-dibromo-4-methyl-cyclohexane-carboxylic acid-(1)	485
3,4-dibromo-dicarboxylic acid-(1,2)	486
1,2-dibromo-3-ethoxy-carboxylic acid-(1)	482
4,5-dibromo-dicarboxylic acid-(1,3)	487
1,2-dibromo-dicarboxylic acid-(1,4)	488
1,2-dibromo-dicarboxylic acid-(1,2)	489
2,3-dibromo-dicarboxylic acid-(1,4)	490
1,2,4,5-tetrabrom-dicarboxylic acid-(1,4)	490
2,3,5,6-tetrabrom-dicarboxylic acid-(1,4)	490
2,3-dibromo-2-methyl-carboxylic acid-(1)	491
4,5-dibromo-2-methyl-carboxylic acid-(1)	491
5,6-dibromo-2-methyl-carboxylic acid-(1)	491
1,6-dibromo-3-methyl-carboxylic acid-(1)	492
ethyl-1,2-dibromo-1-acetate	493
1,2-dibromo-3-phenyl-4-benzoyl	494
Derivatives of Cyclohexenes:	

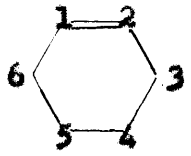


TABLE V (Continued)

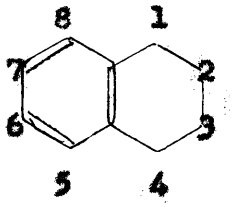
Compound	Reference
Derivatives of Cyclohexenes: (cont'd)	
1,2-dibromo	495
4,5-dibromo	496
2,4-dichloro-3,4,5-dibromo-6,6-dimethyl	497
3,4-dibromo	498
3,4-dibromo-dicarboxylic acid-(1,4)	490
4,5-dibromo-dicarboxylic acid(1,4)	488
5,6-dibromo-dicarboxylic acid-(1,4)	490
2,3-dibromo	499
1,2-dibromo-4-methyl	500
Derivatives of Tetralin:	
	
1,2-dibromo	501,502
2,3-dibromo	503,504,505
1,2,3,4-tetrabrom	506
1,2,3,4,5,6-hexabrom	507
12,-dibromo-1-carboxylic acid	508
2,3-dibromo-1-carboxylic acid	508
1,2-dibromo-2-carboxylic acid	509
2,3-dibromo-2-carboxylic acid	509

TABLE V (Continued)

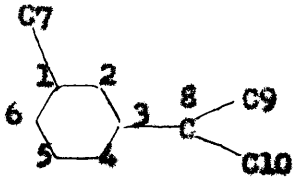
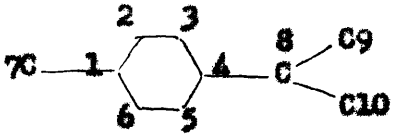
Compound	Reference
Derivatives of Tetralin: (cont'd)	
3,4-dibromo-2-carboxylic acid	509
Derivatives of m-Menthane:	
	
2,3-dibromo	510
3,4-dibromo	475
5,6-dibromo	511
1,2,8,9-tetrabromo	512
Derivatives of p-menthane:	
	
1,2-dibromo	513,514
3,4-dibromo	515
1,2,8-tribromo	516
1,3,4,7-tetrabromo	517
1,2,4,8-tetrabromo	518
1,2,8,9-tetrabromo	519
1,2,8,9,9-pentabromo	520

TABLE V (Continued)

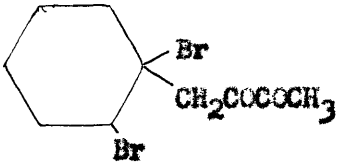
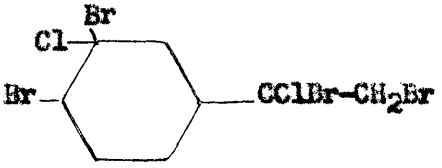
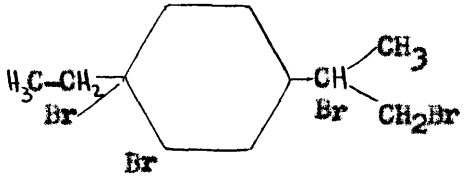
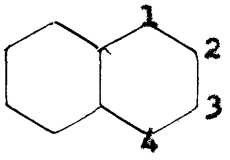
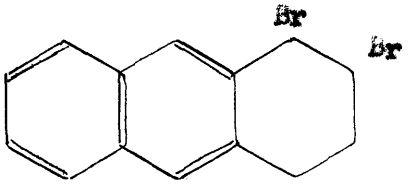
Compound	Reference
Derivatives of p-menthane: (cont'd)	
1,2,3,4-tetrabromo	521
2,3,8,9-tetrabromo	522
	523
	524
	525
	
1,2-dibromo	526
2,3-dibromo	526
	527

Table VI is a general compilation of vicinal dibromides of five- and six-membered non-aromatic rings containing only carbon or carbon and oxygen in the ring which because of their complicated nature or because of the influence of an activating functional group were not included in Table V. Furan derivatives are excluded as well as compounds too complex to be related to 2-ethoxy-3, 4-dibromotetrahydropyran.

TABLE VI

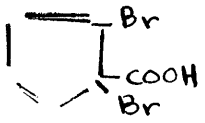
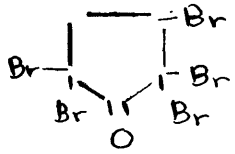
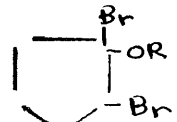
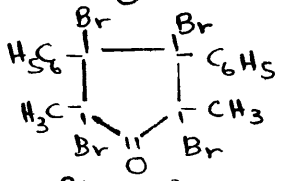
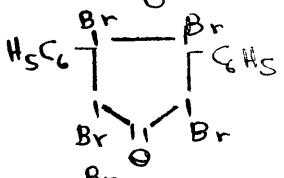
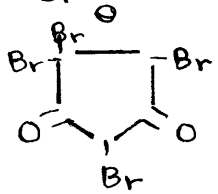
Compound	Reference
	528, 529
	530
	531
	532
	533
	534

TABLE VI (Continued)

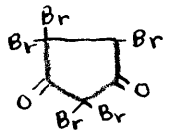
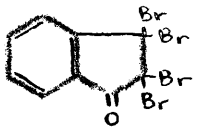
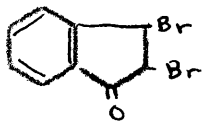
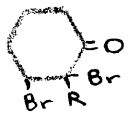
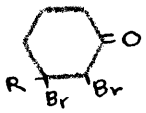
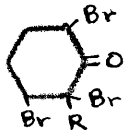
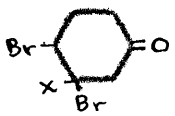
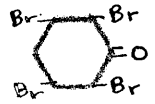
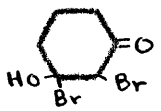
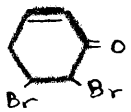
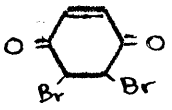
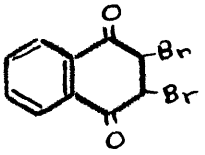
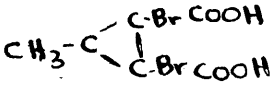
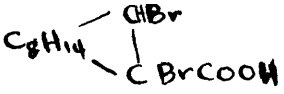
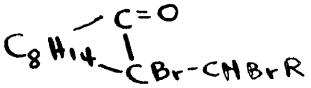
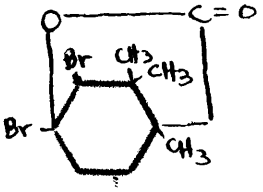
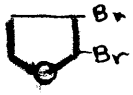
Compound	Reference
	534
	535
	448, 536, 537
	538–545 incl. 555
	538, 539, 546, 547
	542
	548
	549
	550
	549

TABLE VI (Continued)

Compound	Reference
	551-554 inclusive
	556-560 inclusive
	561
	562,563,564
	565,566,567
	568
	569
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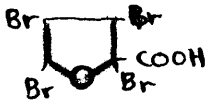
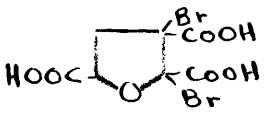
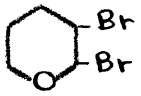
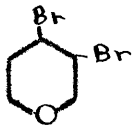
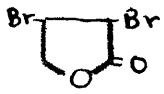
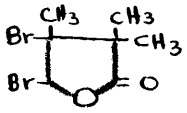
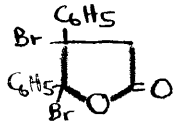
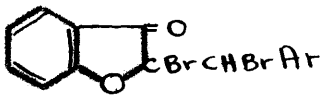
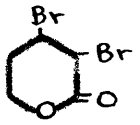
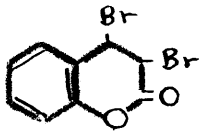
	572,573
	574

TABLE VI (Continued)

Compound	Reference
	576
	577
	578
	579
	580
	581
	582,583,584
	585
	586-595 inclusive

Non-aromatic conjugated polyenes containing one or more bromine atoms with at least one bromine atom attached to an olefinic carbon atom are not too common. Some of these reported in the literature are of uncertain structure.

One general method of preparation of the above substances is the reaction of a polybromo compound with an alkaline reagent. Thus 1-bromobutadiene-1,3, CH_2=CHCH=CHBr, was prepared by the action of powdered potassium hydroxide on 1,4-dibromobutene-2, CH_2BrCH=CHCH_2Br, at 75°,[596,597,616] and in a similar manner with the same reagent the 1,2-dibromide obtained by brominating butadiene, CH_2BrCHBrCH=CH_2, gave 2-bromobutadiene-1,3, CH_2=CBrCH=CH_2.[596] Upon treatment with alcoholic potassium hydroxide, the 3,4-dibromide obtained by adding bromine to phenylbutadiene, C_6H_5CH=CHCHBrCH_2Br, yielded 1-phenyl-4-bromobutadiene-1,3, C_6H_5CH=CHCH=CHBr.[612] Bromoprene dibromide, CH_2BrCBr=CHCH_2Br treated with alcoholic potassium hydroxide and the product steam-distilled gave 1,2-dibromobutadiene-1,3.[606] Lespieu and Prevost[603] mixed alcoholic solutions of erythrene-tetrabromide and sodium ethoxide in the cold to obtain 2,3-dibromobutadiene-1,3, CH_2=CBrCBr=CH_2. An impure compound believed by Prevost[605] to be 3,4-dibromohexadiene-2,4, CH_3CH=CBrCBr=CHCH_3 was obtained by the action of sodium ethoxide on 2,3,4,5-tetrabromohexane.

There are a few examples of preparing bromotriene compounds

from dibromodienes by the action of alkaline reagents. Farmer[601] treated what he thought was γ,δ-dibromo-$\overset{\alpha,\epsilon}{\triangle}$-hexadiene, $CH_2=CH_2CHBrCHBrCH=CH_2$, with sodium ethoxide in ethanol and reported he obtained some γ-bromohexatriene, $CH_2=CHCH=CBrCH=CH_2$. This product polymerised completely in twenty-four hours. Again he treated what he thought was cis-α,β-dibromo-$\overset{\alpha,\epsilon}{\triangle}$-hexadiene, $CH_2=CHCH=CHCHBrCH_2Br$, with alcoholic sodium ethoxide and obtained what he called cis-α (or β)-bromohexatriene which polymerized extensively in 24 hours. Starting with the so-called trans isomer, Farmer obtained what he called trans α (or β)-bromohexatriene. This material polymerised completely in two hours.[601]

Other bromopolyenes have been obtained by treating an alcoholic or acetylenic precursor with an agent such as PBr_3 or HBr. Thus adding hydrogen bromide to $(CH_3)_2C(OH)C\equiv CH$ gave 3-methyl-1-bromobutadiene-1,3, $CH_2=C(CH_3)CH=CH_2Br$.[599] Bromoprene, $CH_2=CBrCH=CH_2$, was obtained by treating vinyl acetylene, $CH\equiv CCH=CH_2$, with hydrogen bromide in the presence of cuprous bromide.[598] Passing vinylacetylene into liquid hydrogen bromide yielded 4-bromobutadiene-1,2, $CH_2BrCH=C=CH_2$.[598] By treating 2,5-dimethylhexine-3-diol-2,5 with hydrogen bromide or phosphorous tribromide without solvent in the cold, or phosphorous tribromide

in benzene the compound 3,4-dibromo-2,5-dimethylhexadiene-2,4 is obtained.[607,608,617] The action of phosphorous tribromide on tetramethyl-butinediol yields a product of which one fraction is probably $(CH_3)_2C{=}CBrCBr{=}C(CH_3)_2$.[608]

The bromopolyene may also be prepared by direct addition of bromine to a highly unsaturated precursor. Thus dimethyldiacetylene yields 2,3,4,5-tetrabrom-hexadiene-2,4, $CH_3CBr{=}CBrCBr{=}CBrCH_3$.[609] By adding bromine to 2-methylpentene-3-ol-2, $CH_3CH{=}CHCOH(CH_3)CH_3$, and distilling the product, 3-brom-2-methyl pentadiene-2,4, $CH_2{=}CHCBr{=}C(CH_3)_2$, is formed.[600] Bergmann obtained what he thought was $C(CH_3)Br{=}C{=}CH_2$ by bromination of isoprene.[618] From tetradecadiine-6,8, $CH_3\overline{(CH_2)}_4C{\equiv}CC{\equiv}C\overline{(CH_2)}_4CH_3$ by bromination was obtained 6,7,8,9-tetrabromotetradecadiene-6,8, $CH_3\overline{(CH_2)}_4CBr{=}CBrCBr{=}CBr\overline{(CH_2)}_4CH_3$.[610] The rearrangement of 1,4-dibromobutyne-2 to $CH_2{=}CBrCBr{=}CH_2$ on standing in air[604] represents another preparation of a conjugated bromopolyene.

Table VII presents some compounds containing one or more bromine atoms in a highly unsaturated, conjugated system in which at least one of the bromine atoms is bonded to an unsaturated carbon atom.

TABLE VII

Compound	Reference
$CHBr=CHCH=CH_2$	596,597
$CH_2=CHCBr=CH_2$	598
$CHBr=CHC(CH_3)=CH_2$	599
$(CH_3)_2C=CBrCH=CH_2$	600
$CH_2=CHCH=CBrCH=CH_2$	601
$CH_2=CHCH=CHCBr=CH_2$ or $CH_2=CHCH=CHCH=CHBr$	601
$CH_2=C(CH_3)CH=CBrCH=CH_2$	602
$CH_2=CBrCBr=CH_2$	603,604
$CH_3CH=CBrCBr=CH_2$	605
$CH_3CH=CBrCBr=CHCH_3$	605
$CH_2=CHCBr=CHBr$	606
$(CH_3)_2C=CBrCBr=C(CH_3)_2$	607,608
$CH_3CBr=CBrCBr=CBrCH_3$	605,609
$CH_3\underline{(CH_2)}_4CBr=CBrCBr=CBr\underline{(CH_2)}_4CH_3$	610
Mixture of: $(CH_3)_2CBrCH=CBrCH=CH_2$ and $(CH_3)_2C=CHCBr=CHCH_2Br$	602

TABLE VII (Continued)

Compound	Reference
$CHBr{=}CBrCBr{=}CBrCBr{=}CHBr$	611
$C_6H_5CH{=}CHCH{=}CHBr$	612
$C_6H_5CBr{=}CHCH{=}CHC_6H_5$	613
$ArCBr{=}CBrCBr{=}CBrAr$	613, 614
$C_6H_5CBr{=}CBrCBr{=}CBrCH_3$	615

B. Reactions*

Any review of the α,β-dibromoacids, carbonyls, and cyclic compounds already presented here should mention the characteristic instability of these substances. Many of the solids melt with decomposition and the liquids readily decompose in contact with the air or upon distillation, even at reduced pressure. In particular, the cyclic compounds with bromine α and β to a carbonyl are markedly unstable.

The dibromides considered in the historical portion of this thesis very often exist in two or more stereoisomeric forms. A great number of isomers were reported and the instances where only one isomer was discovered probably represent unusual conditions or those where separation of isomers was not attempted.

The treatment of 2-ethoxy-3,4-dibromotetrahydropyran with alkaline reagents led to (1) elimination of hydrogen bromide, (2) displacement of bromine, and (3) concurrent elimination of hydrogen bromide and displacement of bromine. Hence the historical portion of this thesis will review similar reactions of α,β-dibromocarbonyls, α,β-dibromoacids and 1,2-dibromocyclopentanes and cyclohexanes.

The elimination of hydrogen bromide from an α,β-dibromoacid to yield an acid of the structure, RCH=CBr-COOH, occurs with various reagents. More stringent conditions or stronger alkaline reagents result in the loss of two molecules of hydrogen bromide and

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*There are a great number of examples of each reaction reviewed here so that only representative references have been given in most cases.

formation of an acetylenic acid. The ease of removal of hydrogen bromide also varies with the structure of the acid. Certain acids, moreover, decarboxylate when treated with alkaline reagents.

Bachmann[183] treated a series of aliphatic α,β-dibromoacids with boiling pyridine and isolated both the α-bromo unsaturated acid (IV) and the bromolefin (V) which resulted from decarboxylation.

$$\underset{}{RCHBrCHBrCOOH} \longrightarrow \underset{IV}{RCH = CBrCOOH} + \underset{V}{RCH = CHBr}$$

With hydrogen atoms in both the α and β positions the yield of bromolefin was very small but replacing the hydrogens with halogen or alkyl groups greatly increased the yield of bromolefin.[9] When 20% aqueous sodium carbonate was used with acids of the type, RCHBrCHBrCOOH, the product was almost exclusively α-bromo unsaturated acid. With most acids pyridine gave greater amounts of bromolefin than did aqueous sodium carbonate.

Other workers found that warming α,β-dibromobutyric acid with pyridine led to α-bromocrotonic acid.[165,619,620] Other amines such as quinoline, quinaldine, and diethylaniline were used by Marvel[621,622] in the formation of α-bromoacrylates from various esters of α,β-dibromopropionic acid. Diethylaniline has also been used to obtain the α-bromo unsaturated acid from a β-aryl-α,β-dibromoacid.[623,624] Secondary amines also may be used to split out hydrogen bromide. Diethylamine,[414,625] piperidine,[626,627] and monoethylaniline[628] have been successfully employed. Similarly, alcoholic ammonia has been used to remove one mole of hydrogen bromide from an α,β-dibromoacid.[629]

The action of stronger bases frequently brings about the loss of two moles of hydrogen bromide with the formation of an acetylenic acid (VII).

$$RCHBrCHBrCOOH \longrightarrow RC \equiv CCOOH \quad VII$$

This has been observed using alcoholic potassium hydroxide for β-aryl-α,β-dibromopropionic acids in a large number of cases.[239, 247,257,274,295,630] Symmetrical dibromosuccinic acid yields acetylenedicarboxylic acid with alcoholic potassium hydroxide, aqueous alkali, or tertiary amines.[631,632,633] α,β-Dibromopropionic acid yields acetylene with alcoholic potassium hydroxide:[189]

$$CH_2BrCHBrCOOH \rightarrow HC \equiv CH$$

The effect of more drastic basic treatment was demonstrated by formation of a substituted propiolic acid by action of hot alcoholic potassium hydroxide upon an α,β-dibromoacid which had yielded only a monobrom derivative (IV) when treated with cold alcoholic KOH or with a tertiary amine.[238,623,634] Another illustration is the formation of an unsaturated bromoacid by treatment with cold sodium carbonate solution upon an α,β-dibromoacid which had yielded an acetylene compound with alcoholic potassium hydroxide.[635] However, alcoholic potassium hydroxide has been frequently employed as a reagent when removal of only one mole of hydrogen bromide from an acid[149,238,288,382,412,636] or nitrile[330] is desired. This emphasizes the effect of duration or temperature of treatment with a particular reagent. Another

illustration is the action of dimethylaniline upon $p\text{-}CH_3OC_6H_4CHBrCHBrCOOC_2H_5$ which gives rise to either a monobromo ester or a substituted propiolic acid ester depending upon the time of heating the reagents. This work was done by Hariharan and Sudborough[623] who also studied the influence of temperature, concentration of alkali, and concentration of alcohol in the dehydrobromination of α,β -dibromoacids with alcoholic potassium hydroxide.

Aqueous alkali hydroxide* is generally used to effect displacement of bromine but on occasion is similar to alcoholic potassium hydroxide in removing one mole of hydrogen bromide.[212,224,247,382,621,631,637,638]

Another reagent commonly employed in a simple dehydrohalogenation reaction is alkali acetate in either acetic acid or an alcohol. The product is an unsaturated α -bromoacid (IV).[149,311,379,639] In aqueous medium sodium acetate may also bring about decarboxylation.[269,271,290,369,376,379,639]

The structure of the acid affects the ease of hydrogen bromide removal. With acids of the type ArCHBrCHBrCOCOOH (where Ar is phenyl or substituted phenyl) very mild conditions suffice to remove one mole of HBr. Reimer[379,381,382,639] found that shaking or short heating with water or alcohol yields an acid of the type ArCH=CBrCOCOOH. Bases readily cause decarboxylation.[233,380]

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*Ingold, Oliver and Thorpe[349] have discussed reduction accompanying hydrogen bromide removal in action of alkali upon α,β -dibromoacids.

In almost every instance where an acid is of the type, RCHBrCHBrCOOH, i.e., possesses hydrogen atoms on both the α and β carbon atoms, the product when dehydrohalogenation occurs is the unsaturated α-bromoacid. However, when the α-carbon is devoid of hydrogen, it is possible to obtain a β-bromoderivative. Thus ethyl-α-methyl-3-nitrocinnamate dibromide (VIII) yields α-methyl-β-bromo-3-nitrocinnamic acid (IX) with alcoholic potassium hydroxide.[288]

$$\underset{\text{VIII}}{m\text{-}O_2NC_6H_4CHBrC(CH_3)BrCOOH} \longrightarrow \underset{\text{IX}}{m\text{-}O_2NC_6H_4CBr{=}C(CH_3)COOH}$$

There are other examples of unsaturated β-bromoderivatives arising from similar α-substituted acids.[172,635,641,642] Substitution of the α-hydrogen of an α,β-dibromoaldehyde or ketone will also give rise to a β-bromoderivative when hydrogen bromide is removed.[21]

Sodium alcoholates, although more often employed in displacement of bromine reactions, can be used to remove hydrogen bromide from α,β-dibromoacids. The product of the reaction is again an α-bromo unsaturated acid of the type (IV).[378,627,643]

The reactions of α,β-dibromoaldehydes with alkaline reagents are limited in number and extent undoubtedly because of the complications possible due to the aldehyde groups' reactivity.

However, even if the alkaline reagent reacts with the carbonyl group, it may be possible to effect halogen removal. Thus when $CH_3CHBrCClBrCHO$ was reacted with 2,4-dichlorophenylhydrazine the product was the substituted hydrazone of β-bromo-α-keto-butyraldehyde.[644] Likewise the phenylhydrazone of α-bromocrotonaldehyde was obtained by treating α,β-dibromobutanal with phenylhydrazine.[645] Harries and Krutzfeld[646] reported $CHOCHBrCHBrCHO$ split out hydrogen bromide with phenylhydrazine. In acetals the reactivity of the aldehyde groups is masked sufficiently to permit dehydrohalogenation reactions without complications. The diethyl acetal of α,β-dibromoisobutyraldehyde (X) when refluxed with sodium ethoxide yielded β-bromo-α-methyl acraldehyde diethyl acetal (XI).[21]

$$CH_2BrCBr(CH_3)CH(OC_2H_5)_2 \longrightarrow CHBr{=}C(CH_3)CH(OC_2H_5)_2$$

X XI

Viquier[647] used aqueous sodium acetate at 150-170° to obtain α-bromocrotonaldehyde from α,β-dibromobutyraldehyde.

The loss of hydrogen bromide from α,β-dibromoketones is roughly similar to the dehydrobromination of α,β-dibromoacids although fewer instances are reported in the literature. The product is an α-bromo unsaturated ketone (XII).

$$RCHBrCHBrCOR' \longrightarrow RCR{=}CBrCOR'$$

XII

The alkaline reagents employed include sodium alkoxides, alcoholic

or aqueous alkali, amines, and alkali acetate.

Weygand[105] produced compounds of type (XII) where R and R' were aryl groups by the action of sodium ethylate, potassium acetate, and pyridine upon various chalcone dibromides. Aqueous alkali was used by Darzens[648] to obtain a ketone of type (XII). Alkali acetate has been used by Barnes[79,111,113,115,649] in a number of instances, and by other workers[32,151,650,651,652] to obtain α-bromo unsaturated ketones. Other investigators have used pyridine,[112,117,122,653] hot aqueous sodium hydroxide,[100] alcoholic KOH,[38] and sodium methoxide[117] to remove one mole of hydrogen bromide from an α,β-dibromoketone.

Compounds of the type RCOCHBrCHBrCOR' (XIII) and RCOCHBrCHBrCOOR' (XIV) have also been treated with alkaline reagents with a consequent loss of hydrogen bromide. Sodium acetate with a compound of type (XIII) yields a monobromoderivative of the type, RCOCH=CBrCOR'.[393,424] The same derivative is obtained using sodium benzoate.[424] A monobrom compound is also obtained from (XIV) with potassium acetate or sodium methoxide but here there is some question as to whether the bromine removed came from a position adjacent to the carbonyl or to the carboxyl group.[376] The product was considered to be of the type RCOCBr=CHCOOH by Bogert and Ritter.[369,377]

The displacement of bromine without concurrent dehydrobromination from α,β-dibromoacids and carbonyls has been effected by a variety of reagents. Even alcoholic potassium hydroxide was

found by Farmer and Ingold[624] to give α,β-dihydroxyglutaric acid XV, in small amount, starting with α,β-dibromoglutaric acid XVI, although aqueous sodium carbonate

$$\underset{\text{XVI}}{COOHCH_2CHBrCHBrCOOH} \longrightarrow \underset{\text{XV}}{COOHCH_2CHOHCHOHCOOH}$$

gave a much better yield of (XVI). Very mild reagents, such as water or alcohol will displace the bromine from an α,β-dibromo-β-aryl acid to yield, respectively, an α-bromo-β-hydroxy and an α-bromo-β-alkoxy acid.[142,247,378,654,655] With compounds of the type RCHBrCHBrCOCOOH even mild conditions seem to give loss of hydrogen bromide rather than displacement of bromine.[378] Ketones of the type ArCHBrCHBrCOAr yield α-bromo-β-alkoxy derivatives on heating with alcohols.[656,657]

However, sodium methoxide can be used to prepare the ethyl ester of α-bromo-β-methoxy butyric acid from ethyl α,β-dibromo-butyrate at 0° C.[658] Other aliphatic α-bromo-β-methoxy acids are prepared similarly.[352,659]

Amines may replace both bromines in α,β-dibromoketones or acids to yield α,β-diamino compounds particularly when milder conditions are employed.[292,643,660,661] Dibromosuccinic acid has been observed to undergo double displacement with various amines.[662,663] Under certain conditions only the α-bromine atom may be replaced.[664] in α,β-dibromoketones.

Ketones of the type ArCOCHBrCHBrAr' give the β-alkoxy

derivative either when treated with alcoholic alkali solution containing chloroform (to increase solubility of the ketone)[120] or upon heating with the corresponding alcohol.[117,656,665]

Water or aqueous alkaline reagents, if mild conditions are used, sometimes lead to displacement of the β-bromine by hydroxyl in α,β-dibromoacids and ketones[192,195,412,624,662,666,667,668] or even displacement of both bromines.[669,670]

The action of alkaline reagents upon α,β-dibromocarbonyls and acids frequently results in a product which has undergone displacement of one bromine atom by some nucleophilic group and loss of the other bromine atom as hydrogen bromide. For example, with sodium ethoxide α,β-dibromobutyric acid yields α-methoxycrotonic acid (XVII).[637,671]

$$CH_3CHBrCHBrCOOH \longrightarrow CH_3CH{=}C(OCH_3)COOH$$
XVII

Likewise the ester (XVIII) yields ethoxycitraconic acid (XIX) with sodium ethoxide.[672]

$$CH_3CBr(COOC_2H_5)CHBrCOOC_2H_5 \longrightarrow CH_3C(COOC_2H_5){=}C(OC_2H_5)COOC_2H_5$$
XVIII XIX

Another example is the use of sodium methoxide to prepare β-methoxyacrylic acid from α,β-dibromopropionic acid.[638]

(Acids of the type ArCHBrCHBrCOOH apparently do not undergo the concurrent dehydrobromination and displacement reaction with

alkaline reagents.)

With α,β-dibromoketones the product of a concurrent displacement and dehydrobromination reaction with alkaline reagents has the β-bromine displaced. For example with alcoholic potassium hydroxide the following reaction occurs:[673]

$$C_6H_5CHBrCHBrCOCH_3 \rightarrow C_6H_5CH(OC_2H_5)=CHCOCH_3$$

With ketones of the type ArCHBrCHBrCOAr', sodium alkoxides have frequently been employed to give products of the type ArC(OR)=CHCOAr'.[69,110,112,113,117,120]

Other reagents that can give rise to a concurrent displacement and dehydrohalogenation reaction are aqueous alkali, alcoholic alkali, alcoholic ammonia, and amines. The product of alcoholic potassium hydroxide with α,β-dibromoketones is of the type ArCOC=C(OR)Ar'.[113,114,115,650,673] Aqueous alkali, and sometimes aqueous alcoholic alkali, yield a product of the type ArCOC=C(OH)Ar from α,β-dibromoketones.[111,113,115] Aqueous sodium carbonate gives a similar result[419] as the following equation shows:

$$C_6H_5CHBrCBr(COC_6H_5)CH_2COOH \rightarrow C_6H_5C(OH)=C(COC_6H_5)CH_2COOH$$

Lutz[392,393,394,674] found diketones of the type ArCOCHBrCHBrCOAr' with sodium alkoxides gave a product of the type ArCOC(OR)=CHCOAr', with aqueous alkali or alcoholic sodium acetate gave ArCOC(OH)=CHCOAr' and with amines in alcohol gave ArCOC(NHR)=CHCOAr'. Reichert and Moldenhauer[664] found that methylamine acting on

α,β-dibromopropiophenone gave an α-amino compound, $C_6H_5COC(NHCH_3)=CH_2$.

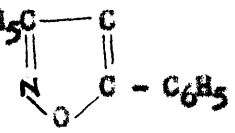
With sodium alkoxides or alcoholic potassium hydroxide compounds of the type ArCOCHBrCHBrCOOR yield compounds of the type $ArCOCH=C(OR')COOR$.[376]

In addition to the concurrent displacement-dehydrobromination reactions presented so far there are very similar reactions occurring with α,β-dibromoketones in which the displacement of one bromine atom is accomplished by a nucleophilic group within the molecule to give a rearranged product. Isoxazole formation and rearrangement of a chalcone dibromide to a coumaranone or a flavone are typical examples.

When the oxime of phenyl α,β-dibromoethyl phenyl ketone (XX) is heated above its melting point, 3,5-diphenylisoxazole (XXI) is formed[116]

$$C_6H_5CHBrCHBrC(=NOH)C_6H_5 \longrightarrow$$

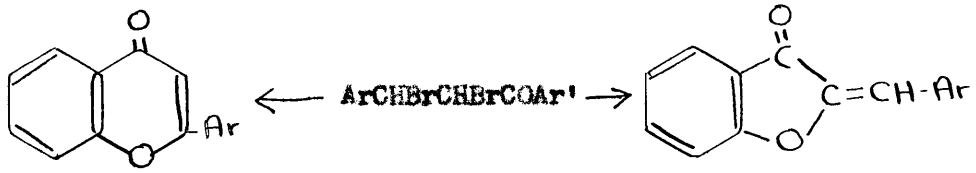
XX



XXI

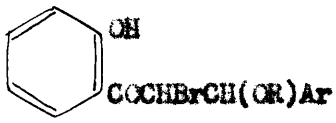
Similarly, oximes of dibromoketones, with the general formula, $ArCHBrCHBrC(=NOH)Ar'$, when treated with alcoholic potassium hydroxide yield 3-Ar'-5-Ar-isoxazoles.[79,117,649]

Chalcone dibromides, ArCHBrCHBrCOAr', when treated with alkaline reagents, particularly alcoholic potassium hydroxide, can give rise to a flavone (XXII) or a coumaranone (XXIII)[100]



XXII XXIII

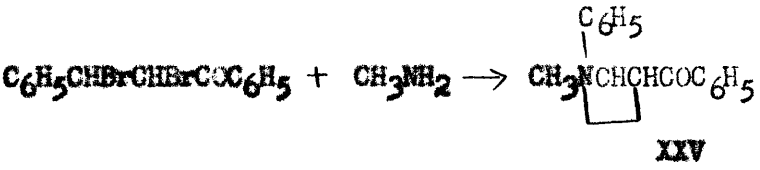
Obviously the phenyl nucleus adjacent to the carbonyl group must be substituted in the ortho position by a hydroxyl group, or derivative of the hydroxyl group. Such a structure may lead either to a coumaranone by reaction of the hydroxyl group with the α-bromine atom or to a flavone by interaction with the β-bromine atom. Von Kostaneki[77,78,85,86,90,92] observed that cold aqueous alkali tended to favor flavone formation while hot aqueous alkali gave the courmaranone. Wheeler, perhaps the most extensive worker in this field,[117,118,120,676,677] explained coumaranone formation as occurring only when the chalcone dibromide yielded a β-alkoxy derivative (XXIV). Failing the formation of this



XXIV

intermediate (XXIV), which is favored by hot alcohol as a solvent, a flavone is formed. Thus the flavone preparation proceeds through an intermediate of the type ArCOC(Br)=CHAr' which is favored by cold alcohol as a solvent or by pyridine.[117,120,678]

An interesting reaction is that reported by Cromwell and Caughlan[679] in which one mole of amine displaced both atoms of bromine in an α,β-dibromoketone to give a substituted imine product (XXV).



XXV

The reactions of vicinal dibromocyclopentanes and dibromocyclohexanes with alkaline reagents resemble those previously described for α,β-dibromocarbonyls and α,β-dibromoacids in that dehydrobromination, displacement of bromine, or both may occur.

Dehydrobromination is illustrated by the action of alcoholic potassium hydroxide on 1,2-dibromocyclopentane to yield cyclopentadiene.[467] Cyclohexadiene-1,3 was obtained from 1,2-dibromocyclohexane on treatment with sodium acetate and acetic acid at 180°C.[680] although dilute alkali hydroxide at 150°C. or aqueous silver oxide at 100°C. are without action.[680] The dibromo gives a small amount of cyclohexadiene with alcoholic potassium hydroxide[681] and a greater amount with quinoline.[682]

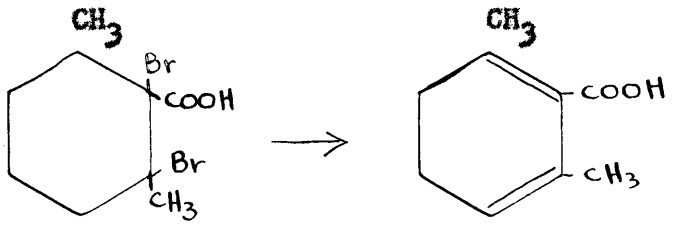
Substituted vicinal dibromocyclopentanes and dibromocyclohexanes are dehydrohalogenated similarly. On heating 1,2-dibromo-1,2-dimethylcyclohexane with quinoline at 190°C. 1,2-dimethylcyclohexadiene-2,6 is yielded.[470] Other alkyl substituted 1,2-dibromocyclohexanes give similar results with quinoline,[465] alcoholic potassium hydroxide,[496,511] or sodium ethoxide.[683] Domnin used dry potassium hydroxide at 200°C. with

1-methyl-3,4-dibromocyclohexane to obtain 1-methylcyclohexadiene-1,3.[500] The loss of two moles of hydrogen bromide has been observed also with vicinal dibromomenthanes using alcoholic potassium hydroxide[510,514,515,684] or sodium acetate in acetic acid.[514]

In general 1,2-dibromocyclohexanes unsubstituted by an activating group are more resistant to simple dehydrobromination than the carbonyls and acids previously discussed. Activation due to the benzene ring probably accounts for the removal of one mole of hydrogen bromide from 1,2-dibromotetralin using a base as weak as magnesium carbonate. The product was reported to be 2-bromo-Δ^{1}-dihydronaphthalene.[502] Using secondary aliphatic amines von Braun and Kirschbaum[501] obtained a monobrom dihydronaphthalene (of undetermined structure) from 1,2-dibromotetralin. Sodium ethoxide gave naphthalene from the dibromotetralin.[501] More highly halogenated cyclohexanes or dibromocyclohexenes yield benzene or benzene derivatives on treatment with alkaline reagents.

The presence of a carboxyl group attached to the cyclohexane ring probably assists the dehydrobromination reaction. Thus 1,2-dibromo-1,3-dimethylcyclohexane carboxylic acid-2 (XXVI) yields 1,3-dimethyl- 1,3-cyclohexadiene carboxylic acid-2 (XXVII)

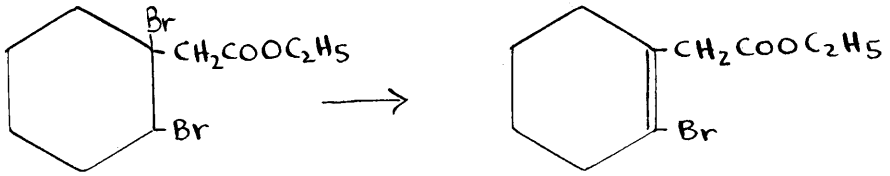
on merely being warmed with 0.1N alkali.[438] Others have observed similar examples of increased ease of dehydrobromination



XXVI XXVII

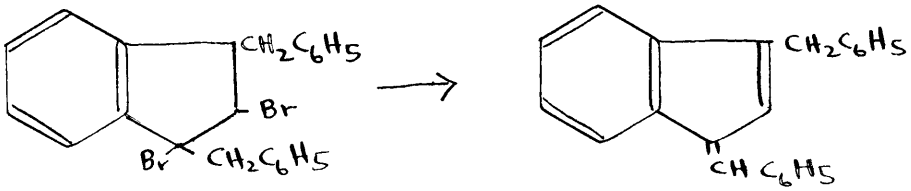
due to activation of the benzene ring.[508,509] or carboxyl group[490,492,509,685] directly attached to the cyclopentane or cyclohexane ring.

Loss of only one mole of hydrogen bromide was observed by Baker[493] when ethyl 1,2-dibromocyclohexane-1-acetate (XXVIII) was treated with sodiomalonic ester to yield ethyl 2-bromo-Δ^{1}-cyclohexeneacetate (XXIX)



XXVIII XXIX

Dehydrobromination with one hydrogen atom coming from a substituent on the ring was observed when 1,3-dibenzyl-1,2-dibromoindane (XXX) yielded 1-benzyl-3-benzal indene (XXXI) with pyridine[443]



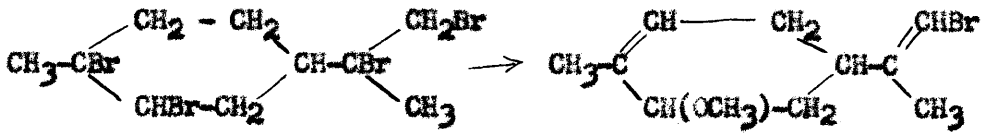
XXX XXXI

When 1-chlor-1,2-dibromocyclohexane was treated with quinoline a mixture of chlorobenzene, 1-chloro-1-cyclohexene, and 1-chloro-1, 5-cyclohexadiene resulted.[686]

Displacement of bromine without concurrent dehydrobromination on treatment with alkaline reagents apparently occurs only with those vicinal dibromocyclopentanes and -cyclohexanes which possess an activating group attached to the ring. Thus 1,2-dibromocyclohexanecarboxylic acid-(1) yields cyclohexandiol-1, 2-carboxylic acid-1 on warming with aqueous sodium carbonate[687] and 1,2-dibromotetralin gives 1,2-dihydroxytetralin on warming with aqueous potassium carbonate.[688] Activation of a benzene ring seems to be indicated again by the reaction of 1,2-dibromotetralin with one percent sodium methoxide or magnesium carbonate in methanol to yield 1-methoxy-2-bromotetralin.[502] Also 1,2-dibromotetralin on short heating with potassium acetate in acetic acid yields 1-acetoxy-2-bromotetralin,[501,688] and aqueous acetone gives 1-hydroxy-2-bromotetralin.[501,688] Short heating of 1,2-dibromohydrindene with magnesium carbonate in aqueous acetone produces 1-hydroxy-2-bromohydrindene.[689] Pyridine and alcohol with 1,2-dibromohydrinene give 1-ethoxy-2-bromoindane.[499] There are many other examples of displacement reactions occurring with vicinal dibromocyclohexanes due to activation of a benzene ring[509] or carboxyl group[509] attached to the cyclopentane or cyclohexane ring.

Likewise 2,3-dibromotetralin yields 2,3-dihydroxytetralin with potassium carbonate solution.[503] 1,2-Dibromocyclopentane gives cyclopentandiol-1,2 on heating with potassium carbonate solution.[690]

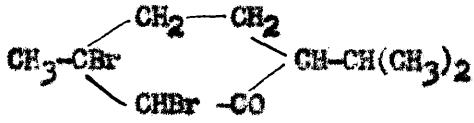
Concurrent dehydrobromination and displacement of bromine with 1,2-dibromocyclohexane occurs on treatment with sodium ethoxide. The product is 1-ethoxy-2-cyclohexene.[691] With sodiomalonic ester the diethyl ester of 2-cyclohexenylmalonate is obtained from 1,2-dibromocyclohexane.[683,692] Alcoholic potassium hydroxide yields chiefly 3-ethoxycyclohexene-1.[496,681] Treatment of 1,2-dibromocyclohexane with alcoholic ammonia under pressure at 100-120° gives a mixture of amino cyclohexene-1 and 3-ethoxy-cyclohexene-1.[693] With dimethylamine at 110-115° 3-dimethylamino-cyclohexene-1 is obtained.[694] An analogous reaction occurs with trimethylamine.[695] Alkyl substituted dibromocyclohexanes behave similarly with alkaline reagents. 1-Ethyl-1,2-dibromocyclohexane with sodium ethoxide yields 2-ethyl-3-ethoxy-1-cyclohexene.[683] Treatment with methylamine at 115-120° converts 1,2-dibromo-1-benzylcyclohexane into 6-methylamino-1-benzyl-cyclohexene-1.[464] The reaction with dimethylamine is analogous.[464] 1,2,8,9-Tetrabromo-p-menthane (XXXII) on warming with sodium methoxide in methanol yields bromo-carveol methyl ether (XXXIII)[696]



XXXII XXXIII

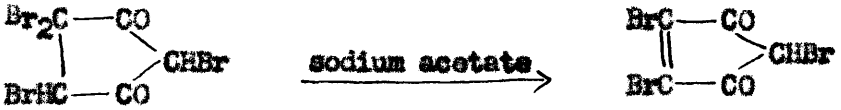
The vicinal dibromocyclopentanones and dibromocyclohexanones when treated with alkaline reagents may undergo dehydrobromination,

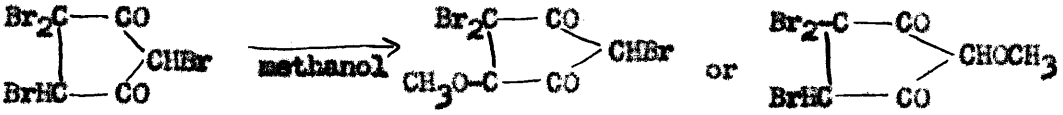
displacement of bromine, or both reactions concurrently. Simple dehydrohalogenation is not often encountered with cyclohexanones since the presence of halogen atoms and a carbonyl group in the same ring makes formation of a phenol[547,548] or, in the case of a diketone, formation of a quinone the preferred course of reaction[553,556,559, 697,698,699]. However, Wallach[539] obtained a monobromo-p-menthenone, of undetermined structure, from 1,2-dibromo-p-menthanone-3 (XXXIV) using potassium hydroxide. (A compound of structure similar to XXXIV will, however, undergo cleavage with potassium hydroxide on occasion to yield a debrominated, saturated aliphatic acid[539].)



XXXIV

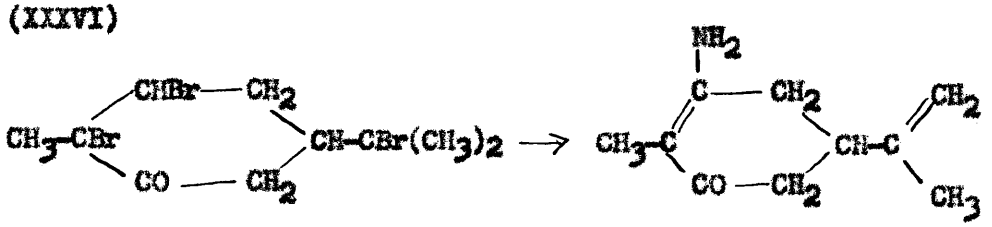
As the following equations show, cyclopentandiones have been known to undergo both dehydrobromination and displacement of bromine[534]





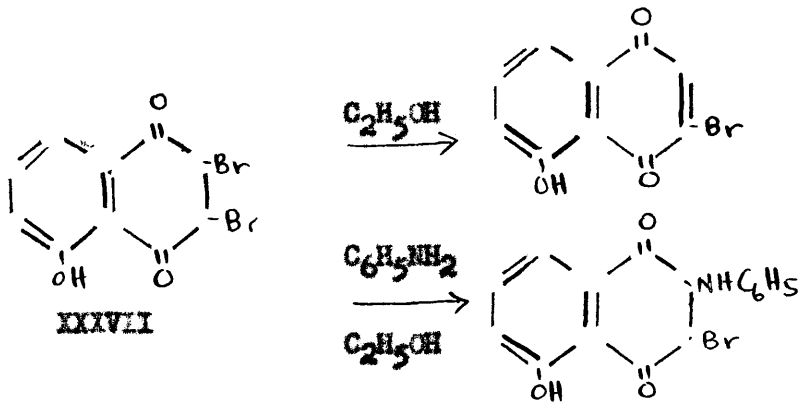
What appears to be a concurrent dehydrobromination-displacement of bromine reaction as reported by Wallach[700] who reacted tribromotetrahydrocarvone (XXXV) with ammoniated amyl

alcohol to obtain a compound, $C_{10}H_{15}OK$, which the writer believes may be (XXXVI)



XXXV XXXVI

Working with 2,3-dibromojuglone (XXXVII) Thomson[560] observed a dehydrobromination reaction by using boiling ethanol and a displacement reaction by employing aniline in boiling ethanol as the following equations show:

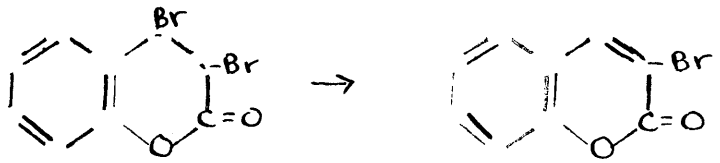


XXXVII

With vicinal dibromides of oxygen heterocyclic compounds straightforward reactions, such as most of those reviewed here so far have been, are not common with alkaline reagents. Ring cleavage and rearrangements frequently occur. Thus (substituted) coumarin dibromide (XXXVIII) may form a (substituted) coumarilic acid (XXXIX) with hot alcoholic potassium hydroxide.[588,591,593]

XXXVIII XXXIX

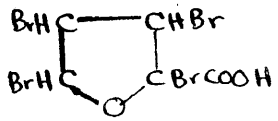
Milder conditions, e.g., cold alcoholic alkali will merely remove one mole of hydrogen bromide to form a monobrom coumarin (XL)[591,593,701]



XL

The coumarin dibromides, incidentally, are quite unstable.[588,591,593,702]

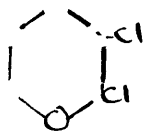
2,3,4,5-Tetrabromotetrahydropyromucic acid (XLI) on being treated with concentrated alcoholic potassium hydroxide yields a mixture containing 5-bromopyromucic acid,



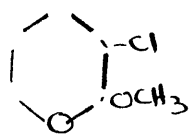
XLI

3,4-dibromopyromucic acid and 3,5-dibromopyromucic acid.[574]

The reactions of dihalogenated dihydropyrans and tetrahydropyrans with alkaline reagents are very limited in number. All of the work reported in the literature is confined to 2,3-dihalides or derivatives. Paul[703] prepared 2,3-dichlorotetrahydropyran (XLII) and treated it with sodium methoxide in methanol to obtain 2-methoxy-3-chlorotetrahydropyran (XLIII). He also reacted XLII with Grignard reagents to prepare 2-alkyl-3-chlorotetrahydropyrans.[703]

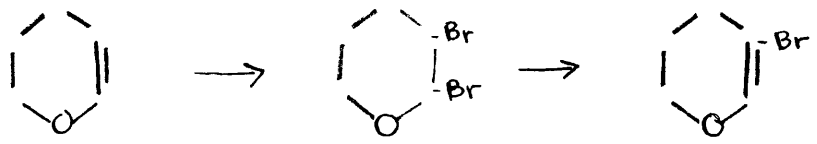


XLII



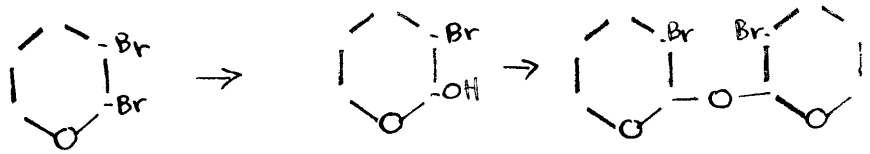
XLIII

Earlier, Paul[577,704] brominated dihydropyran (XLIV) at -17°C. in ether solution to obtain unstable 2,3-dibromotetrahydropyran (XLV) which he treated with quinoline to yield 3-bromodihydropyran (XLVI). When 2,3-dibromotetrahydropyran was added dropwise to lead



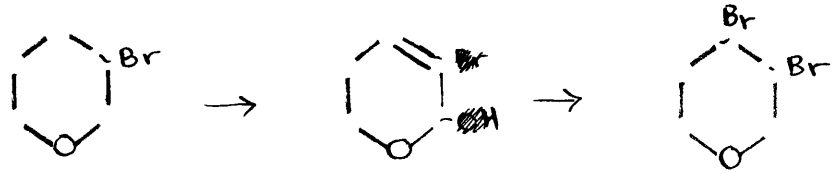
XLIV XLV XLVI

hydroxide, the product was 2-hydroxy-3-bromotetrahydropyran (XLVII) which when covered with water for several days or treated with (XLV) yielded bis-(3-bromotetrahydropyran-2) oxide (XLVIII) which



XLVII XLVIII

may be considered as the di-ether of XLVII. Paul[578] also prepared 3,4-dibromotetrahydropyran (LI) by the bromination of Δ^3-dihydropyran (L) which was obtained by distilling 3-bromotetrahydropyran (XLIX) from excess potassium hydroxide in glycol. LI,

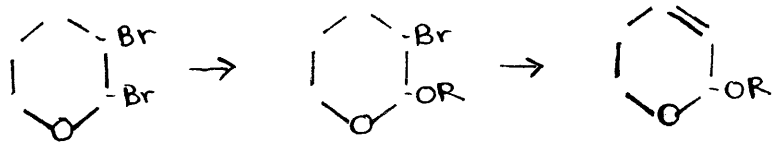


XLIX L LI

unlike the 2,3-dibromo analog, was reported as very stable. Some English workers[705] have prepared chloro compounds analogous to

XLVII and XLVIII. Others[706] have patented the displacement of one mole of halogen from a di-or polyhalogenated tetrahydropyran using anhydrous sodium acetate in acetic acid. Thus 2,3-dibromotetrahydropyran yields 2-acetoxy-3-bromotetrahydropyran.

Woods and Sanders[707] treated 2,3-dibromotetrahydropyran with ammoniated alcohols in the cold to obtain the 2-alkoxy-3-bromotetrahydropyran (LII). When this product was refluxed with excess

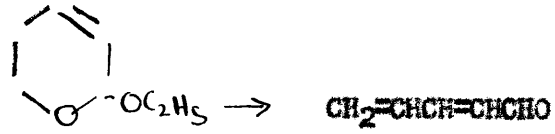


LII LIII

alcoholic potassium hydroxide, the formation of 2-alkoxy-Δ^3-dihydropyran(LIII) occurred. Cleaving (LIII) by dilute aqueous acids in the presence of 2,4-dinitrophenylhydrazone gave the 2,4-dinitrophenylhydrazone of 5-hydroxy-Δ^2-pentenal (LIV). When 2-ethoxy-Δ^3-dihydropyran (LV) was subjected to steam distillation from a strongly

LIV

acid medium, the product obtained was a pentadienal (LVI). The compound (LV) was the starting material for the work reported in

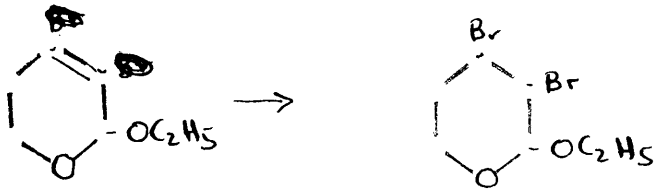


LV LVI

this thesis.

DISCUSSION

The object of this work originally was to extend our knowledge of simple tetrahydropyrans and dihydropyrans. Further, it seemed possible that certain anticipated reactions of these substances might lead to a synthesis of 3-bromohexatriene. In a sense these goals were attained. The starting compound for this investigation was the 3,4-dibromo-2-ethoxy-tetrahydropyran (LVII) which was obtained by the addition of bromine to 2-ethoxy- Δ^3-dihydropyran (LV).[707]



LV LVII

The addition of bromine to (LV) was a rapid, exothermic reaction at temperatures below -20° C. using either carbon tetrachloride or petroleum ether as a solvent. The reaction medium soon became opaque and orange colored. On removal from the cooling bath the contents of the bromination flask took on a reddish color with evolution of hydrogen bromide. It was expected that (LVII) would be an unstable compound like 2,3-dibromotetrahydropyran[577,704] or a 2,3-dibromocyclohexanone.[538,546,549] Efforts to distill the crude product after bromination led to decomposition with evolution of hydrogen bromide. Poor yields of a yellowish product were thus obtained. Consequently, the crude product after bromination was added immediately and directly to alkaline reagents in an effort to study the reactions of (LVII). It soon became apparent, however, that the product isolated from treatment of the crude bromination product with

either pyridine or cold alcoholic potassium hydroxide was, almost entirely, unreacted 2-ethoxy-3,4-dibromotetrahydropyran. This material distilled at reduced pressure without decomposition and indicated that, if properly purified, (LVII) was actually a stable substance.

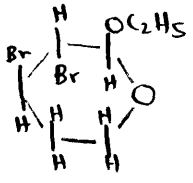
Several different techniques were employed in an effort to discover a simple means of purification. The carbon tetrachloride solution, immediately after bromination, was shaken with aqueous potassium hydroxide until the disappearance of the orange-red color. The organic layer was then separated and after removal of solvent, distillation of the residue at reduced pressure attempted. Again decomposition occurred to a large extent. Using alcoholic sodium ethoxide or aqueous sodium bicarbonate in place of the aqueous potassium hydroxide did not alter the results. As another experiment the crude bromination sludge was poured into peroxide-free ether and this solution shaken with an aqueous solution of equal parts of sodium carbonate and sodium sulfite. The organic layer was taken off and the residue distilled at reduced pressure after removal of solvent. Again marked decomposition resulted.

It was finally discovered that adding the crude bromination product to an aqueous solution of sodium carbonate and sodium sulfite and then steam distilling the mixture effectively removed whatever impurity caused the decomposition of (LVII). The product obtained in this way could be distilled at reduced pressure with total absence of decomposition. A distilled sample was stable and colorless for more than a year when stored in a stoppered flask even if exposed to light. The extraordinary stability of this dibromo compound was later exhibited by its resistance to hydrolysis by strong

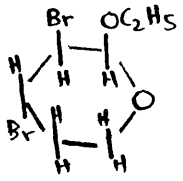
sulfuric acid and by its resistance to removal of bromine by various alkaline reagents. These experiments will be discussed later.

When the problem of purification and isolation was solved sufficiently to permit accumulation of reasonable amounts of pure 2-ethoxy-3,4-dibromotetrahydropyran, the discovery of stereoisomeric forms of this compound was made. One form, a solid crystallizing in long white needles from aqueous ethanol or petroleum ether and melting at 60-1° C. was isolated in pure form. The other isomer, a colorless, viscous liquid boiling at 120-125° at 10 mm. was never obtained completely free from traces of the solid isomer dissolved in it. A partial separation of these isomers could be made by distillation. If the mixture were fractionated and the distillate collected in three equal portions, the last fraction would almost entirely crystallise upon standing in the ice box. The second fraction deposited a small quantity of crystals on cold storage; but no crystals, even after seeding, could be obtained from the first fraction which was probably largely the liquid isomer. The solid isomer could also be separated by crystallization from a petroleum ether solution of the original mixture on cooling to -50 to -70° C.

The stereochemical configuration of the isomeric 2-ethoxy-3, 4-dibromotetrahydropyrans is not known although the two bromine atoms are undoubtedly trans to each other. The two isomers are therefore represented by formulas (LVIII) and (LIX).

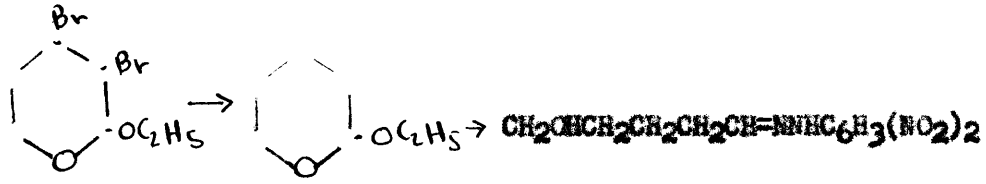


LVIII



LIX

Hydrogenation of 2-ethoxy-3,4-dibromotetrahydropyran with palladium-charcoal in the presence of sodium carbonate, yielded a liquid from which a yellow 2,4-dinitrophenylhydrazone (LX) could be prepared. This derivative showed no depression in a mixed melting point determination with the 2,4-dinitrophenylhydrazone derived from 2-ethoxytetrahydropyran (LXI).[707]



LVII LXI LX

This demonstrates that bromination did not alter the ring structure.

Reaction of 2-Ethoxy-3,4-dibromotetrahydropyran with Sodium Ethoxide

The reaction of 2-ethoxy-3,4-dibromotetrahydropyran with sodium ethoxide was first studied. It was hoped that by this treatment one molecule of hydrogen bromide would be eliminated from the molecule and that a product, 2-ethoxy-3-bromo- Δ^3-dihydropyran, could be obtained.

The crude bromination product was added directly to a warm solution of sodium ethoxide with which it reacted vigorously. The two materials combined to give a brick red mixture that gradually became almost black and from which sodium bromide precipitated. The appearance of the reaction was the same even when pure, colorless dibromo compound (LVII) was employed or when the reactants were mixed in the cold and subsequently heated. Later, both the solid isomer and a mixture very rich in the liquid isomer were treated the same way. In every instance the major products isolated from the reaction were

the same. Moreover, and this emphasizes the stability of (LVII), a small amount of unchanged dibromo compound was recovered even after forty-eight hours refluxing with alcoholic sodium ethoxide. When the reactants were brought to reflux temperature and then allowed to stand for two days at room temperature, half of the product isolated was unreacted dibromo compound. Neither the liquid nor the solid isomer reacted with sodium ethoxide below about 60° C. However, there is some indication that the liquid isomer reacted more readily. In several instances where a mixture of isomers, of such proportions that the solid would not precipitate out on cooling, was reacted, the dibromo compound recovered was largely the solid isomer. This was evidenced by crystallization of a large portion of the recovered material on cooling.

The contents of the reaction flask after heating (LVII) with sodium ethoxide was first flooded with water and then extracted with ether, and the residue distilled at reduced pressure. Two fractions were obtained of which the higher boiling was revealed to be unchanged (LVII). As mentioned before, the relative amount of this fraction varied with the time of heating the reactants. The lower boiling product appeared to be a single entity on the basis of its distillation behavior. However, bromine analysis of this material revealed it to be a mixture. One compound was later isolated and shown to be a bromine-free diethoxydihydropyran. The other compound contained bromine. The bromine analysis of the lower boiling mixture gave values ranging from 27% to 16% bromine. Since a monobromo-ethoxydihydropyran would contain 38% bromine, it was assumed that this material was a mixture of diethoxydihydropyran and a monobromo-ethoxydihydropyran.

It should be observed here that the contribution of a bromine atom to the boiling point of a compound is almost the same as that of an ethoxyl group. Hence the diethoxydihydropyran and the monobromo-ethoxydihydropyran should have very nearly the same boiling point. It was found in this case that separation of the two compounds by ordinary fractionation procedure was not feasible.

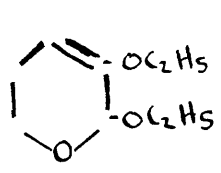
Additional treatment of this mixture with sodium ethoxide reduced the bromine content. Thus the mixture containing 16% bromine yielded a bromine-free compound on refluxing longer with more sodium ethoxide solution. In another experiment a sample containing 14% bromine was reduced in bromine content to 1% upon heating for 30 hours with alcoholic sodium ethoxide. Again, a sample containing 23-24% bromine was given two treatments with sodium ethoxide and then overnight heating with alcoholic potassium hydroxide to obtain a bromine-free product. Usually a final treatment with metallic sodium was employed to remove the last traces of the bromine-containing compound.

Analyses for carbon and hydrogen content of the bromine-free compound gave values that corresponded to a diethoxydihydropyran. This compound on heating with dilute mineral acids in the presence of 2,4-dinitrophenylhydrazine yielded an orange derivative. This 2,4-dinitrophenylhydrazone (LXII) had a carbon and hydrogen content corresponding to that of a derivative of an ethoxyhydroxypentenal which may have the structure shown.

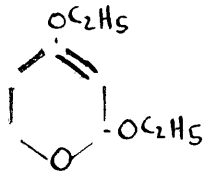
$$CH_2OHCH_2C(OC_2H_5)=CH-CH=NNHC_6H_3(NO_2)_2$$

LXII

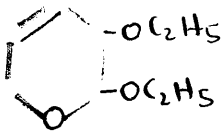
The diethoxydihydropyran probably has one of the structures, (LXIII), (LXIV), or (LXV) shown below:



LXIII



LXIV

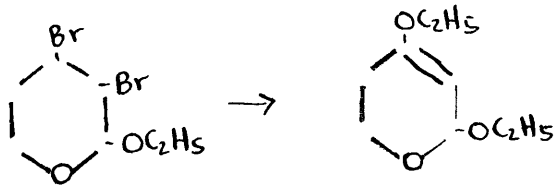


LXV

Hydrogenation of this product using paladium-charcoal catalyst at one atmosphere pressure in the presence of sodium carbonate showed a hydrogen uptake corresponding to one double bond in the molecule. The product gave carbon and hydrogen analyses corresponding to values calculated for a diethoxytetrahydropyran.

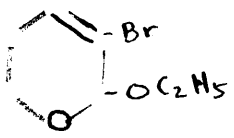
Treatment of the diethoxydihydropyran with cold 1:1 sulfuric acid resulted only in charring, while treatment of the bromine-containing mixture, resulting from sodium ethoxide action on (LVII), with the same reagent yielded a solid which was recrystallized in long white needles from aqueous acetone. This solid contained bromine. Its identity was discovered later and will be discussed in connection with later experiments in which the precursor, bromoethoxydihydropyran (LXVI) was isolated.

Thus the reaction of (LVII) with sodium ethoxide is not a simple one. Both dehydrobromination and displacement of bromine occur to give a mixture as depicted below:



LVII

LXIV



LXVI

Reaction of 2-Ethoxy-3,4-dibromotetrahydropyran with Alcoholic Potassium Hydroxide

The action of alcoholic potassium hydroxide on (LVII) was similar to the action of alcoholic sodium ethoxide. A mixed product resulted. The bromine content varied according to the time of treatment. Thus dibromo compound heated with five parts of 15% alcoholic potassium hydroxide for over twelve hours, yielded a product containing about 4% bromine as well as a little unreacted (LVII). A low-boiling fraction containing 13% bromine was obtained by four hours heating with 17% alcoholic potassium hydroxide. The mixed product contained both (LXIV) and (LXVI). Consequently, alcoholic potassium hydroxide was considered unsuitable as a reagent for the preparation of (LXVI).

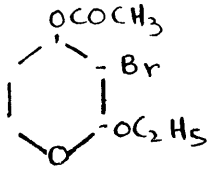
Reaction of 2-Ethoxy-3,4-dibromotetrahydropyran with Tertiary Amines

The treatment of (LVII) with tertiary amines was not productive. Triethanolamine as a reagent led to a vigorous reaction from which the only product isolated was a nitrogen containing substance while use of dimethylaniline caused no reaction other than decomposition of the amine. When (LVII) was refluxed with pyridine and toluene, the dibromo compound was quantitatively recovered. Attempts to remove one molecule of hydrogen bromide from (LVII) with tertiary amines were discontinued after these experiments.

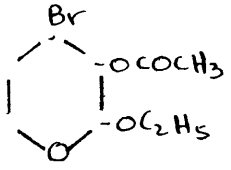
Reaction of 2-Ethoxy-3,4-dibromotetrahydropyran with Potassium Acetate

Potassium acetate and 2-ethoxy-3,4-dibromotetrahydropyran were heated in diethylene glycol under reflux. The reaction commenced with vigor followed by a darkening of the solution and separation of a precipitate of potassium bromide. The weight of potassium bromide obtained was roughly equivalent to replacement of one

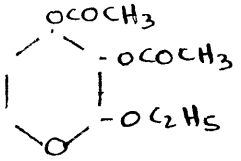
bromine atom in (LVII). The odor of acetic acid became evident. After neutralization of the acid, water was added, and the mixture extracted with ether. A low-boiling fraction as well as a high-boiling fraction containing some unreacted (LVII) was obtained. The low-boiling fraction is mainly a bromoacetoxyethoxytetrahydropyran (LXVII or LXVIII) contaminated with what is probably some diacetoxy-ethoxytetrahydropyran (LXIX). The carbon and hydrogen analyses of



LXVII



LXVIII

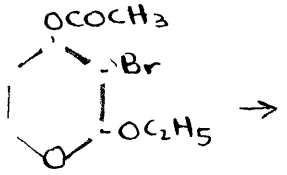


LXIX

this liquid, apparently due to presence of (LXIX) gave values somewhat higher than those calculated for (LXVII or LXVIII) (3.5% too high for carbon, 5% too high for hydrogen). All other possible contaminants, e.g. unreacted (LVII) or a product resulting from dehydrobromination, would tend to give low values for carbon and hydrogen content. (Preparation of (LXIX), which distilled only about 15° higher than (LXVII or LXVIII) was not attempted since it was formed only on longer heating of (LVII) with potassium acetate and consequently at the expense of (LXVII) which decomposes in the presence of the acetic acid formed in the reaction.)

When (LXVII) was reacted with 2,4-dinitrophenylhydrazine in the usual manner, an orange to red-orange derivative was obtained.

This could be recrystallised to remove any contaminating derivative of (LXIX). The values obtained on carbon and hydrogen analyses of the 2,4-dinitrophenylhydrazone corresponded to those calculated for a derivative of an ~~ethoxy~~hydroxyacetoxybromopentanal (LXX).



$\rightarrow$ $CH_2OHCH_2CH(OCOCH_3)CHBrCH{=}NNHC_6H_3(NO_2)_2$

LXVII LXX

Thus the reaction of (LVII) with potassium acetate at high temperature led to displacement of bromine and was unsuitable for the preparation of a bromodihydropyran.

Reaction of 2-Ethoxy-3,4-dibromotetrahydropyran with Molten Potassium Hydroxide

Alcoholic sodium ethoxide and alcoholic potassium hydroxide yielded some bromoethoxydihydropyran but only in a mixture from which it could not be readily isolated, and anhydrous potassium acetate led only to displacement of bromine. So it was decided to investigate the use of potassium hydroxide without solvent in the hope that dehydrobromination without accompanying displacement of bromine would result.

Preliminary experiments in glass vessels indicated that (LVII) yielded a monobromo compound when added to potassium hydroxide at temperatures around 250° C. This temperature was selected in the expectation that the bromoethoxydihydropyran (LXVI), which boils at about 200° C., would distill out of the reaction vessel while (LVII) would remain behind until dehydrobrominated.

The preliminary experiments indicated that a large excess of potassium hydroxide should be used to avoid extensive decomposition of the organic material. Also mixing the reagents cold and then heating led to a very violent reaction.

Eventually a steel cylinder fitted with a large rubber stopper through which passed two inlet tubes, an outlet tube, a thermometer well, and a sleeve for a stirrer was procured. One inlet tube was used to add (LVII) to already molten potassium hydroxide and the other served to pass nitrogen into the cylinder. The outlet tube led to an air condenser which entered a receiver cooled in an ice bath.

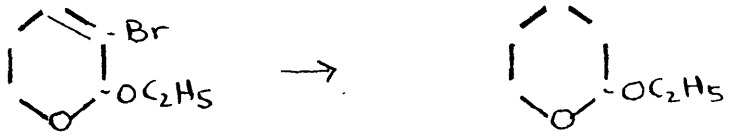
Using this apparatus and preheating the potassium hydroxide to about 250° C. it was possible to obtain a distillate that yielded a lower-boiling fraction and a higher-boiling fraction which was unreacted (LVII). The presence of (LVII) in the distillate is probably partly due to a kind of steam distillation. Commercial potassium hydroxide always contains water which was observed along with the organic material in the distillate. Also the temperature of the cylinder walls was never recorded but may have been sufficient to force some (LVII) over before reaction could occur. Again this emphasises the unusual stability of the dibromo compound (LVII).

The lower-boiling fraction was a single entity. The bromine content of this compound corresponded to that calculated for bromo-ethoxydihydropyran (LXIV). There was no evidence of any product resulting from bromine displacement in this reaction.

The technique was still unsatisfactory due to the excessive decomposition occurring in the steel cylinder. It was decided to

employ an inert diluent with (LVII). Toluene was found satisfactory. Dropping a solution of equal parts of toluene and (LVII) unto the molten potassium hydroxide markedly decreased the decomposition. Later it was discovered that the nitrogen sweep was unnecessary. Thus molten potassium hydroxide treatment of (LVII) made possible the synthesis of (LXVI) in acceptable yields.

Retention of the ring structure of this compound was demonstrated by hydrogenation over palladium-charcoal catalyst. A quantity of hydrogen corresponding to one double bond and one bromine atom in the molecule was absorbed to form 2-ethoxytetrahydropyran (LXI). The identity of the hydrogenated product was established by preparing the 2,4-dinitrophenylhydrazine derivative (LXII). This



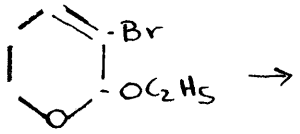
LXVI LXI

derivative gave no depression in a mixed melting determination with a

LXI LX

known sample of the 2,4-dinitrophenylhydrazone of (LXI).

Carbon, hydrogen, and bromine analyses of the low-boiling compound all corresponded to that calculated for the structure (LXVI). Moreover, on treatment with 2,4-dinitrophenylhydrazine in the presence of mineral acids an orange derivative was obtained. This 2,4-dinitrophenylhydrazone (LXXI) on analysis gave values for carbon and hydrogen content that agreed with those calculated for a hydroxy-bromopentenal derivative (LXXI).

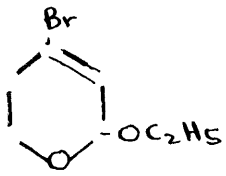


$\rightarrow$ $CH_2CHCH_2CH{=}CBrCH{=}NNHC_6H_3(NO_2)_2$

LXVI LXXI

The compound (LXVI) was a fairly stable liquid although difficult to obtain colorless. Usually obtained as a straw-colored liquid it gradually deepened in color on standing but with apparently only minor decomposition.

An alternative structure for the bromoethoxydihydropyran is (LXXII). However, as the historical portion of this thesis reveals,

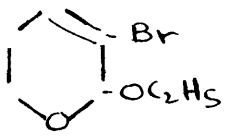


LXXII

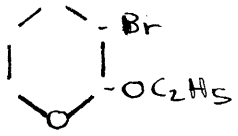
the product of dehydrobromination of an α,β-dibromocarbonyl compound is always that which has lost bromine from the β carbon and hydrogen from the α carbon. Hence structure (LXVI), 2-ethoxy-3-bromo-Δ^3-dihydropyran, is preferred for the product obtained in this

investigation.

Attempts to prepare a known material, 2-ethoxy-3-bromotetrahydropyran (LXXIII)[707] from 2-ethoxy-3-bromo-Δ^3-dihydropyran (LXVI) by hydrogenation of only the double bond without removal of bromine



LXVI

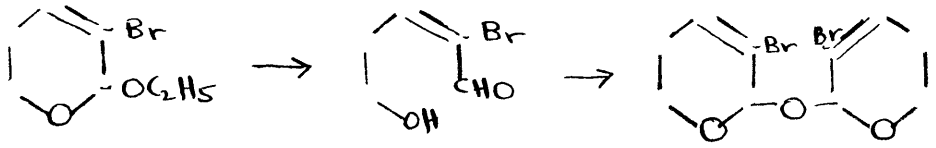


LXXIII

were unsuccessful, but did yield the reduced product from which bromine had been eliminated.

Preparation of Di-2-(3-bromo-Δ^3-dihydropyranyl) ether

When (LXVI) was added with stirring to a cold solution of equal volumes of concentrated sulfuric acid and water, a solid was obtained. This white stable solid on treatment with 2,4-dinitrophenylhydrazine in the usual manner yielded an orange derivative which proved to be identical with that obtained from (LXVI). Thus structure (LXXIV) was assigned to this solid. Apparently, (LXXIV) arises by cleavage of (LXVI) to form the intermediate (LXXV). Subsequent condensation of two molecules of the hydrated aldehyde yields (LXXIV). The values given on analyses of carbon, hydrogen,



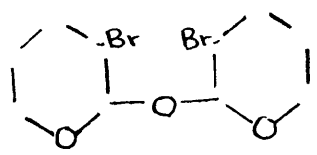
LXVI LXXV LXXIV

and bromine content corresponded closely to those calculated for

(XXIV). Moreover, a Rast molecular weight determination using camphor gave a value fairly close to the calculated value. Later, it will be shown that (LXVI) and (LXXIV) yield the same product on acid hydrolysis.

The solid (LXXIV) is the same compound as that which was obtained from the mixture resulting from the action of sodium ethoxide upon (LVII). This confirms the presence of (LXVI) as the bromine-containing component in that mixture.

It should be noted here that compound (XLVIII) prepared by Paul[577,704] bears a close resemblance to (LXXIV). Due to the inability



XLVIII

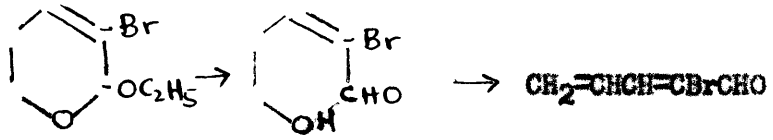
to hydrogenate the double bond without removing bromine in (LXVI), no attempt was made to convert (LXXIV) to (XLVIII).

Preparation of 2-Bromopentadien-2,4-al

This aldehyde,2-bromopentadien-2,4-al,could be prepared from 2-ethoxy-3,4-dibromotetrahydropyran (LVII) by treatment with strong acids. First (LVII) was shaken with warm 1:1 sulfuric acid. The mixture was then added gradually to a solution of about 30% sulfuric acid under steam distillation conditions. The distillate contained a small amount of the bromopentadienal (LXVI) which was isolated by ether extraction. This preparation was unsatisfactory because most of the distillate was unreacted material. Again this emphasizes the remarkable stability of 2-ethoxy-3,4-dibromotetrahydropyran. The

resistance of a compound containing an acetal link to strong mineral acids at elevated temperatures was not expected.

A better but still not satisfactory preparation of (LXXVI) could be effected by steam distillation of 2-ethoxy-3-bromo-Δ^3-dihydropyran from a 30% phosphoric acid solution. The mechanism of this reaction is evidently a hydrolysis of the acetal link of (LXVI) to form the bromohydroxypentenal (LXXV) which eliminates a molecule of



LXVI LXXV LXXVI

water on heating in the presence of acids. The intermediate (LXXV) was not isolated except through its 2,4-dinitrophenylhydrazone derivative (LXXI) mentioned before. Although (LXVI) was added very slowly to the steam-distilling acid solution, the product obtained contained some unreacted (LXVI). This result was also unexpected since a similar treatment of 2-ethoxy-Δ^3-dihydropyran by Woods and Sanders[707] yielded a pentadienal free from any unaltered starting material. The presence of unreacted (LXVI) in the aldehyde product was unfortunate. It persisted through a subsequent Grignard reaction and then decomposed in a following step to contaminate the bromohexatriene being prepared. Otherwise the yield was satisfactory.

Pure 2-bromopentadien-2,4-al free from contamination of starting material could be obtained by subjecting the ether (LXXIV) to

steam distillation from phosphoric acid solution. This solid did not steam distill so only the hydrolysis product, bromopentadienal (LXXVI) was isolated in the distillate. This preparation of the same aldehyde from (LXVI) and (LXXIV) helps confirm the structure assigned to the ether.

This aldehyde is a yellow, unstable liquid with a deeply penetrating, acrolein-like odor. It attacks the mucous membrane and functions as a very effective lachrymator. Distillation, even at a pressure of 2-3 mm. under a nitrogen atmosphere, is accompanied by decomposition. On two occasions at a pressure of about 20 mm., under a nitrogen atmosphere, a pure sample decomposed so rapidly near the end of the distillation that the top of the thermometer and capillary tube were blown out and the fractionating column broken.

Carbon and hydrogen analysis of this compound gave values corresponding to structure (LXXVI). (The analysis was not as good as desired due to the instability of the material. On combustion it left a black deposit in the capillary employed to weigh the sample. This deposit occurred on sealing the capillary and persisted even on extreme heating) It very readily formed a red 2,4-dinitrophenylhydrazone (LXXVIA). The carbon and hydrogen content given by

$$CH_2{=}CHCH{=}CBrCH{=}NNHC_6H_3(NO_2)_2$$

LXXVI-A

analysis of this derivative corresponded very closely to the values calculated for (LXXVIA). A white semicarbazone (LXXVI-B) was also

obtained from this aldehyde. This derivative gave analysis values corresponding only fairly well to the carbon and hydrogen content

$$CH_2=CHCH=CBrCH=NNHCONH_2$$

LXXVI-B

calculated for (LXXVI-B) probably because of its instability. It gradually decomposed without melting and even drying at slightly above room temperature under vacuum caused some decomposition. This behavior resembles that of the semicarbazone of pentadienal.[707]

Preparation of 3-Bromohexadien-3,5-ol-2.

Addition of the 2-bromopentadien-2,4-al to excess methylmagnesium bromide in ether caused a vigorous reaction with formation of 3-bromohexadien-3,5-ol-2 (LXXVII). No derivative was obtained from this alcohol. Treatment with phenylurethane or α-naphthylurethane apparently caused elimination of water since the only products isolated were the corresponding urea and a tar. It was necessary to establish the structure of this alcohol by other means.

The alcohol was hydrogenated to a bromine-free saturated alcohol (LXXVIII). The quantity of hydrogen absorbed agreed with that calculated for a molecule containing two double bonds and a bromine atom. Oxidation of the saturated alcohol with dichromate yielded a ketone (LXXIX) which was identified as n-butyl methyl ketone by preparation of the semicarbazone and 2,4-dinitrophenylhydrazone derivatives. These gave no depression with authentic derivatives in mixed melting point determinations. Hence the saturated alcohol must

have been hexanol-2 (LXXVIII) and the product of the Grignard reaction must have been 3-bromohexadien-3,5-ol-2(LXXVII).

$CH_2=CHCH=CBrCHO \longrightarrow CH_2=CHCH=CBrCHOHCH_3 \longrightarrow$

LXXVI LXXVII

$CH_3CH_2CH_2CH_2CHOHCH_3 \longrightarrow CH_3CH_2CH_2CH_2COCH_3$

LXXVIII LXXIX

The unsaturated bromoalcohol (LXXVII) was a colorless, viscous liquid which formed a thick yellow-brown tar if heated above its boiling point for about one-half hour. Carbon and hydrogen analysis of pure (LXXVII) gave values close to those calculated for that structure.

Preparation of 3-Bromohexatriene-1,3,5

Passing 3-bromohexadien-3,5-ol-2 through a column of activated aluminum oxide heated to about 320° C. yielded a product consisting of water and a yellow liquid with a powerful but not unpleasant odor. This liquid was identified as 3-bromohexatriene-1,3,5 (LXXX), derived from (LXXVII) by elimination of a molecule of water.

$CH_2=CHCH=CBrCHOHCH_3 \longrightarrow CH_2=CHCH=CBrCH=CH_2$

LXXVII LXXX

Upon distillation a colorless liquid was obtained leaving behind an intensely blue material. The dark cobalt blue residue was a characteristic intermediate polymerization or decomposition product obtained from (LXXX) which was itself colorless when pure.

It was previously mentioned that some samples of (LXXVII) contained some unreacted bromoethoxydihydropyran. This material, present

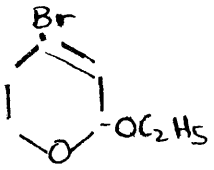
in the aldehyde precursor, carried through the Grignard step still unchanged but upon passage over heated alumina gave rise to bromopentadienal (LXXVI). Consequently pure samples of bromohexatriene could not be prepared unless the ether (LXXIV) was used as starting material in the synthesis of (LXXVI).

An attempt to prepare bromohexatriene by distillation with iodine of a sample of bromohexadieneol (LXXVII) contaminated with (LXVI) led to formation of bromopentadienal. The alcohol (LXXVII) was unchanged.

3-Bromohexatriene was previously observed by Farmer[60] to be a yellow liquid. His sample, for which no data other than the boiling point was reported, polymerized completely in twenty-four hours. The colorless material prepared in this work was also quite unstable and very difficult to maintain free from color. Usually it was stored at dry ice temperatures in presence of hydroquinone. Under these conditions samples remained unchanged for weeks. Slow polymerization occurred at icebox temperatures in presence of hydroquinone. One sample remained at least partially liquid for two months at room temperature in a stoppered flask in the presence of hydroquinone.

Quantitative hydrogenation of pure 3-bromohexatriene-1,3,5 showed a hydrogen absorption equivalent to that calculated for a molecule containing three double bonds and one bromine atom. Carbon, hydrogen, and bromine content were shown by analysis to correspond to that calculated for (LXXX).

The position of the bromine atom in the bromohexatriene prepared in this work is definitely established. The immediate precursor may have had the structure (LXXXI) if the bromoethoxydihydropyran prepared by molten potassium hydroxide treatment of (LVII) had the 4-bromo structure (LXXII).



LXXII

$$\xrightarrow[\text{steps}]{\text{several}} \quad CH_2{=}CHCBr{=}CHCHOHCH_3$$

LXXXI

But dehydration of (LXXXI) would still lead to 3-bromohexatriene-1,3,5. Thus regardless of any doubt attached to the position of the bromine atom in (LXVI), (LXXIV), (LXXVI), or (LXXVII), the product obtained

$$CH_2{=}CHCBr{=}CHCHOHCH_3 \longrightarrow CH_2{=}CHCBr{=}CHCH{=}CH_2$$

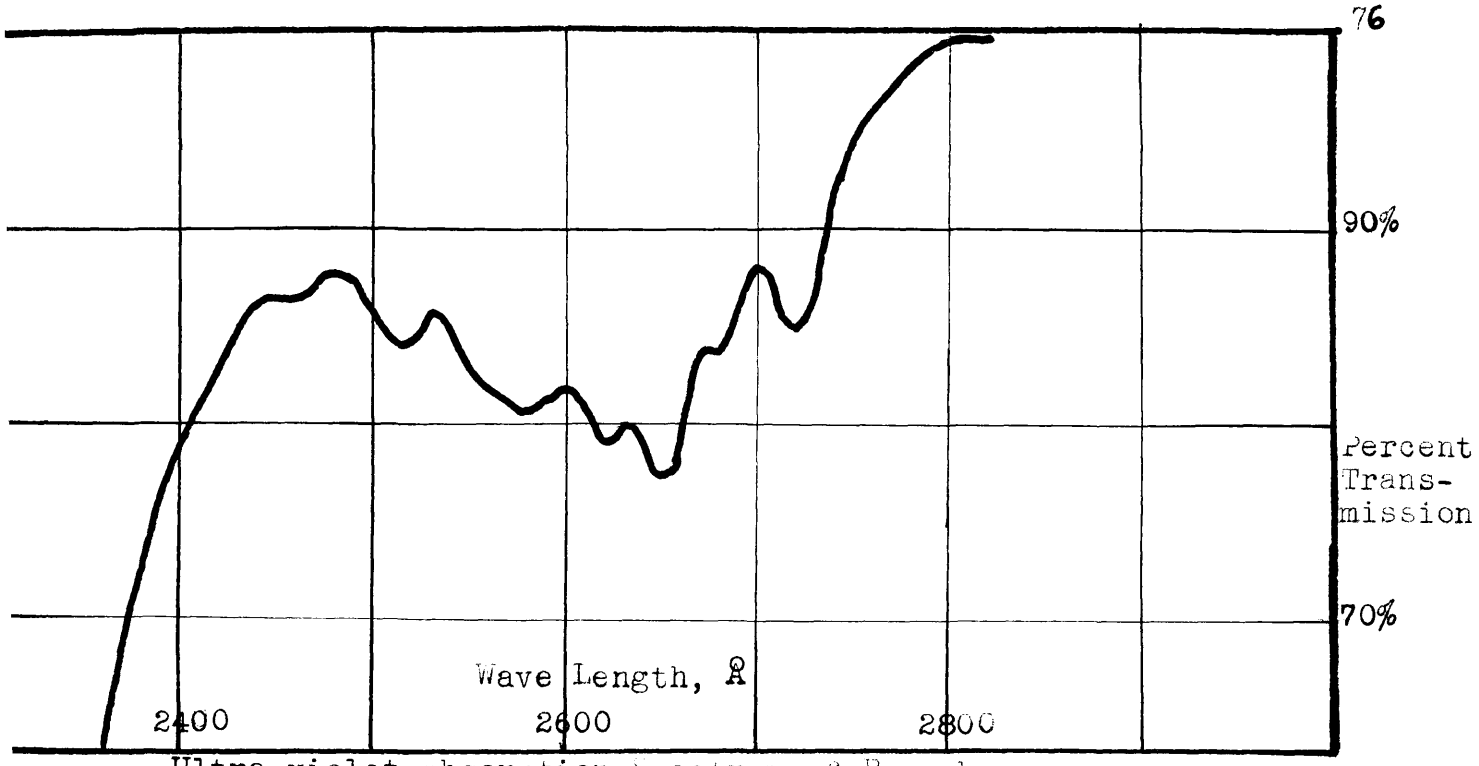
(LXXXI) (LXXX)

in this work was 3-bromohexatriene-1,3,5.

The ultraviolet absorption spectrum obtained from what was considered to be a pure sample of 3-bromohexatriene-1,3,5 is given in Fig. Ib. The ultraviolet absorption spectrum of bromobenzene is given in Fig. Ia, for comparison because of the obvious relationship between bromohexatriene and brombenzene.

The infrared absorption spectrum of 3-bromohexatriene-1,3,5 is given in Fig. II. It closely resembles the infrared absorption spectrum of hexatriene-1,3,5.[70S] Addition of bromine to (LXXX) yielded a stable white solid. Elementary analysis of this solid indicated it to be a pentabromo compound since the empirical formula corresponds fairly well to $C_6H_7Br_5$.

The preparation of a 3-bromohexatriene-1,3,5 marks the third straight chain analog of benzene or its derivatives to be synthesized in this laboratory. Previously, hexatriene-1,3,5, analogous to benzene, and vinylhexatriene (octatetraene-1,3,5,7), analogous to styrene, were prepared[708]. Bromohexatriene is, obviously, the straight chain analog of bromobenzene.



Ultra-violet Absorption Spectrum of Bromobenzene

Figure Ia.

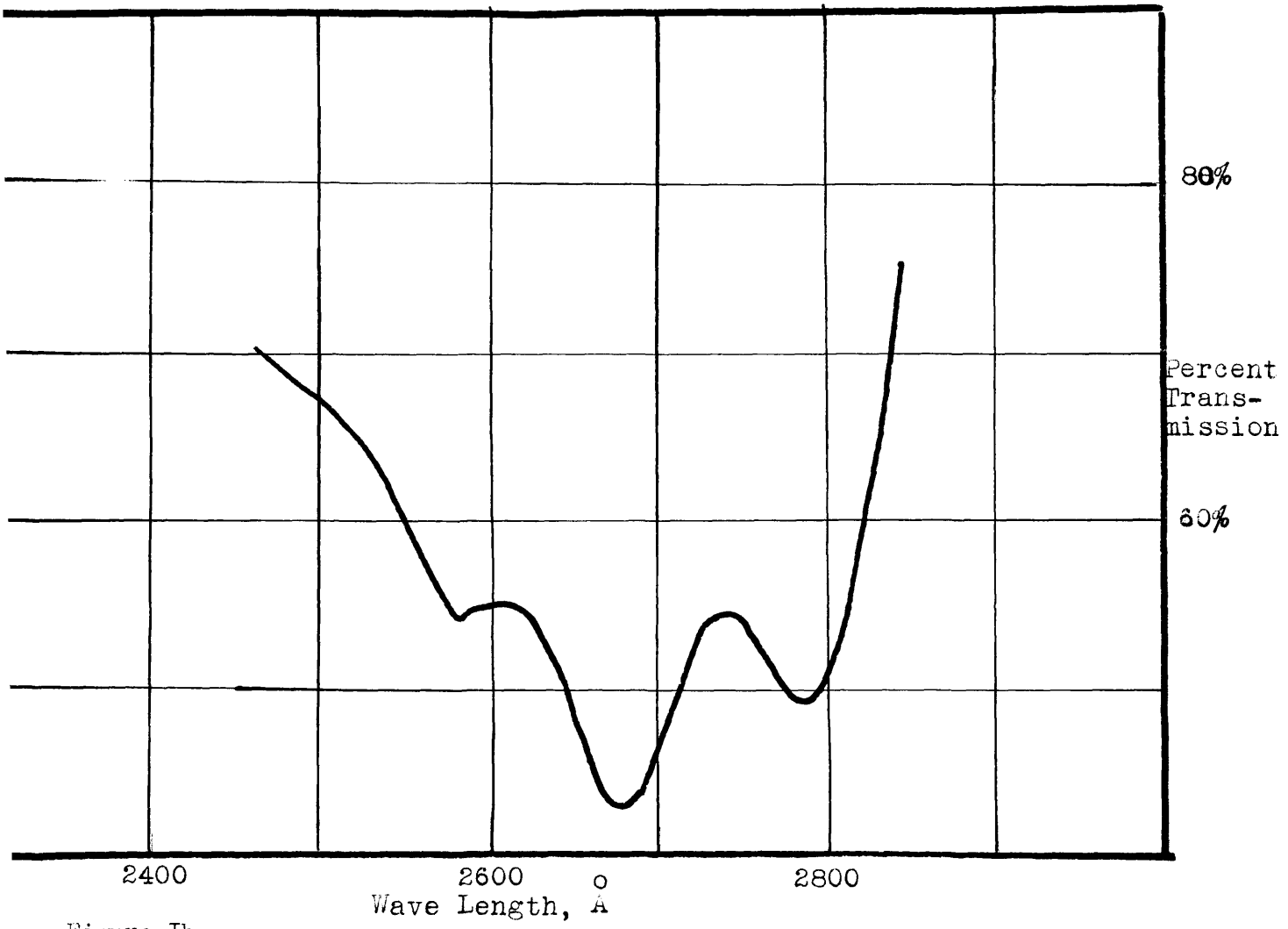


Figure Ib.

Ultra-violet Absorption Spectrum of 3-Bromohexatriene-(1,3,5)

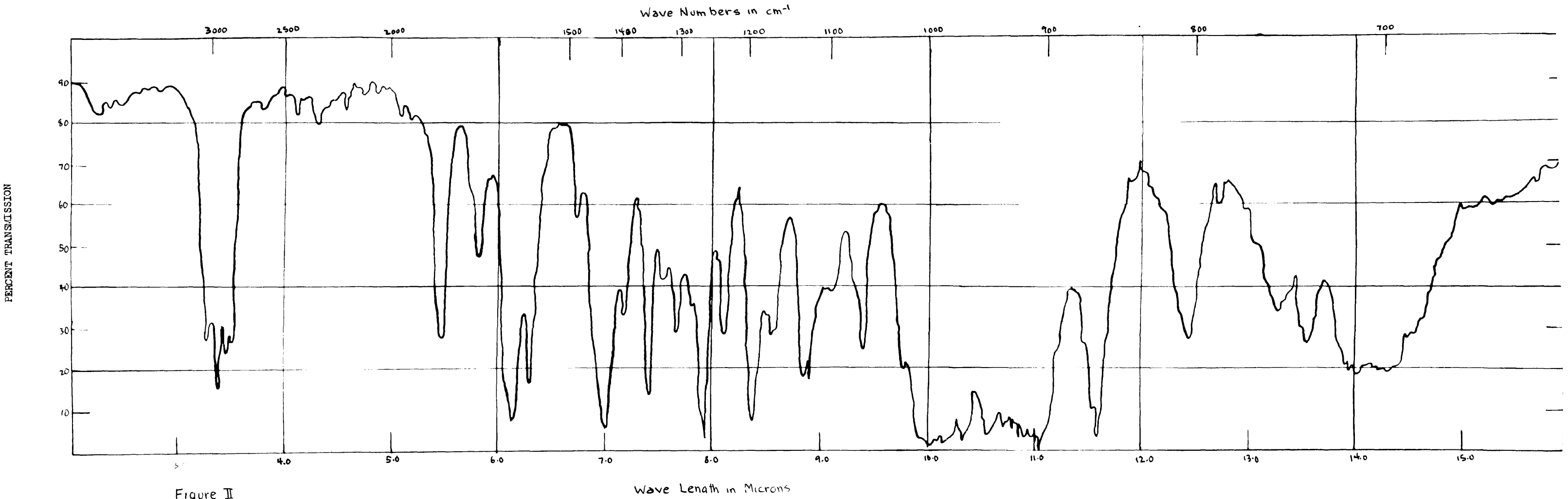

Wave Numbers in cm⁻¹
3000
2500
2000
1500
1480
1300
1200
1100
1000
900
800
700
PERCENT TRANSMISSION
90
80
70
60
50
40
30
20
10
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
14.0
15.0
Wave Lenath in Microns

Figure II

EXPERIMENTAL

2-Ethoxy-Δ^3-dihydropyran (LV). The procedure used for the preparation of 2-ethoxy-Δ^3-dihydropyran is a modification of that described by Woods and Sanders.[707] In a 1-liter, 3-neck flask immersed in a Dry Ice-acetone cooling bath was placed 294 g. of commercial dihydropyran* (3.5 moles) and about 150 ml. of carbon tetrachloride. The flask was fitted with a dropping funnel, an efficient stirrer, and a low pressure thermometer. When the stirred contents of the flask reached a temperature of about -40°., a solution of 560 g. of bromine (3.5m.) in about 100 ml. carbon tetrachloride was added through the dropping funnel at such a rate that the temperature stayed between -20° and -40°. Any excess bromine, which was evidenced by its color, was removed by addition of more dihydropyran. Most of the carbon tetrachloride was removed by vacuum distillation using a water bath, kept between 60° and 70°, as a source of heat.

The straw-colored residue of 2,3-dibromotetrahydropyran was cautiously added to a 3-liter flask containing 1500 ml. of 95% alcohol which had previously been saturated with ammonia. The alcohol was cooled in an ice-water bath and slowly stirred during the addition of the dibromide. After about one hour the flask was removed from the ice-water bath and the contents filtered. The precipitate of ammonium bromide was washed with 95% alcohol and the washings added to the filtrate. The weight of ammonium bromide obtained varied with the temperature at which the solution was filtered due to the

*Commercial dihydropyran is yellow and far from pure. Better yields of 2-ethoxy-Δ^3-dihydropyran may be obtained by using dihydropyran distilled from sodium.

solubility of ammonium bromide in alcohol.

The filtrate of 2-ethoxy-3-bromotetrahydropyran in alcohol was cautiously added in portions of about 300 ml. each to a cold solution of 400 g. of potassium hydroxide (7 m.) dissolved in a minimum of 95% alcohol (about 1500 ml.). The evolution of ammonia was allowed to subside between additions. The mixture was then refluxed for six to ten hours while removing about 2 liters of alcohol. Distilled water was added to the residue until most of the precipitated potassium bromide dissolved and the aqueous alcoholic solution was extracted three times with peroxide-free ether. The ether extract was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. A solution of sodium ethoxide prepared from 2 g. of sodium in a minimum of alcohol was then added and the distillation continued. The distillate boiling above 40° under water aspirator vacuum was collected and treated again with more sodium ethoxide and redistilled. The fraction boiling between 140° and 160° at atmospheric pressure was collected and redistilled from metallic sodium. Yield of 2-ethoxy-Δ^3-dihydropyran boiling at 152-155° was 180-210 g. (40-47%). A product so prepared remained without color for many weeks.

2-Ethoxy-3,4-dibromotetrahydropyran (LVII)

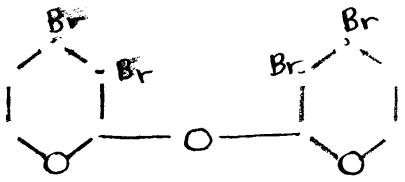
In a 1-liter 3-neck flask immersed in a dry-ice acetone bath were placed 430 g. of 2-ethoxy-Δ^3-dihydropyran (3.36 m.) and 200 ml. of carbon tetrachloride (or 30°-60° pet ether). The flask was fitted with an efficient stirrer, a dropping funnel, and a low-temperature thermometer. A solution of 537 g. of bromine (3.36 m.) in about 80 ml. of carbon tetrachloride (or 30-60° pet ether) was added through the

dropping funnel at such a rate that the temperature was maintained below -30°.

The red-orange sludge of crude 2-ethoxy-3,4-dibromotetrahydropyran was transferred to a 3-liter flask containing 100 g. each of sodium sulfite and sodium carbonate in 400 ml. of water and steam distilled as rapidly as possible. About 10 liters of distillate were collected before a clear distillate, free of the dibromo compound, was obtained. The water was separated from the more dense 2-ethoxy-3,4-dibromotetraphydropyran and extracted with a small amount of carbon tetrachloride. The carbon tetrachloride washings and dibromo compound were combined and dried over magnesium sulfate.

The carbon tetrachloride solution was filtered and the solvent removed under reduced pressure. The residue was distilled at low pressure. 2-Ethoxy-3,4-dibromotetrahydropyran boiled at 80-85° at 0.3 mm. pressure. Yield: 670 g. (68%) of a mixture of isomers. $n_D^{32°} = 1.5140$. $D_4^{29°} = 1.55$. Analysis: Calculated for $C_7H_{12}Br_2O_2$: Br,55.5
Found: Br,55.5,55.4

On one occasion when 2-ethoxy-3,4-dibromotetrahydropyran (mixture of isomers) was added dropwise, with stirring, to cold concentrated sulfuric acid, a small amount of gummy solid was obtained which recrystallized in long, white needles from aqueous acetone. This melted at 201° and was believed to have the structure shown below:



Analysis: Calculated for $C_{10}H_{14}Br_4O_3$: C, 23.94; H, 2.81; Br, 63.7
Found: C, 24.27; H, 3.00; Br, 64.1

It was not possible to duplicate the results of this one experiment using either one of the isomers or a mixture of the isomers of 2-ethoxy-3,4-dibromotetrahydropyran although a number of attempts were made.

Isolation of Solid Isomer. Two hundred and twenty grams of 2-ethoxy-3,4-dibromotetrahydropyran, obtained by bromination of 2-ethoxy-Δ^3-dihydropyran, was dissolved in 800 ml. petroleum ether (20-40°) and the solution cooled in a Dry Ice-acetone bath. White crystals precipitated which were collected by suction filtration and washed with cold petroleum ether (20-40°). After recrystallization the solid isomer of 2-ethoxy-3,4-dibromotetrahydropyran melted at 60-1°. Yield: 56 g. Analysis: Calculated for

$C_7H_{12}Br_2O_2$: C, 29.20; H, 4.20
Found: C, 29.19; H, 4.25

Preparation of Impure Liquid Isomer. The petroleum ether solution remaining after removal of the solid isomer was placed in a distilling pot and the solvent removed. The residue was distilled at reduced pressure (123° at 12 mm.) and the first two-thirds of the distillate collected separately. This product was believed to be mainly the liquid isomer. It did not yield crystals upon seeding at very low temperatures. $n_D^{25°} = 1.5158$

Hydrogenation of 2-Ethoxy-3,4-dibromotetrahydropyran. Five and one-half grams of 2-ethoxy-3,4-dibromotetrahydropyran (mostly liquid isomer), 4 g. of sodium carbonate, 0.5 g. of 5% palladium charcoal catalyst, and 75 ml. of 95% ethanol were shaken under hydrogen at

atmospheric pressure in a quantitative hydrogenation apparatus. Absorption of hydrogen was rapid at first but progressively decreased in rate. After 740 ml. of hydrogen was absorbed (two hours) the reaction arrested itself. The theoretical absorption of hydrogen required for hydrogenolysis of both bromine atoms was 800 ml.

The product was not isolated but a yellow 2,4-dinitrophenylhydrazone was prepared by adding an alcoholic solution, containing hydrochloric acid, of 2,4-dinitrophenylhydrazine to the liquid remaining after removal of solvent. This derivative was recrystallized from ethyl acetate and melted at 107-107.5°. A mixed melting point determination was made with a known sample of the 2,4-dinitrophenylhydrazone prepared from 2-ethoxytetrahydropyran. The mixture melted at 107.5-108°.

Treatment of 2-Ethoxy-3,4-dibromotetrahydropyran with Pyridine. Into a 300 ml. flask were placed 72 g. (0.25 moles) of 2-ethoxy-3,4-dibromotetrahydropyran, 40 g. (0.50 moles) of pyridine, and 100 ml. of toluene. The mixture in the flask was heated under reflux for two hours by an oil bath maintained at 140-5°. Except for a small amount of tar at the bottom of the flask there was no evidence of reaction. After cooling, water was added and the mixture extracted with petroleum ether (30-60°). The petroleum ether solution was dried over sodium sulfate and filtered. The only products obtained on distillation of the filtrate were petroleum ether, pyridine and toluene (boiled at 30-35° at 20 mm.) and unreacted 2-ethoxy-3,4-dibromotetrahydropyran (boiled at 130-135° at 20 mm.). Sixty-seven grams of

2-ethoxy-3,4-dibromotetrahydropyran were collected which, including forerun and residue, accounted for all of that compound employed in this experiment.

2-Ethoxy-3(or 4)-bromo-4(or 3)-acetoxytetrahydropyran. Into a 250 ml. flask fitted with an air condenser were placed 50 g. of 2-ethoxy-3,4-dibromotetrahydropyran, 32 g. of anhydrous potassium acetate, and 75 ml. of diethylene glycol. The non-homogeneous mixture of which the more dense dibromide formed the lower layer was heated with a small free flame. The potassium acetate dissolved in the glycol. After about ten minutes a vigorous reaction occurred with a consequent darkening of the mixture and the precipitation of potassium bromide. The contents of the flask was boiled for five minutes after the major violence of the reaction was spent and then cooled to room temperature. The odor of acetic acid was apparent. Concentrated potassium carbonate solution was added until the mixture was alkaline as determined by litmus paper. The mixture was filtered and water added to the filtrate which was then extracted with ether. The ether extract was dried over magnesium sulfate, filtered, and the ether removed under reduced pressure. The residue yielded 8 g. of material boiling from 90° to 100° at 10 mm. pressure and 14 g. of material boiling from 100 to 130° at 10 mm. The higher-boiling material was mainly unreacted 2-ethoxy-3,4-dibromotetrahydropyran. The lower-boiling fraction was 2-ethoxy-3-(or 4)bromo-4(or 3)acetoxytetrahydropyran which upon redistillation boiled at 90° at 12 mm. A redistilled sample of 2-ethoxybromoacetoxytetrahydropyran ($n_D^{25°} = 1.4754$) was analyzed.

Calculated for $C_9H_{15}BrO_4$: C, 40.47; H, 5.66; Br, 29.9
Found: C, 41.95; H, 6.00; Br, 29.2

When the original reactants were boiled for thirty minutes, instead of five minutes, a large fraction boiling at 110-115° at 10 mm. was obtained. This was believed to be 2-ethoxy-3,4-diacetoxytetrahydropyran; but a clean separation of this from either 2-ethoxybromoacetoxytetrahydropyran or 2-ethoxy-3,4-dibromotetrahydropyran could not be made.

2,4-Dinitrophenylhydrazone of 2-(or 3) Bromo-3-(or 4) acetoxy-5-hydroxypentanal. One gram each of 2-ethoxybromoacetoxytetrahydropyran and 2,4-dinitrophenylhydrazine were heated in 75 ml. of aqueous alcohol containing 2 ml. of concentrated hydrochloric acid. Under these conditions the acetal link of the 2-ethoxybromoacetoxytetrahydropyran was cleaved with the elimination of an ethoxyl group and formation of the free aldehyde, 2-(or 3)bromo-3-(or 4)acetoxy-5-hydroxypentanal. An orange derivative was obtained which was recrystallized from aqueous alcohol and then benzene. It melted at 145-6° with decomposition. Analysis: Calculated for $C_{13}H_{15}BrO_7N_4$: C, 37.25; H, 3.61
Found: C, 37.41; H, 3.31

Bromine Analysis. The analyses of the mixtures of diethoxydihydropyran and bromoethoxydihydropyran were made by a modified Stephanow method. Samples were carefully weighed from a small vial, fitted with a ground glass joint with a pipette, directly into 50 ml. and 100 ml. round-bottom flasks. A sample of about 100 mg. was added to the smaller flask and a sample of about 200 mg. added to the larger. Sixty-eight milliliters of 95% alcohol for each gram of sample was then added and a reflux condenser attached. The flasks were placed on the steam cone and small pieces of sodium totalling

8.5 times the weight of sample were dropped through the condenser into the solution. After addition of sodium the flask was heated for fifteen minutes. Then about 25 ml. of distilled water was cautiously added through the condenser and the alcohol evaporated by heating for fifteen to twenty minutes with no water running through the condenser. The contents of the flask were then cooled and washed into a small erlenmeyer flask. To the smaller sample 5 ml. of concentrated nitric acid was added and 8 ml. of the same acid was added to the larger. Then 20 ml. of 0.1 Normal standard silver nitrate was added and the excess silver nitrate back titrated with standard potassium thiocyanate solution using 2 ml. of concentrated ferric sulfate solution as indicator.

Preparation of Diethoxydihydropyran. A series of preliminary reactions were carried out employing both the liquid (impure) and solid isomers of 2-ethoxy-3,4-dibromotetrahydropyran with sodium ethoxide and alcoholic potassium hydroxide. The results of these investigations were so poor in terms of yields, difficulty of isolation, and multiplicity of products that the reactions of the dibromo compounds with these reagents were not explored further than as indicated by the experiments given below.

A. The reaction of potassium hydroxide dissolved in ethanol did yield a product identified as a diethoxydihydropyran. In a 1-liter flask were placed 290 g. (one mole) of 2-ethoxy-3,4-dibromotetrahydropyran (mixture of isomers) and 200 g. (3.5 moles) of potassium hydroxide dissolved in 600 ml. of alcohol. The flask was heated on the steam cone for a few minutes until the reaction

commenced. So violent is the reaction that material can be lost through the top of the condenser. The flask was removed from the steam cone and 190 g. (.63 moles) of potassium bromide (one-third of that theoretically available) filtered from the contents. The filtrate was added to 500 ml. of a solution of sodium ethoxide prepared from 30 g. (1.3 moles) of sodium and refluxed for forty-eight hours while removing 500 ml. of alcohol. The dark red sludge remaining was dissolved in distilled water and that solution extracted with ether. The ether extract was dried over magnesium sulfate for three hours in the cold and then filtered. After removal of solvent, the residue was fractionated. The first fraction, boiling at 98-101° at 17 mm. was 23 g. of bromine-free material. In addition 9 g. of unreacted 2-ethoxy-3,4-dibromotetrahydropyran and about 10 g. of tar were obtained. The 23 g. of lower-boiling material, diethoxydihydropyran, distilled at atmospheric pressure at about 205° with decomposition. After removal of a forerun fraction, the distillate was collected in four fractions for which the indices of refraction were as follows: $n_D^{36°}$ = 1.4410, 1.4408, 1.4408, 1.4410. A middle fraction was analysed for carbon and hydrogen content. Calculated for

$C_9H_{16}O_3$: C, 62.77; H, 9.32
Found: C, 62.69; H, 9.73

The 2,4-dinitrophenylhydrazone of 5-hydroxyethoxypentenal was prepared by heating one gram each of diethoxydihydropyran and 2,4-dinitrophenylhydrazine in aqueous alcohol containing hydrochloric acid. Under these conditions, the acetal link of the diethoxydihydropyran is cleaved with loss of an ethoxyl group and formation of the free aldehyde, 5-hydroxyethoxypentenal. An orange derivative was

obtained which after recrystallization from aqueous alcohol melted at 145°. Analysis: Calculated for $C_{13}H_{16}O_6N_4$: C, 48.14; H, 4.97
Found: C, 48.14; H, 5.16
C, 48.08; H, 5.11

B. The reaction of both the liquid and solid forms of 2-ethoxydihydropyran with sodium ethoxide was explored. The results were essentially the same. The yield of material was very low and a product which was free of bromine was obtained only with the greatest of difficulty. To 500 ml. of a solution of sodium ethoxide prepared from 28 g. (1.2 m.) of sodium was added 310 g. (1.08 m.) of 2-ethoxy-3,4-dibromotetrahydropyran containing relatively little of the solid isomer. The solution was brought to boiling on the steam cone and then filtered to remove 90 g. (0.9 mole) of impure sodium bromide. The filtrate was placed in a 1-liter and refluxed for twelve hours at the end of which time the reaction medium was again filtered. An additional 42 g. of impure sodium bromide was obtained making a total of 132 g. (1.3 moles) or about 60% of that potentially available from the starting material. The slightly acidic filtrate was poured into an equal volume of water and extracted with ether. The ether extract was dried over sodium sulfate and filtered. After removal of the ether the residue was distilled. A lower-boiling fraction, 90-104° at 14 mm. was shown by analysis to contain 23.5% bromine. In addition considerable unreacted 2-ethoxy-3,4-dibromotetrahydropyran was obtained of which a major portion crystallized when stored in the ice box. The lower-boiling product and the unreacted dibromo compound were added to a 1-liter flask containing 500 ml. of a solution of sodium ethoxide prepared from 28 g. (1.2 moles) of sodium. The contents of the flask

was heated for twelve hours during which time 250 ml. of alcohol was removed. The residue was filtered to remove sodium bromide and the filtrate heated for three hours with 200 ml. of a solution of sodium ethoxide prepared from 8 g. of sodium. More sodium bromide precipitated. This was removed by filtration and the filtrate refluxed for another ten hours during which time most of the alcohol was removed. The residue was added to 300 ml. of water and the mixture extracted with ether. The ether extract was dried over sodium sulfate in the ice box and filtered. After removal of solvent, the residue was distilled to obtain 58 g. of a crude fraction containing about 7-10 g. of unreacted 2-ethoxy-3,4-dibromotetrahydropyran. This product was added to a 500 ml. flask containing 30 g. of potassium hydroxide dissolved in 200 ml. of alcohol and refluxed for twelve hours during which time most of the alcohol was removed. A precipitate of potassium bromide was evident. Distilled water was added to the residue which was then extracted with ether. The ether extract was dried over magnesium sulfate in the ice box and then filtered. After removal of solvent the residue was distilled. In addition to some tarry residue and a little high-boiling material there was obtained about 30 g. of diethoxydihydropyran free from bromine. $n_D^{27^\circ} = 1.4445$. This material yielded the same 2,4-dinitrophenylhydrazone on appropriate treatment as was yielded by the material obtained in preparation A above.

Hydrogenation of Diethoxydihydropyran.

A. Eight grams of a sample of diethoxydihydropyran, obtained from 2-ethoxy-3,4-dibromotetrahydropyran by one alcoholic potassium hydroxide followed by one sodium ethoxide treatment, (preparation A above) was dissolved in 20 ml. of absolute alcohol and hydrogenated

in the quantitative apparatus over 0.5 g. of 5% palladium-charcoal catalyst. Theoretical absorption of hydrogen was calculated to be 1120 ml. After one hour the hydrogenation arrested itself after 1145 ml. of hydrogen had been absorbed. The product (7.3 g.) of diethoxytetrahydropyran had $n_D^{28^\circ} = 1.4311$.

B. Twenty-one grams of the diethoxydihydropyran obtained in preparation B described above was placed in a 200 ml. bottle containing 1 g. of 5% palladium-charcoal, 1 g. of potassium carbonate and 75 ml. of absolute alcohol. Hydrogen was forced into the bottle to give a starting pressure of 25 p.s.i. and the bottle rapidly shaken. The pressure at which the hydrogenation arrested itself was 16 p.s.i. For this apparatus the calculated pressure drop required for the hydrogenation of one double bond was 8.7 p.s.i. The reaction medium was filtered, the alcohol removed, and the residue distilled. Diethoxytetrahydropyran (18 g.) boiling at 93° at 15 mm., $n_D^{28^\circ} = 1.4315$, was obtained. Analysis: Calculated for $C_9H_{18}O_3$: C, 61.74; H, 10.34
Found: C, 61.74; H, 10.57
61.71; 10.39

Acid Treatment of 2-Ethoxy-3,4-dibromotetrahydropyran.

Thirty grams of 2-ethoxy-3,4-dibromotetrahydropyran was vigorously shaken with 300 ml. of hot 50% sulfuric acid for fifteen minutes. The brown emulsion resulting was slowly added to a solution of 50 ml. of 85% phosphoric acid in 200 ml. of water which was undergoing steam distillation. The distillate was continued until the odor of

bromopentadienal could no longer be detected in the distillate which was repeatedly extracted with peroxide-free ether. The ether extract was dried over magnesium sulfate and filtered. After removal of the solvent, 3 g. of a yellow liquid, boiling at 93-4° at 20 mm. were collected. The same 2,4-dinitrophenylhydrazone was obtained from this liquid that was yielded by 3-bromopentadien-2,4-al. However, analysis of the yellow liquid revealed that a large part of it was unreacted 2-ethoxy-3,4-dibromotetrahydropyran.

2-Ethoxy-3-bromo-Δ^3-dihydropyran (LXVI). A thick-walled steel cylinder, 9 inches high and with an internal diameter of 3 3/4 inches was fitted with a rubber stopper through which passed a thermometer well, reaching almost to the bottom of the cylinder, a brass sleeve for a stainless steel stirrer, a short piece of 11 mm. glass tubing, and a long piece of 13 mm. glass tubing. The long piece of tubing was bent so as to convey the exiting gases from the cylinder into a 500 ml. erlenmeyer flask immersed in an ice-water bath. The 11 mm. piece of tubing was fitted with a dropping funnel. About 500 g. of potassium hydroxide pellets was placed in the steel cylinder which was supported by an iron ring just above a Meeker burner. The cylinder was heated until the potassium hydroxide melted at which time stirring was commenced. The heating was continued until a thermometer placed in the well registered 250-260°. This temperature was maintained while a solution of 120 g. of 2-ethoxy-3,4-dibromotetrahydropyran in 120 ml. of toluene was added through the dropping funnel over a period of one hour.

The distillate was washed with water in a separatory funnel and the toluene solution (more dense than water) withdrawn and dried

over magnesium sulfate. The solution was filtered, the solvent removed, and the residue distilled under reduced pressure. The fraction boiling at 85-100° at 10 mm. was crude 2-ethoxy-3-bromo-Δ^3-dihydropyran. Yield: 41 g. (48%). In addition unreacted 2-ethoxy-3,4-dibromotetrahydropyran boiling at 125° at 10 mm. was obtained. Yield: 35 g. (29% recovery). Based on the 2-ethoxy-3,4-dibromotetrahydropyran recovered the crude yield was 67%. The overall yield of pure 2-ethoxy-3-bromo-Δ^3-dihydropyran from a batch of 2-ethoxy-3,4-dibromotetrahydropyran, when the latter was recovered and reused, was about 50%. Redistilled material boiled at 88° at 10 mm. $n_D^{21°} = 1.4900$ $D_4^{21°} = 1.385$. Analysis: Calculated for

$C_7H_{12}BrO_2$: C, 40.60; H, 5.35; Br, 38.58
Found: C, 40.68; H, 5.49; Br, 38.51

2,4-Dinitrophenylhydrazone of 2-Bromo-5-hydroxypenten-2-al (LXXI). One gram each of 2-ethoxy-3-bromo-Δ^3-dihydropyran and 2,4-dinitrophenylhydrazine were heated on the steam bath with 50 ml. of 95% alcohol. A clear solution resulted in a few minutes. Then 2 ml. of concentrated hydrochloric acid was added and the heating continued while about 20 ml. of water were gradually added. Under these conditions the acetal link in 2-ethoxy-3-bromo-Δ^3-dihydropyran was cleaved with elimination of an ethoxyl group to form the free aldehyde, 2-bromo-5-hydroxypenten-2-al (LXXV). The hot aqueous alcoholic solution was filtered and an orange solid crystallized from solution on cooling. It was isolated by suction filtration, washed several times with water and dried in the air. After one recrystallization from benzene-pet ether mixture and two from aqueous alcohol, the derivative (LXXI)

melted at 159-160° with decomposition. Analysis: Calculated for $C_{11}H_{11}BrO_5N_4$: C, 36.78; H, 3.09
Found: C, 36.94; H, 3.21

Hydrogenation of 2-Ethoxy-3-bromo-Δ^3-dihydropyran. Eleven grams of 2-ethoxy-3-bromo-Δ^3-dihydropyran, 12 g. of sodium carbonate, 1.5 g. of 5% palladium-charcoal catalyst, and 25 ml. of distilled ethanol were placed in a bottle. Hydrogen at a pressure of 20.5 p.s.i. was forced into the bottle which was then rapidly shaken for two hours. The hydrogenation arrested itself at a pressure of 12.5 p.s.i., a drop of 8 p.s.i. The theoretical pressure drop required for saturation of one double bond and hydrogenolysis of one bromine atom was 7.4 p.s.i. Water was added to the bottle and the contents then extracted with ether. The ether extract was dried over sodium sulfate and filtered. After removal of solvent, a colorless liquid, 2-ethoxytetrahydropyran, boiling at 44° at 13 mm., $n_D^{27^\circ} = 1.4260$, was obtained. The liquid yielded a yellow 2,4-dinitrophenylhydrazone which gave no depression in a mixed melting point determination with the derivative obtained from a known sample of 2-ethoxytetrahydropyran.

Numerous other attempts to hydrogenate 2-ethoxy-3-bromo-Δ^3-dihydropyran in order to obtain 2-ethoxy-3-bromotetrahydropyran were unsuccessful. Using Raney nickel, palladium-charcoal or Adams' catalyst either hydrogenolysis of bromine occurred (to form 2-ethoxytetrahydropyran) or the hydrogenation quickly arrested itself as if the catalyst were poisoned.

Di-2-(3-bromo-Δ^3-dihydropyranyl) ether (LXXIV). To a solution of 250 ml. of concentrated sulfuric acid in 250 ml. of water, contained

in a 1-liter flask immersed in ice water, 138 g. of 2-ethoxy-3-bromo-Δ^3-dihydropyran was slowly added. The acid solution was kept below 5° and rapidly stirred during the addition. Solid appeared very quickly. The stirring was continued for fifteen minutes after all the 2-ethoxy-3-bromo-Δ^3-dihydropyran had been added. About 200 g. of ice was added to the contents of the flask which was then filtered. (The odor of bromopentadienal was evident.) The precipitate was washed thoroughly with water, then alcohol, and dried in the air. Yield: 78 g. (69%). Di-2-(3-bromo-Δ^3-dihydropyranyl) ether melted sharply at 143° after recrystallization from aqueous acetone. Analysis:

Calculated for $C_{10}H_{12}Br_2O_3$: C, 35.23; H, 3.56; Br, 47.00
Found: C, 35.12; H, 3.58; Br, 47.24

A 2,4-dinitrophenylhydrazone was prepared from di-2-(3-bromo-Δ^3-dihydropyranyl) ether by boiling the ether with 2,4-dinitrophenylhydrazine in aqueous alcohol to which hydrochloric acid had been added. The orange precipitate obtained melted at 159-160° and gave no depression in a mixed melting point determination with the 2,4-dinitrophenylhydrazone (LXXI) obtained from 2-ethoxy-3-bromo-Δ^3-dihydropyran.

2-Bromopentadien-2,4-al (LXXVI). Thirty grams of di-2-(3-bromo-Δ^3-dihydropyranyl) ether was added to a warm solution of 185 ml. of 85% phosphoric acid in 300 ml. of water in a 2-liter flask and steam distilled. Each 200 ml. portion of distillate was collected, some ice and salt added, and finally extracted three times with peroxide-free ether. After about 3-4 liters of distillate had been collected, another 30 g. of di-2-(3-bromo-Δ^3-dihydropyranyl) ether was added to the steam distillation flask. Distillation and extraction

were continued until the odor of 2-bromo-pentadien-2,4-al could no longer be detected in the distillate. The contents of the flask were a clear amber with only slight evidence of decomposition having occurred.

The ether extract of about 1-liter volume, now a light green, was dried over magnesium sulfate in the cold and filtered. The ether was removed under a nitrogen atmosphere at reduced pressure. The residue was transferred to a smaller flask, a little hydroquinone added, and distilled in a nitrogen atmosphere. The fraction boiling at 48-52° at 2-3 mm. (or 78° at 10 mm.) was 2-bromopentadien-2,4-al, still yellow after redistillation. Yield: 27.2 g. (48%) $n_D^{25°} = 1.5862$.

Analysis: Calculated for C_5H_5OBr: C, 37.30; H, 3.13
Found: C, 37.66; H, 3.60

(Mrs. Aldridge, the analyst, reported this aldehyde to be an unusually difficult sample to analyse as mentioned in the discussion section of this thesis.)

2,4-Dinitrophenylhydrazone of 2-Bromopentadien-2,4-al (LXXVI-A). When treated in the usual manner with 2,4-dinitrophenylhydrazine, 2-bromopentadien-2,4-al yielded a derivative very readily. This red 2,4-dinitrophenylhydrazone darkened before melting at 155° with decomposition. Analysis: Calculated for $C_{11}H_9BrO_4N_4$: C, 38.73; H, 2.66
Found: C, 38.76; H, 2.67

Semicarbazone of 2-Bromopentadien-2,4-al (LXXVI-B). An aqueous suspension or alcoholic solution of 2-bromopentadienal added to a solution of semicarbazide hydrochloride and potassium acetate in water readily yielded a flocculent white precipitate. This semicarbazone derivative (LXXVIII) recrystallized from aqueous alcohol in

lustrous plates. It gradually darkened on heating and decomposed at about 150-160° without melting. Analysis: Calculated for

$C_6H_8BrON_3$: C, 33.05; H, 3.70
Found: C, 33.46; H, 3.86

3-Bromohexadien-3,5-ol-2 (LXXVII). Methylmagnesium bromide was prepared by bubbling methyl bromide into a mixture of 200 ml. of anhydrous ether and 8 g. (.33 moles) of magnesium contained in a 3-neck flask fitted as usual for a Grignard reaction. When all the magnesium had dissolved, an ice-water bath was placed about the flask and a solution of 20 g. (.13 moles) of bromopentadienal in 50 ml. of ether was slowly added. A vigorous reaction ensued. The reaction medium was stirred for an additional twenty minutes with the cooling bath removed. The product was poured into a 1-liter separatory funnel containing an intimate mixture of cracked ice and ammonium chloride. After shaking the funnel an emulsion was obtained between the ether and water layers. This emulsion was treated with anhydrous sodium sulfate and the ether derived from the emulsion combined with the original ether layer. The combined ether extract was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure in a nitrogen atmosphere. The residue, distilled in a nitrogen atmosphere in the presence of hydroquinone yielded 18.5 g. (83%) of 3-bromohexadien-3,5-ol-2 boiling at 56° at 0.8 mm. $n_D^{26} = 1.5335$. Analysis:

Calculated for C_6H_9BrO: C, 40.70; H, 5.12
Found: C, 40.75; H, 5.46
C, 40.88; H, 5.37

When 3-bromohexadien-3,5-ol-2 was treated with phenylurethan or ∝-naphthylurethane in the usual manner, marked decomposition occurred. The only product isolated was the corresponding urea.

Hydrogenation of 3-Bromohexadien-3,5-ol-2 to Hexanol-2 (LXXVIII). Three grams of 3-bromohexadien-3,5-ol-2 in 95% ethanol was hydrogenated over 0.1 g. platinum oxide at approximately one atmosphere pressure. The starting pressure was 18.4 p.s.i. After twenty-seven minutes the hydrogenation arrested itself at 14.9 p.s.i. Using this apparatus the calculated pressure drop was 3.5 p.s.i., the same as the observed pressure drop. In a similar experiment 4 g. of bromohexadienol was hydrogenated and the product isolated from the solvent alcohol. The boiling point of this product was 138°. (The literature value for the boiling point of hexanol-2 is 136°)

Oxidation of Hexanol-2 to Hexanone-2 (LXXIX). Six grams of potassium dichromate, 10 ml. of water, and 0.6 g. of hexanol-2 (obtained by reduction of 3-bromohexadien-3,5-ol-2) were placed in a 100 ml. round-bottom flask and rapidly stirred. A solution of 3.3 ml. of concentrated sulfuric acid in 10 ml. of water was added in small portions while cooling the flask. A beaker of warm water was then placed around the flask and a temperature of 50° was maintained during fifteen minutes of stirring the acid solution. The contents of the flask was then steam distilled and hexanone-2 was obtained in the distillate.

2,4-Dinitrophenylhydrazone of Hexanone-2. The distillate from the oxidation experiment described above was treated with an acidic solution of 2,4-dinitrophenylhydrazine in aqueous alcohol. An orange derivative was obtained which melted at 107-109°. When mixed with a known sample of the 2,4-dinitrophenylhydrazone of hexanone-2 the melting point was 107-109°.

Semicarbazone of Hexanone-2. The distillate obtained on steam distillation of hexanone-2 yielded a semicarbazone melting at 123-124°. A mixed melting point determination with a known sample of the semicarbazone of hexanone-2 showed no depression.

3-Bromohexatriene-1,3,5 (LXXI). Sixteen grams of 3-bromohexadien-3,5-ol-2 was distilled under a nitrogen atmosphere into a column, 19 mm. in diameter, packed with 8-14 mesh activated aluminum oxide for a length of 25 cm. The column was wrapped with nichrome wire by which it was electrically heated to 315-325°, the temperature at which it was maintained during the dehydration. A pressure of less than 1 mm. was obtained by means of an oil pump. The product exiting from the column was caught in a receiver immersed in a Dry Ice-acetone bath. After distillation of the alcohol (which always left behind a tarry residue) was complete, the receiver was disconnected and anhydrous potassium carbonate added to the contents which included water and 3-bromohexatriene-1,3,5. The contents of the receiver was washed into a small Buchner funnel by means of peroxide-free ether and suction filtered. The filtrate was transferred to a small flask arranged for distillation under a nitrogen atmosphere and a little hydroquinone added. After removal of the solvent, 4 g. (20%) of 3-bromohexatriene-1,3,5 distilled at 42° at 10 mm. $n_D^{28°} = 1.5683$ $D_4^{23°} = 1.320$. Analysis: Calculated for

C_5H_7Br: C, 45.31; H, 4.44; Br, 50.25
Found: C, 45.85; H, 4.63; Br, 50.62

The distilling pot contained a residue of deep blue color which was always observed in this distillation. The bromohexatriene itself quickly took on color. At Dry Ice temperatures samples could be kept

for a period of weeks in the presence of hydroquinone. A sample remained essentially unchanged after twenty-four hours in the ice box over hydroquinone. The instability of bromohexatriene was clearly shown by analyses of first, a sample of freshly distilled material and secondly, a sample taken from the same product after two hours at room temperature. Analysis of first sample: C, 45.91; H, 4.80. Analysis of second sample: C, 46.23; H, 5.64.

Quantitative Hydrogenation of 3-Bromohexatriene-1,3,5. Into a 200 ml. bottle were placed 0.312 g. of bromohexatriene, 0.2 g. of platinum oxide and about 60 ml. of 95% ethanol. The bottle was connected to the quantitative hydrogenation apparatus and the bromohexatriene hydrogenated at atmospheric pressure. In forty minutes the reaction arrested itself after an absorption of 258 ml. of hydrogen. Theoretical absorption calculated for reduction of the platinum oxide, saturation of three double bonds, and hydrogenolysis of one bromine atom was 215 ml. (10% error).

Ultraviolet Absorption Spectrum of 3-Bromohexatriene-1,3,5. Four drops (approximately 0.09 g.) of pure 3-bromohexatriene-1,3,5 were dissolved in 25 ml. of purified cyclohexane. Two ml. of this solution was dissolved in 100 ml. of cyclohexane and then 4 ml. of this second solution dissolved in another 100 ml. of cyclohexane. This final dilution gave a suitable concentration (approximately 2×10^{-5} moles per liter). No attempt was made to weigh the bromohexatriene because of its instability in air. Hence only the relation of percent transmission to wave length could be obtained. The results as determined in a Beckmann quarts spectrophotometer using a cell

1.000 cm. thick are given below and plotted in Fig. Ib (p-76).

Wave Length in Millimicrons	Percent Transmission	Wave Length in Millimicrons	Percent Transmission
340	100	268	43.4
330	99.2	267.5	43.0
320	99.8	267	43.3
310	99.8	266	45.4
300	98.8	265	48.0
298	98.1	264	51.0
296	97.1	263	53.1
294	95.5	262	54.7
292	94.2	261.5	55.0
290	91.9	261	55.1
288	88.2	260.5	55.0
286	81.8	260	55.1
284	72.1	259.5	54.8
283	65.3	259	54.8
282	59.9	258.5	54.5
281	54.2	258	54.2
280	51.0	257.5	55.0
279	49.2	257	55.2
278.5	49.1	256	56.8
278	49.2	255	58.7
277.5	50.1	254	61.5
277	50.9	253	63.1
276	52.4	252	65.1
275	54.1	251	66.3
274.5	54.1	250	67.2
274	54.2	249	67.9
273.5	54.1	248	68.8
273	54.2	246	71.0
272	52.5	244	73.3
271	50.0	242	76.0
270	46.7	240	78.1
269	44.2	230	84.4
268.5	44.1		

Infrared Absorption Spectrum of 3-Bromohexatriene-1,3,5. A sample of pure 3-bromohexatriene-1,3,5 in an absorption cell 0.1 mm. thick was used for the determination of the infrared absorption spectrum. The instrument was a Perkins and Elmer Infrared Spectrophotometer. The work was kindly done in Dr. Plyler's laboratory in the Radiometry Section of the Bureau of Standards, Washington, D. C. The spectrum is presented in Fig. II (p-77). There was no spectrum of a similar compound available for comparison purposes. Dr. Plyler

believes the absorption band at 13.9-14.5 microns may be attributed to the carbon-bromine bond stretching.

Bromination Product of 3-Bromohexatriene-1,3,5. About 0.3 g. of bromohexatriene was dissolved in 5 ml. of carbon tetrachloride and cooled in an ice-water bath. A solution of equal volumes of bromine and carbon tetrachloride was slowly added until the bromine color persisted. The reaction medium was then heated on the steam cone until all solvent had been removed. Petroleum ether (30-60°) was added to the dark residue and crystals appeared when the mixture was cooled to about -60°. After recrystallization the melting point was 87-8°.

Analysis: Calculated for $C_6H_7Br_5$: C, 15.05; H, 1.49; Br, 83.6
Found: C, 15.39; H, 1.66; Br, 84.1

Attempt to Prepare Maleic Anhydride Adduct of 3-Bromohexatriene-1,3,5. One gram of bromohexatriene and 1.5 g. of recrystallised maleic anhydride were dissolved in 10 ml. of anhydrous benzene. After briefly heating the flask was stoppered and left for forty-eight hours. The solvent was then partially removed and the solid formed isolated by suction filtration. This solid, slightly colored, was not soluble in any of a large number of organic solvents tested. It did dissolve in 10% sodium hydroxide solution but no solid was yielded upon subsequent acidification. Since this product could not be purified, further investigation was abandoned.

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ABSTRACT

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Title of Thesis: "Studies in Pyran Chemistry: Synthesis of 3-Bromohexatriene-1,3,5."

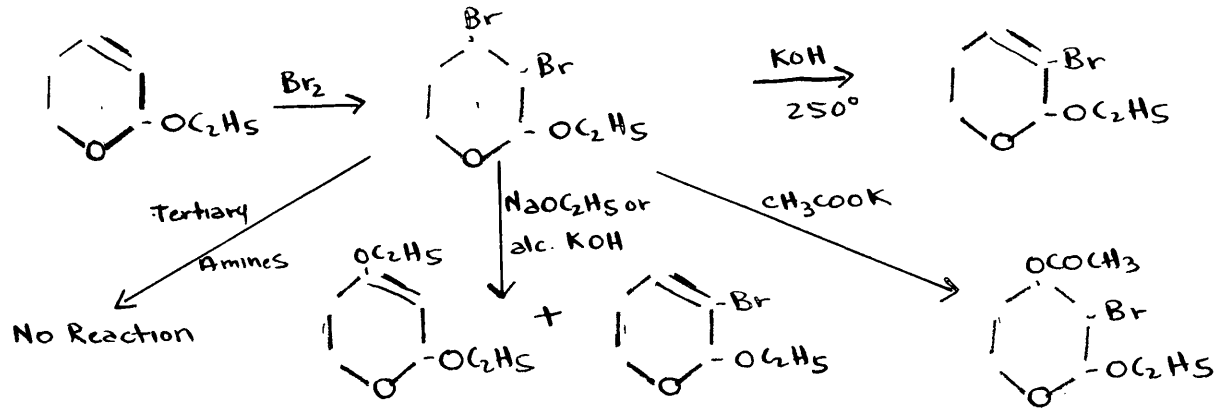
Thesis directed by Dr. C. Forrest Woods

Major: Organic Chemistry

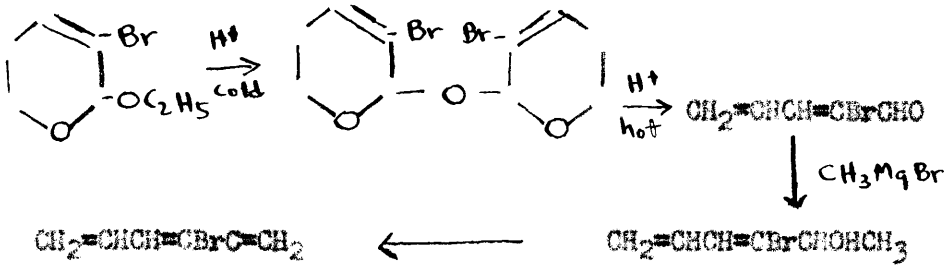
Minors: Physical Chemistry, Inorganic Chemistry

Pages in Thesis: 127 Words in abstract: 160

2-Ethoxy-3,4-dibromotetrahydropyran was prepared by bromination of 2-ethoxy-Δ^3-dihydropyran. Two geometrical isomers of this substance were obtained. The reactions of 2-ethoxy-3,4-dibromotetrahydropyran with alkaline reagents were studied. A mixture of a diethoxydihydropyran and 2-ethoxy-3-bromo-Δ^3-dihydropyran was obtained using sodium ethoxide. Alcoholic potassium hydroxide gave similar results. Potassium acetate in diethylene glycol led to a displacement of bromine by acetate ion. No reaction was effected by tertiary amines. The addition of a toluene solution of 2-ethoxy-3,4-dibromotetrahydropyran to molten potassium hydroxide at about 250° C. gave acceptable yields of 2-ethoxy-3-bromo-Δ^3-dihydropyran.



2-Ethoxy-3-bromo-Δ^3-dihydropyran yielded an ether, di-2-(3-bromo-Δ^3-pyrenyl) ether on treatment with cold 1:1 sulfuric acid. The ether was added to a phosphoric acid solution and the mixture steam distilled. 2-Bromopentadien-2,4-al was obtained and treated with methylmagnesium bromide. The product, 3-bromohexadien-3,5-ol-2, was catalytically dehydrated in a nitrogen atmosphere at reduced pressure to yield 3-bromohexatriene-1,3,5.



A pentabromo compound was obtained by the addition of bromine to 3-bromohexatriene-1,3,5. The ultraviolet and infrared absorption spectra of 3-bromohexatriene-1,3,5 were determined.

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