OXIDATIONS AND DEHYDROGENATIONS WITH N-BROMOSUCCINIMIDE AND RELATED N-HALOIMIDES

ROBERT FILLER

Department of Chemistry, Illinois Institute of Technology, Chicago 16, Illinois

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I. INTRODUCTION

The use of N-bromoacetamide as an agent for allylic bromination was first reported by Wohl (218) in 1919. However, it was not until 1942 that Ziegler and his co-workers (227) published the results of their detailed studies on the application of N-bromosuccinimide for allylic brominations.

This type of halogenation has come to be known as the Wohl–Ziegler reaction and an excellent review on the subject has been published (55).

Under different conditions, these N-halo compounds also react with olefins to add bromine to the double bond or act as a source of hypohalous acid in aqueous solution.

This earlier work stimulated tremendous interest in this group of compounds, which also includes N-chlorosuccinimide, N-iodosuccinimide, N-bromophthalimide, isocyanuric bromide, and isocyanuric chloride. These compounds have been used successfully not only as halogenating agents, but several of them have been found to be effective agents for oxidations and dehydrogenations.

The reactions and uses of N-bromosuccinimide were reviewed in 1951 (211) and more recently an excellent survey of the chemistry of this compound has been published (103). In both of these reviews, references were made to a number of oxidation and dehydrogenation reactions. However, in light of the rapidly growing literature on this subject, a comprehensive, unified discussion of this important application of N-halogen compounds appears to be warranted.

This review covers the literature through the June 30, 1960, *Chemical Abstracts*. Several journals, including the *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, *Journal of the Chemical Society*, *Bulletin of the Chemical Society of Japan*, and *Tetrahedron*, were checked through the end of 1961. The

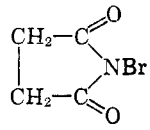
Organic sections of *Current Chemical Papers* through 1961 also were covered.

II. Scope of the Review

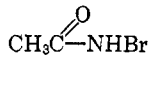
The body of this review will consist of two major subdivisions, one dealing with various *oxidative processes*, including cleavage reactions, the other with reactions involving *dehydrogenations*. It is recognized that the difference between these two classifications is often a matter of viewpoint. On an arbitrary basis, therefore, we have classified as oxidations those transformations in which functional groups are raised to a higher oxidation state by removal of valence electrons in the molecule, as well as reactions involving the indirect introduction of oxygen into the molecule. Reactions by which supplementary double bonds are introduced and aromatization of cyclic structures occur, are termed dehydrogenations. The detailed breakdown into various categories may be found in the Table of Contents.

III. Nomenclature and Notations

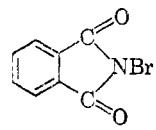
In the course of this review, mention will be made frequently of various N-haloimides and related compounds. In order to simplify the discussion and to avoid repetition, abbreviations have been adopted for these reagents. These will be used often in the text and consistently in the tables. The structural formulas and the abbreviated notations are shown for the compounds involved.



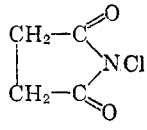
N-Bromosuccinimide (NBS)



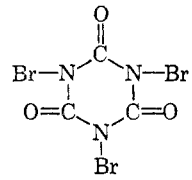
N-Bromoacetamide (NBA)



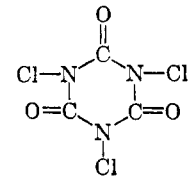
N-Bromophthalimide (NBP)



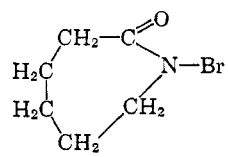
N-Chlorosuccinimide (NCS)



Isocyanuric bromide* (ICB)



Isocyanuric chloride* (ICC)



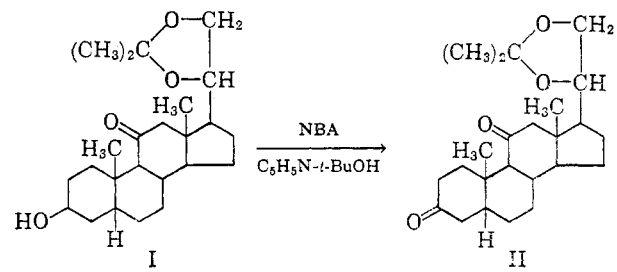
N-Bromocaprolactam (NBC)

* The *Chemical Abstracts* nomenclature names for these compounds are: trichloro (or tribromo)-s-triazine-2,4,6(1H,3H,5H)-trione.

IV. Oxidation

A. Alcohols

One of the earliest reports of the use of N-halogen compounds as oxidizing agents was the demonstration by Reich and Reichstein (174) that N-bromoacetamide in aqueous acetone smoothly oxidizes secondary alcohols to ketones. Sarett (189) found that these conditions were unsuitable for molecules containing acid-sensitive functional groups and therefore used NBA in dry pyridine-*tert*-butyl alcohol for the oxidation of the triolone acetonide, I, to the dioldione acetonide, II.



I II

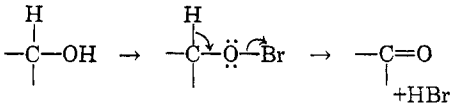
At about this time, Fieser and Rajagopalan (66, 67, 68, 70) described the selective oxidation of steroid alcohols by N-bromosuccinimide. Studies on the oxidation of primary and secondary alcohols to aldehydes and ketones using N-chlorosuccinimide (80, 86, 87, 88) also were reported and, in the years that followed, an extremely large number of papers were published which dealt either directly or indirectly with the use of these and structurally related reagents for the oxidation of alcohols to carbonyl functions. By far the widest application of these compounds as oxidizing agents for alcohols has been in the steroid field, due in large measure to the mildness of the reaction conditions and to the fact that these reagents frequently exhibit remarkable stereoselectivity, of particular value in steroid synthesis.

A variety of reaction conditions have been used to effect the oxidation of alcohols with these reagents. The ease of reaction is often dependent on the solvent employed. Mild oxidations with NBS or NBA are carried out frequently in aqueous acetone or aqueous dioxane. The intensity of the reaction increases and selectivity decreases when aqueous *tert*-butyl alcohol or *tert*-butyl alcohol-pyridine are used as solvents. The role of pyridine is that of a proton acceptor, to remove the hydrogen bromide formed, which otherwise would react with NBS or NBA to form bromine. Light is not necessary and the reaction often proceeds readily in the dark. It is quite evident that in these polar media the reaction proceeds *via* a "positive" halogen and not by a free radical path.

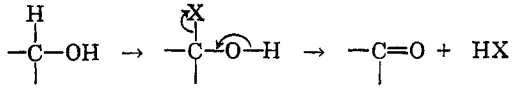
The oxidation of benzyl alcohol to benzaldehyde using N-chlorosuccinimide proceeds more readily in chlorobenzene, *tert*-butyl alcohol or pyridine than in benzene

or carbon tetrachloride (88). Occasionally, mixtures of solvents (*e.g.*, benzene and pyridine), have been employed. In addition, the oxidation is accelerated by ultraviolet or even ordinary light. In this case, the mechanism is not as clear and it is possible that the initial halogenation proceeds both by ionic and radical paths.

The mechanism of the oxidation has not been clearly established, although two interpretations have been advanced. While it is generally accepted that a "positive" halogen is the attacking species in polar media, the site of attack may be open to question. It has been suggested that the primary or secondary alcohol forms a hypobromite (122) which readily loses hydrogen bromide to form the carbonyl product:



An alternate mechanism has been suggested (133) in which it is proposed that oxidation proceeds through halogen substitution of a hydrogen on the carbon atom bearing the –OH group, with rapid loss of hydrogen halide



Here, the rate-determining step is the cleavage of the C–H bond to form the halo intermediate.

There are several lines of evidence in support of the second mechanism. For example, the oxidative cleavage of ethyl benzyl ether, which cannot form a hypobromite, is effected readily by NBS to form benzaldehyde (133). Also, the rupture of the C–H bond and the formation of a C–Cl bond is illustrated by the conversion of benzaldehyde to benzoyl chloride using N-chlorosuccinimide (88). An even more convincing argument is the similarity of these oxidations to the chromic acid oxidation of alcohols. Westheimer (212) has shown that the rate-determining step is the cleavage of the C–H bond after the formation of a chromate ester. Thus, an *equatorial* alcohol is usually less susceptible to oxidation by either chromic acid or the N-halo compounds than is its *axial* epimer, because in the former case the C–H bond is less accessible in the axial orientation (*vide infra* under selective oxidations).

1. *Primary and Secondary Alcohols*

In general, secondary alcohols are oxidized more readily by these reagents than are primary alcohols. The ease of oxidation of an alcohol depends not only on its structure, but on the nature of the N-halo compound and the reaction conditions.

Thus, both primary and secondary aromatic alcohols, having the –OH group on the carbon adjacent to the aromatic nucleus, are oxidized by NBA to aldehydes and ketones in good yields (132). Aromatic alcohols in which the hydroxyl group is not so located, *e.g.*, 2-phenylethanol, 3-phenyl-1-propanol, cinnamyl alcohol, benzylisopropylcarbinol $C_6H_5CH_2CHOHCH(CH_3)_2$, and $(C_6H_5CH_2)_2CHOH$, dibenzylcarbinol, give the corresponding carbonyl compounds in yields below 1%. Cyclic secondary alcohols react readily with NBA or NBS to yield the corresponding ketone. Recently, N-bromocaprolactam (NBC) has also been shown to be effective in oxidizing secondary alcohols (202).

Whereas NBA and NBS fail to oxidize aliphatic primary alcohols, N-chlorosuccinimide is a stronger oxidizing agent and has been used successfully for the oxidation of these compounds (80, 81, 185, 186).

In addition to the corresponding aldehyde, high yields of an ester frequently are obtained. These esters are derived from the primary alcohol and the carboxylic acids formed on further oxidation of the aldehyde. For example, isoamyl alcohol, on heating at 90–95° for two hours with NCS in pyridine–benzene, gave a 40% yield of isoamyl isovalerate (81, 185).

When polyvinyl alcohol was heated with NBS in aqueous pyridine, approximately 2–6% of the –OH groups were oxidized to carbonyl functions (187).

These oxidation reactions form the basis of convenient qualitative color tests for the presence of primary, secondary, and tertiary alcohols (the latter type fails to react with these reagents) (122). Similar color changes for differentiation of primary, secondary, and tertiary amines also have been described (10, 122), and the reactions involved will be discussed later. In Tables I and II are listed primary and secondary alcohols which have been oxidized by the N-haloimides, the products isolated, and the reaction conditions employed.

One of the most useful applications of these halogen compounds has been in the oxidation of steroid secondary alcohols. There are many such examples in the literature and a number of these are listed in Table III.

2. *Selective Oxidations*

a. Stereoselectivity

Advantage has been taken of the relatively mild conditions under which these oxidations are run to bring about the *stereoselective oxidation* of steroid alcohols, thereby making available compounds not easily obtained when stronger conditions are used. As mentioned earlier, *equatorial* alcohols generally are more difficult to oxidize than are their *axial* epimers, due to the greater inaccessibility of the C–H bond in the *axial* orientation, the rate-determining step being the rupture of this linkage. Relative rates of oxidation of *equatorial* and *axial* alcohols with chromic acid in acetic

TABLE I

OXIDATION OF PRIMARY ALCOHOLS BY N-HALOAMIDES AND -IMIDES

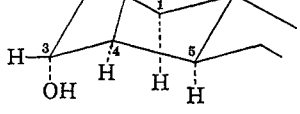
Alcohol	Product	Yield, %	Reaction conditions	References
CH_3OH	$HCOOCH_3$	45	NCS, C_5H_5N, C_6H_6, 90–5°, 2 hr.	185
C_2H_5OH	$CH_3CHO + CH_3COOC_2H_5$	15, 25	NCS, C_5H_5N, C_6H_6, 90–5°, 2 hr.	185
n-C_3H_7OH	$C_2H_5CHO + C_2H_5COOC_3H_7$	6, 39	NCS, C_5H_5N, C_6H_6, 90–5°, 2 hr.	185
n-C_4H_9OH	$C_3H_7CHO + C_3H_7COOC_4H_9$	0.8, 41	NCS, C_5H_5N, C_6H_6, 90–5°, 2 hr.	185
$HOCH_2CH_2OH$	CHO | CHO	9	NCS, C_5H_5N, C_6H_6, 90–5°, 2 hr.	185
$(CH_3)_2CH—CH_2CH_2OH$	Isovaleraldehyde +isoamyl isovalerate	0.8, 40	NCS, C_5H_5N, C_6H_6, 90–5°, 2 hr.	185
$(CH_3)_2CH—CH_2CH_2OH$	Isoamyl isovalerate + high-boiling chlorinated products		NCS, C_5H_5N, CCl_4, reflux, 12 hr.	81
$C_6H_5CH_2OH$	C_6H_5CHO	85, 89	NCS, C_5H_5N,C_6H_6, 90–5°, 2 hr.	185, 81
$C_6H_5CH_2OH$	C_6H_5CHO	45	1,3-Dibromo-5,5-dimethylhydantoin, *t*-BuOH-H_2O + NaOAc	163
$C_6H_5CH_2OH$	C_6H_5CHO	75	NBA, C_5H_5N + C_6H_6	133
$C_6H_5CH_2OH$	C_6H_5CHO	74, 70	NCS, C_5H_5N + light; NCS, C_6H_5Cl	87, 88
o-$CH_3C_6H_4CH_2OH$	*o*-$CH_3C_6H_4CHO$	71	NCS, C_6H_5Cl or C_5H_5N	88
m-$CH_3C_6H_4CH_2OH$	*m*-$CH_3C_6H_4CHO$ + chlorinated products	30–49	NCS, C_6H_5Cl or C_5H_5N	88
p-$CH_3C_6H_4CH_2OH$	*p*-$CH_3C_6H_4CHO$	62	NCS, C_6H_5Cl or C_5H_5N	88
o-$C_6H_4(CH_2OH)_2$	*o*-$C_6H_4(CHO)_2$	22	NCS, C_6H_5Cl or C_5H_5N	88
1-$C_{10}H_7CH_2OH$	1-$C_{10}H_7CHO$	12, 26	NCS, C_6H_5Cl or C_5H_5N	86, 88
1-$C_{10}H_7CH_2OH$	1-$C_{10}H_7CHO$	65	NBA, $CHCl_3$, C_5H_5N	133
2-$C_{10}H_7CH_2OH$	2-$C_{10}H_7CHO$	27	NCS, C_6H_5Cl or C_5H_5N	88
p-$O_2NC_6H_4CH_2OH$	*p*-$O_2NC_6H_4CHO$	35	NBA, $CHCl_3$, C_5H_5N	133
p-$MeOC_6H_4CH_2OH$	*p*-$MeOC_6H_4CHO$	71	NBA, C_5H_5N, C_6H_6	132
$C_6H_5CH=CH—CH_2OH$	$C_6H_5CH=CHCHO$		NCS	80

acid have been determined and the results demonstrate the preferential oxidation of alcohols with *axial* –OH groups (C–H equatorial) (210). Thus, epicholestanol (III, ring A shown) is oxidized at room temperature about 8.5 times as rapidly as cholestanol (IV, ring A only) by Cr(VI) in 90% acetic acid and 15 times faster in 95% acid.

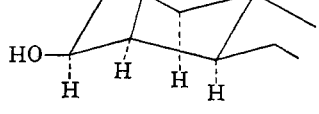
In synthetic practice, however, the conditions for chromic acid oxidations of saturated steroid secondary alcohols are quite vigorous and reaction proceeds very rapidly with relatively little discrimination between *equatorial* and *axial* alcohols.

On the other hand, NBS or NBA in aqueous acetone or aqueous dioxane provide considerably milder oxidation conditions and there are many examples which illustrate the use of these reagents for the selective oxidation of axial alcohols. Until recently, there had been no comparative rate studies of such oxidations using N-halogen compounds (118).

Oliveto, Herzog, and Hershberg, in their studies on 11-oxygenated steroids, oxidized 11-β-hydroxy (axial-OH) steroids to the 11-oxo compound with NBA in



III (3α–OH, axial)



IV (3β–OH, equatorial)

aqueous acetone, but found that they could carry out partial, selective oxidations of compounds containing the 11-α-hydroxy group (equatorial-OH). They observed that under these mild conditions, NBA selectively oxidized 3α- and 17β-OH groups, the 11α-OH remaining intact. Thus, etiocholane-3α,11α,17β-triol was converted to etiocholan-11α-ol-3,17-dione by NBA in aqueous methanol–acetone at room temperature (97). In contrast, when this triol was treated with chromic acid at room temperature, there was no oxidative selectivity and the trione was obtained.

Similarly, NBA oxidation of pregnane-3α,11α-diol-20-one produced the 11α-ol-3,20-dione in 85–90% yield (95). Other examples may be found in Table III.

In aqueous *tert*-butyl alcohol or *tert*-butyl alcohol–pyridine, NBS and NBA are much more powerful oxidizing agents and under these conditions, the stereoselectivity is lost. Both axial and equatorial secondary alcohol functions are readily oxidized to the corresponding oxo compound. For example, 3β-hydroxyergostan-11-one was converted to ergostan-3,11-dione in 70% yield by NBA in pyridine-*tert*-butyl alcohol at 20°, although the reaction period was 20 hr. (64). NBS behaved similarly in *tert*-butyl alcohol-water to oxidize either 3α- or 3β-hydroxy-17, 21-dibromopregnan-20-one to the 3, 20-dione (26).

b. Other Preferential Oxidations

Even among axial alcohols there may be significant differences in oxidation rates. These differences are often due to the greater relief of steric strain in one compound relative to another. Thus, cholestan-1α-ol (V) is subject to *three*-OH(a):H(a) interactions, which are removed on oxidation. In cholestan-4β-ol (VI), two OH(a):H(a) interactions are the same as in V but, in addition, there is a more significant OH:CH_3 interaction, the relief of which should lead to a faster rate of oxidation than for V. This, in fact, has been

TABLE II

OXIDATION OF SECONDARY ALCOHOLS BY N-HALOAMIDES AND -IMIDES

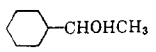
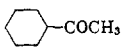
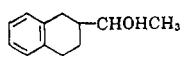
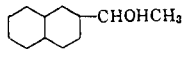
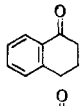
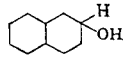
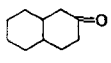
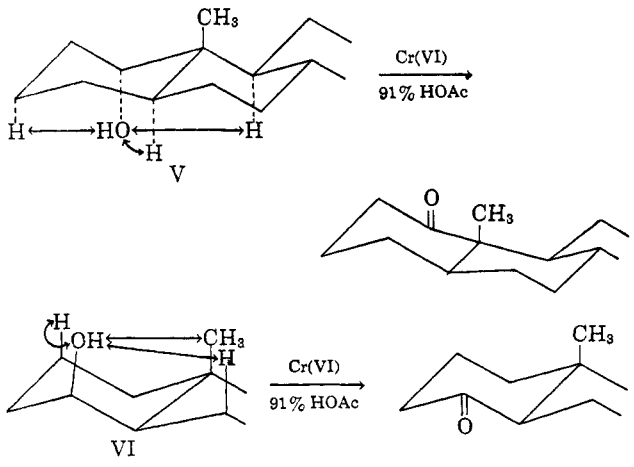
Alcohol	Product	Yield, %	Reaction conditions	References
$(CH_3)_2CHOH$	$(CH_3)_2CO$	60	NBS, CCl_4, C_5H_5N, reflux	199
$(CH_3)_2CHOH$	$(CH_3)_2CO$	93.5	NCS, C_5H_5N, C_6H_6, 90–5°, 2 hr.	185
$CH_3CHOHCO_2C_2H_5$	$CH_3COCO_2C_2H_5$	10	NBS, CCl_4, reflux	199
	$^+BrCH_2COCO_2C_2H_5$	20		
	$CH_3COCO_2C_2H_5$	58		
$CH_3CHOHCO_2C_2H_5$			NBS, CCl_4, $CaCO_3$, reflux	199
	$^+BrCH_2COCO_2C_2H_5$	19		
$CH_3CHOHCO_2C_2H_5$	$CH_3COCO_2C_2H_5$	42	NBS, CCl_4, C_5H_5N, reflux	199
$C_2H_5CHOHCO_2C_2H_5$	$C_2H_5COCO_2C_2H_5$	50	NBS, CCl_4, C_5H_5N, reflux	199
$ClCH_2CHOHCO_2C_2H_5$	$ClCH_2COCO_2C_2H_5$	72	NBS, CCl_4, reflux	199
		61	NBS, CCl_4, C_5H_5N, reflux	199
		45	NBA, $CHCl_3$, C_5H_5N	133
		50	NCS, C_5H_5N	81
		82	NBC, C_5H_5N, C_6H_6, 18 hr.	202
		60	NBA, $CHCl_3$, C_5H_5N	133
		60	NBA, $CHCl_3$, C_5H_5N	133
Borneol or isoborneol	Camphor	80	ICC, C_5H_5N, C_6H_6, heat, 5 min.	154
Borneol or isoborneol	Camphor	90	NCS, heat, 1 hr.	154
$C_6H_5CHOHCH_3$	$C_6H_5COCH_3$	80	NBA, C_5H_5N, C_6H_6	132
$C_6H_5CHOHCH_3$	$C_6H_5COCH_3$	65	NBS, CCl_4, C_5H_5N, reflux	199
$C_6H_5CHOHCH_3$	$C_6H_5COCH_2Br$		NBS, CCl_4, reflux 5 hr.	121
$C_6H_5CHOHC_2H_5$	$C_6H_5COC_2H_5$	85	NBA, C_5H_5N, C_6H_6	132
$C_6H_5CHOHCH_2C_6H_5$	$C_6H_5COCH_2C_6H_5$	95	NBA, C_5H_5N, C_6H_6	132
$C_6H_5CH_2CHOHCH_3$	$C_6H_5CH_2COCH_3$	35	NBA, C_5H_5N, C_6H_6	132
$C_6H_5CHOHC_4H_9$	$C_6H_5COC_4H_9$	63	NCS	86, 88
$(C_6H_5)_2CHOH$	$(C_6H_5)_2CO$	77, 97	NCS, C_5H_5N, heat	81, 87, 88
$(C_6H_5)_2CHOH$	$(C_6H_5)_2CO$	55–60	NBS, CCl_4, reflux 0.5 hr.	13
$(C_6H_5)_2CHOH$	$(C_6H_5)_2CO$	80	NBA, C_5H_5N, C_6H_6	132
$(C_6H_5)_2CHOH$	$(C_6H_5)_2CO$	88	NBC, C_5H_5N, C_6H_6, 18 hr.	202
$C_6H_5CHOHCOC_6H_5$	$C_6H_5COCOC_6H_5$	95	NBS, CCl_4, reflux 1.5 hr.	13
p-$CH_3OC_6H_4CHOHCOC_6H_4OCH_3$-*p*	*p*-$CH_3OC_6H_4COCOC_6H_4OCH_3$-*p*	82	NBS, CCl_4, reflux 0.5 hr.	13
Fluorenyl alcohol	Fluorenone	89	NBS, CCl_4, reflux 0.5 hr.	13
Xanthydrol	Xanthone	92	NBS, CCl_4, reflux 3 hr.	13
		65	NBA, $CHCl_3$, C_5H_5N	133
		50	NBA, $CHCl_3$, C_5H_5N	133
		65	NBA, $CHCl_3$, C_5H_5N	133
		60	NBA, $CHCl_3$, C_5H_5N	133
		70	NBA, $CHCl_3$, C_5H_5N	133
		70	NBA, $CHCl_3$, C_5H_5N	133
		70	NBA, $CHCl_3$, C_5H_5N	133
$CH_3CHOHCO_2C_2H_5$	$BrCH_2COCO_2C_2H_5$	64	NBS, CCl_4, reflux 6 hr.	121
$C_2H_5CHOHCO_2C_2H_5$	$CH_3CHBrCOCO_2C_2H_5$	66	NBS, CCl_4, reflux 5 hr.	121
$C_6H_5CH_2CHOHCO_2C_2H_5$	$C_6H_5CHBrCOCO_2C_2H_5$		NBS, CCl_4, reflux	121
$C_6H_5CHOHCO_2C_2H_5$	$C_6H_5COCO_2C_2H_5$	78	NBS, CCl_4, reflux 8 hr.	121

TABLE III

OXIDATION OF STEROID SECONDARY ALCOHOLS BY N-HALO COMPOUNDS

Steroid alcohol	Product	Yield, %	Reaction conditions	Reference
Cholesterol	Cholest-5-en-3-one		NCS	80
Cholestan-3β-ol	Cholestan-3-one		ICC, C_5H_5N, C_6H_6	
	2α-chlorocholestan-3-one		ICC, *t*-BuOH	154
Cholestane-3β,5-diol	Cholestan-5-ol-3-one		ICC, C_5H_5N, *t*-BuOH	154
Cholestane-3β,6β-diol	Cholestane-3,6-dione	75	ICC, C_5H_5N, C_6H_6	154
Cholestane-3β,5,6β-triol	Cholestane-3β,5-diol-6-one	80	ICC, C_5H_5N, C_6H_6	154
5-Methoxycholestane-3β,6β-diol	5-Methoxycholestan-3β-ol-6-one	71	ICC, C_5H_5N, C_6H_6	154
Cholesterol	Cholestane-3β,5α-diol-6-one + cholesterol dibromide	49	NBS, HOAc, aq. $(CH_3)_2CO$	68
Cholesterol	Cholestane-3β,5α,6β-triol + cholesterol dibromide		ICB, HOAc, aq. $(CH_3)_2CO$	149
Cholesterol	Cholestane-3β,5α,6β-triol		N,N-Dibromobenzenesulfonamide	207
Cholestane-3β,5α,6β-triol	Cholestane-3β,5α-diol-6-one	80	ICC, C_5H_5N or ICB, *t*-BuOH	149
Cholic acid	Desoxycholic acid (etherate)	57	NBA, aq. $(CH_3)_2CO$	67
Methyl cholate	Methyl desoxycholate (etherate)	68	NBP	67
Cholic acid	Desoxycholic acid	68	NBS, aq. $NaHCO_3$	67
Pregnane-3α,11α-diol-20-one	Pregnan-11α-ol-3,20-dione	85–90	NBA	162
Pregnane-3α,11α,17α-triol-20-one	Pregnane-11α,17α-diol-3,20-dione	85–90	NBA	162
23,24-Dinorchol-4-ene-3α,22-diol or 3β compound	23,24-Dinorchol-4-en-22-ol-3-one		NBA (or ICB), C_5H_5N, C_6H_6	151
Cholest-4-ene-3β,6β-diol	Cholest-4-en-6β-ol-3-one		NBA	151
Cholest-4-ene-3β,6α-diol	Cholest-4-en-6α-ol-3-one		NBA	151
4-Androstene-3α,17β-diol + 3β,17β-diol	Testosterone	33–74	NBA, C_5H_5N, C_6H_6; ICB, *t*-BuOH, C_5H_5N	150
4-Pregnene-3α,20β-diol + 3β,20β-diol	4-Pregnen-20β-ol-3-one	76	NBA, C_5H_5N, C_6H_6	150
16β-Methylpregnane-3α,17α,21-triol-11,20-dione 21-acetate	16β-Methylpregnane-17α,21-diol-3,11,20-trione 21-acetate		NBS, aq. *t*-BuOH	203
D-Homopregnane-3α,17aα-diol-11,20-dione	D-Homopregnan-17aα-ol-3,11,20-trione	30	NBA, aq. $(CH_3)_2CO$, 5°, 4 hr.	43, 45
21-Bromo-3α,17α-pregnanediol-11,20-dione + 3β,17α-diol	21-Bromo-17α-pregnanol-3,11,20-trione		NBS, aq. MeOH	201, 159
3β-Hydroxyergostan-11-one	Ergostane-3,11-dione	70	NBA, *t*-BuOH, C_5H_5N, 20°, 20 hr.	64
21-Acetoxypregnan-3α-ol-20-one	21-Acetoxypregnane-3,20-dione	80	NBS, *t*-BuOH	27
3α-Succinoyloxycholanic acid-12β-ol-11-one	3α-Succinoyloxycholanic acid-11,12-dione	86	NBS, *t*-BuOH, 50°, 90 min.	28
18-Nor-17β-methyl-17-isopregnane-3α,20β-diol	18-Nor-17β-methyl-17-isopregnan-3α-ol-20-one	73	NBA, aq. $(CH_3)_2CO$, 0°, 3 hr.	96
3α,6α-Pregnanediol-20-one	6α-Pregnanol-3,20-dione		NBS, aq. $(CH_3)_2CO$, r.t., 90 hr.	119
2-Methyl-4-pregnene-11β,17α,20β,21-tetrol-3-one-20β, 21-diacetate	2-Methyl-4-pregnene-17α,20β,21-triol-3,11-dione-20β,21-diacetate		NBA, aq. $(CH_3)_2CO$, r.t., 3 hr.	190
6α-Methyl-9α-fluoro-4-pregnene-11β,17α-diol-3,20-dione	6α-Methyl-9α-fluoro-4-pregnen-17α-ol-3,11,20-trione		NBA, C_5H_5N	136
6α,9α-Difluoro-4-pregnene-11β,17α,21-triol-3,20-dione	6α,9α-Difluoro-4-pregnene-17α,21-diol-3,11,20-trione		NBA, *t*-BuOH, C_5H_5N	141
Allopregnane-3β,17α,21-triol-11,20-dione-21-acetate	Allopregnane-17α,21-diol-3,11,20-trione-21-acetate		NBA, C_5H_5N	178
5α-Cholest-1-en-3β-ol	5α-Cholest-1-en-3-one	36	NBS, aq. *t*-BuOH, $HClO_4$	91
	1α-Bromo-5α-cholestane-2β,3β-diol	60		

observed experimentally, the ratio of rate constants being V:VI = 1:2.7 at 25° (195).



In steroids containing the 11β-hydroxyl group (axial –OH), there is severe steric strain brought about by *two* OH:CH_3 interactions, both angular methyl groups being involved. Oxidation of this hydroxyl group provides considerable steric relief and causes the most rapid rate observed among axial alcohols when chromic acid is used.

The N-haloamides and imides have been found to be extremely useful in such preferential oxidations. Especially noteworthy along these lines are the pioneer studies of Fieser and Rajagopalan (66, 67, 68, 69, 70).

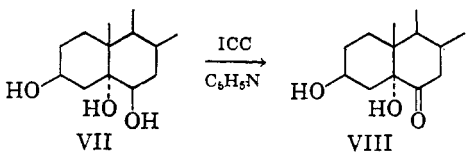
These workers were the first to demonstrate the high selectivity of NBS in the oxidation of steroid alcohol functions. Thus, in cholic acid, which possesses three α-hydroxyl groups (all axial) at positions 3, 7, and 12, the C_7-OH was selectively oxidized by excess NBS in aqueous sodium bicarbonate to desoxycholic acid in 68% yield, the C_3 and C_{12}-OH groups being unaffected. When desoxycholic acid was treated under the same conditions with excess NBS, starting material was recovered unchanged. While chromic acid also effects selective oxidation at C_7, this reagent also brings about

successive oxidations at C_{12} and C_3. The latter results are also true of bromine in aqueous alkali (39) and of microbiological oxidation (102).

Lardon (127) observed that NBA in aqueous acetone selectively oxidized methyl etiocholate to the 7-oxo derivative. Reich and Reichstein (174) had shown earlier that under more vigorous conditions (NBA in aqueous *tert*-butyl alcohol) discrimination is lost and 3α, 12α, 12β, and 17β hydroxyl groups are all oxidized at room temperature. Thus, all three alcohol functions of cholic acid are oxidized rapidly by NBS under these conditions (69).

Other cases of selectivity have been observed, such as preferential oxidation of a 20β-OH over a 3α-OH or an 11β-OH in preference to a 17α-OH. Examples of these are found in Table III.

More recently, Mukawa and Morita have studied these oxidations with isocyanuric chloride (ICC) and isocyanuric bromide (ICB). Like N-chlorosuccinimide, ICC is a stronger oxidizing agent than NBS in the same solvent, while ICB is milder than NBS. Whereas ICB failed to act as an allylic brominating agent, Ziegler (227) had reported previously that ICC could be used successfully for allylic chlorination. Cholestan-3β-ol in benzene was easily converted to cholestan-3-one when warmed with ICC and pyridine for ten minutes (154). This reagent converted cholestane-3β,6β-diol to the dione in 75% yield, but selective oxidation of cholestane-3β,5α,6β-triol (VII) with ICC gave an 80% yield of cholestane-3β,5α-diol-6-one (VIII).



VII VIII

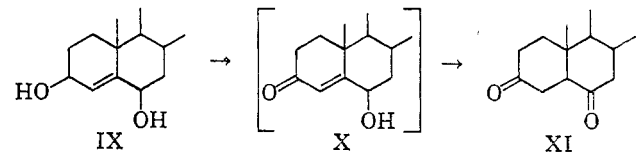
Under the same conditions, isocyanuric bromide failed to react with VII, but in *tert*-butyl alcohol, VIII was formed (149).

The reduced reactivity of ICB relative to NBS is shown by the behavior of the two agents toward cholesterol. Whereas NBS reacts with cholesterol in acetic acid and aqueous acetone to give VIII and cholesterol dibromide (68), ICB under the same conditions gave the triol, VII, and the dibromide, but compound VIII could not be isolated (149).

Recently the mechanism of oxidation of steroidal alcohols by NBS was studied (118) by determination of the order of susceptibility to oxidation of the hydroxyl groups in the epimeric 3,6-dihydroxy-5β-cholanoic acids (rings A/B *cis*) and the corresponding 5α-cholanoic acids (rings A/B *trans*). For the former case, the order was: 6β (a) > 3β (a) > 3α (e) > 6α (e); in the latter, 6β (a) > 3β (e) >6α (e).

It was concluded that the most significant factor in the oxidation of the less reactive *equatorial* alcohols is the ease of approach of base to the *axial* C–H bond of the carbon atom whose –OH group is being oxidized. Thus, in α-hyodeoxycholic acid (rings A/B *cis*), the 3α-OH is oxidized more easily than the 6α-OH, due to the greater vulnerability of the 3β-hydrogen. The less accessible C–H bonds in the 6α- or 11α-alcohols of this series are unaffected by treatment with NBS.

The N-halogen compounds have found wide application in the selective oxidation of *allylic alcohols*. For example, cholest-4-ene-3β,6β-diol (IX), with two allylic alcohol functions, was oxidized by NBS in aqueous dioxane mainly to 3,6-cholestanedione (XI) (42% yield), presumably through the intermediate formation of cholest-4-ene-6β-ol-3-one (X), which was isolated in 17% yield (177).



IX X XI

Here it is to be noted that the 3β (quasi equatorial) hydroxyl group is preferentially oxidized and the 6β (quasi axial) hydroxyl group remains intact. In the corresponding saturated 3β,6β-diol, only the 6β-OH group (axial) is affected. The oxidation path of IX (*i.e.*, the initial oxidation of the 3β-OH) is understandable in terms of a half-chair conformation for ring A in the unsaturated diol (50).

This reversal in allylic alcohols of the general rule that axial hydroxyl groups are more vulnerable to oxidation than equatorial hydroxyl groups is further exemplified by the observation that IX is selectively oxidized to X in high yield by one equivalent of NBA, no dione (XI) being isolated. With cholest-4-ene-3β,6α-diol (6α-OH is quasi equatorial), only cholest-4-en-6α-ol-3-one is obtained (151). In the latter reaction, this selectivity is lost when manganese dioxide is the oxidizing agent. Only the dione is obtained, even under mild conditions (3).

The conversion of cholest-5-ene-3β,4β,7α-triol 3-monoacetate to cholest-5-ene-3β,4β-diol-7-one 3-monoacetate by NBA or chromic acid (134) involves the preferential oxidation of the quasi axial 7α-hydroxyl group with the axial 4β-OH remaining unaffected.

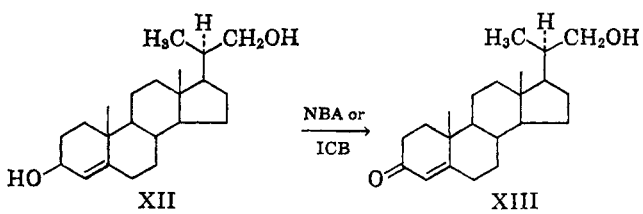
Morita has also shown (151) that dihydroxy steroids containing an allylic secondary alcohol group and a primary alcohol function are selectively oxidized by NBA or ICB in benzene–pyridine to the α,β-unsaturated ketone. The primary alcohol, as expected, remains intact. This is illustrated by the conversion of XII to XIII.

It is also of interest that 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) selectively oxidizes steroidal allylic alcohols to the corresponding α,β-unsaturated

TABLE IV

OXIDATION OF ALDEHYDES AND ACETALS WITH NBS

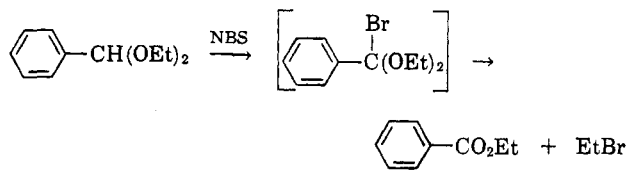
Starting material	Product	Yield, %	Conditions	Reference
Pyruvaldehyde diethylacetal	Ethyl pyruvate	78	CCl_4, light, reflux, 3 hr.	219
Pyruvaldehyde dibutylacetal	Butyl pyruvate	72	Same	219
t-Butylglyoxal diethylacetal	Ethyl α,α,α-trimethylpyruvate	78	Same	219
Phenylglyoxal diethylacetal	Ethyl benzoylformate	73	Same	219
p-Nitrobenzaldehyde	*p*-Nitrobenzoic acid + *p*-nitrobenzamide (NH_3 treatment)		$CHCl_3$	220
p-Nitrobenzaldehyde dimethylacetal	Methyl *p*-nitrobenzoate	93	CCl_4, reflux, 4 hr.	144
Piperonal	Piperonic acid, 6-bromopiperonal, protocatechaldehyde		Bz_2O_2, $CHCl_3$, heat 11 hr.	223
6-Bromopiperonal	6-Bromopiperonic acid		Same	222



ketones in excellent yield (33). Saturated alcohols are unaffected.

B. ALDEHYDES AND ACETALS

Marvel and Joncich (145) observed that acetals of aliphatic aldehydes reacted with N-bromosuccinimide under photocatalytic conditions to give 24–68% yields of the corresponding α-bromoacetals. In addition, by-products containing a more reactive bromine were detected. This latter observation led them to determine whether bromination can occur on the carbon bearing the two ether linkages by treating benzaldehyde diethylacetal with NBS. Ethyl benzoate was the sole isolable product. These investigators therefore suggested a mechanism for the reaction



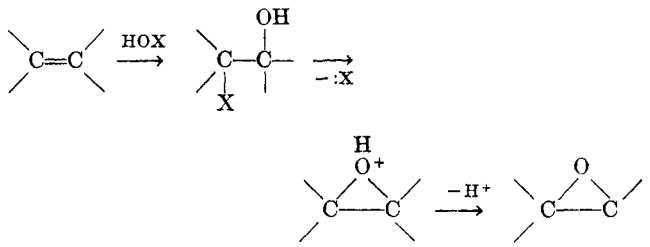
A criticism of this proposed course was their failure to isolate any ethyl bromide.

It also has been shown (123) that ketene acetal is converted to ethyl chloroacetate by N-chlorosuccinimide.

Several other acetals or aldehydes have been oxidized to esters or carboxylic acids with NBS. These results are summarized in Table IV.

C. EPOXIDE FORMATION VIA HALOHYDRINS

The conversion of olefins to halohydrins and subsequent dehydrohalogenation to epoxides may properly be regarded as an oxidative process and constitutes an excellent method for indirect epoxidation.



The bromohydrins, for example, usually are prepared by the addition of the elements of hypobromous acid (in a *trans* manner) to the alkene linkage. Either NBA (191, 215, 216) or NBS (83) in aqueous media has been used as the source of HOBr and the yields of bromohydrin generally range from 30–80%. Frequently it is unnecessary to isolate the bromohydrin, for the reaction mixture may be treated directly with aqueous alkali to give the epoxide.

While epoxidation with peroxy acids is often the method of choice, the bromohydrin route in some cases offers the advantages of shorter reaction times and greater purity of product. Thus, 1-methylcyclohexene gave a 50% yield of pure epoxide, whereas both perbenzoic and monoperphthalic acids gave products which were contaminated with appreciable amounts of the isomeric 2-methylcyclohexanone, formed by acid-catalyzed rearrangement (72). However, there are also examples in which isomeric ketones are formed *via* the bromohydrin path (82, 217).

In Table V are listed a number of examples of the conversion of olefinic compounds to epoxides *via* bromohydrins.

The method also has been applied to a vast number of steroids and the epoxides thus formed frequently are converted to products in which the oxide ring is opened, *e.g.*, by hydrogen fluoride, to give fluorinated steroids. In this field, NBA has been used most frequently and the dehydrohalogenation step is often effected by such combinations as potassium acetate in refluxing acetone or ethanol (20, 60) or anhydrous pyridine and freshly precipitated, dry silver oxide (213). The steroid literature, especially in the form of patents, contains numerous examples of such indirect epoxidations. A special case of epoxide formation *via* an

TABLE V

CONVERSION OF OLEFINS TO EPOXIDES *via* BROMOHYDRINS USING NBS AND H_2O

Olefinic compound	Time	Bromohydrin, %	Epoxide, % (from olefin)	References
Cyclohexene	10 min.	79.3	81.2[a]	83
1-Methylcyclohexene			50[a]	72
Trimethylethylene	25 min.	76.5	78.2[a]	83, 217
Allylbenzene	48 hr.		56.3[a]	83
1,4-Dihydronaphthalene	12 hr.	30		83
Indene	3 hr.	59.1		83
Mesityl oxide	15 min.		56.1[a]	83
Fumaric acid (Na salt)	48 hr.		60.6[a]	83
Cinnamic acid (K salt)	2 hr.	35		83
1,4-Dichloro-2-butene	21.5 hr.		48	2
1-Chloro-1,3-butadiene			29	2
1,4-Dimethoxy-2-butene			57	2
1,1-Diphenylethylene			[b]	61

[a] Bromohydrin not isolated. [b] Yield not given; NBA used.

unstable bromohydrin is the NBS oxidation in the cevine alkaloid field (126).

Isocyanuric chloride and bromide also have been used as sources of HOCl and HOBr for addition to Δ^5-steroids (148, 149, 155).

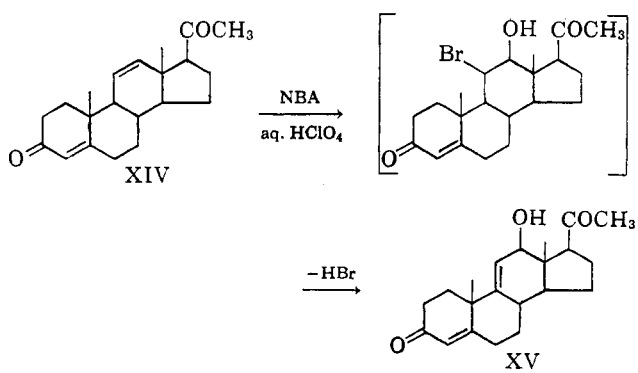
D. HYDROXYLATION

The N-bromoimides may be used for the introduction of an allylic hydroxyl group. The method is indirect and usually involves allylic bromination and the conversion of the resulting bromide into alcohols *via* the formate or acetate. Thus, 3-*p*-menthen-5-yl bromide was prepared from 3-*p*-menthene using NBS in chloroform and ultraviolet light. The bromide was converted to 3-*p*-menthen-5-yl formate by sodium formate and the crude ester, on treatment with methanolic sodium carbonate, gave *dl-trans*-3-*p*-menthen-5-ol (139).

A mixture of *cis* (38%) and *trans* (62%) cyclodecene formed the bromide which, on reaction with silver acetate in glacial acetic acid, gave the crude acetate, from which 2-cyclodecen-1-ol was obtained on treatment with methanolic potassium hydroxide (48).

Similarly, *p*-tolylboronic acid and NBS gave a 90% yield of *p*-$BrCH_2C_6H_4B(OH)_2$, which was hydrolyzed to *p*-$HOCH_2C_6H_4B(OH)_2$ (204).

An example of the hydroxylation of steroids is illustrated by the transformation of 11-dehydroprogesterone (XIV) to $\Delta^{4,9(11)}$-pregnadien-12α-ol-3,20-dione (XV) (73).

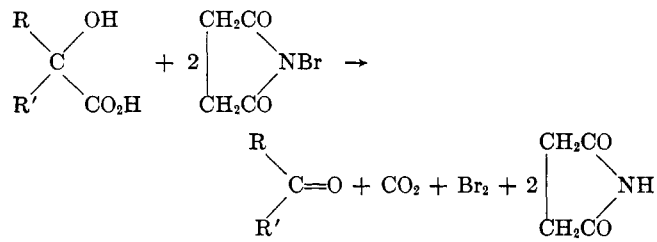


E. OXIDATIVE BOND CLEAVAGE

1. *Carbon–Carbon Bonds: Carboxylic Acids*

NBS reacts with formic acid in aqueous solution with the evolution of carbon dioxide and the formation of HBr and succinimide (13). Oxalic acid behaves similarly, and with higher homologs the same products are obtained, although heating is required. Maleic and fumaric acids are oxidatively cleaved to give acetaldehyde in addition to CO_2 and HBr (15).

In aqueous medium, NBS reacts readily on heating with aliphatic α-hydroxy acids to give aldehydes and ketones containing one less carbon atom according to the equation



The following examples illustrate the scope of this oxidative cleavage (12).

$HOCH_2CO_2H \rightarrow HCHO$

$CH_3CHOHCO_2H \rightarrow CH_3CHO$

$C_6H_5CHOHCO_2H \rightarrow C_6H_5CHO$

$(C_6H_5)_2C(OH)—CO_2H \rightarrow (C_6H_5)_2C{=}O$

This reaction forms the basis of a titrimetric method for estimation of Vitamin C (11), by taking advantage of the observation that ascorbic acid is oxidized selectively by NBS *before* other reducing substances which are present.

Oxidative degradation of phenylacetic acid by NBS in carbon tetrachloride gives benzaldehyde. Polycarboxylic acids form aldehydes and ketones under these conditions. Thus, citric acid was degraded to acetone (1).

TABLE VI
OXIDATIVE CLEAVAGE OF TERTIARY AMINES USING NBS

Amine	Solvent	Aldehyde product	Yield, %	Other Products	Reference
$(CH_3CH_2CH_2)_3N$	Dioxane–H_2O	CH_3CH_2CHO	68	$(n\text{-}C_3H_7)_2NH$	58
$(C_6H_5CH_2)_3N$	Dioxane-H_2O	C_6H_5CHO	85–90	$(C_6H_5CH_2)_2NH$	58
	CCl_4	C_6H_5CHO		$(C_6H_5CH_2)_2NH$	161
	C_6H_6 (80°)	C_6H_5CHO		$(C_6H_5CH_2)_2NH$	104
$(C_2H_5)_3N$	C_6H_6	CH_3CHO		$(C_2H_5)_2NH$	104
$(C_6H_5)_3N$	C_6H_6			$p\text{-}BrC_6H_4N(C_6H_5)_2$	104
$C_6H_5CH_2N(CH_3)_2$	Dioxane–H_2O	C_6H_5CHO	66	$(CH_3)_2NH$	58
$C_6H_5CH_2N(C_2H_5)_2$	CCl_4	$CH_3CHO + C_6H_5CHO$			161
$C_6H_5N(CH_3)_2$	CCl_4	HCHO		$BrC_6H_4N(CH_3)_2$	161
$2,4,6\text{-}Br_3C_6H_2N(CH_3)_2$	CCl_4	HCHO		$2,4,6\text{-}Br_3C_6H_2NHCH_3$	161
$C_6H_5N(C_2H_5)_2$	C_6H_6			*p*-Br deriv.	104
$C_6H_5CH_2N(C_6H_5)_2$	CCl_4	C_6H_5CHO		$C_6H_5(BrC_6H_4)NH$	161
$(C_6H_5CH_2)_2NC_6H_5$	C_6H_6			$p\text{-}BrC_6H_4N(CH_2C_6H_5)_2$	104
$C_6H_5N(CH_3)CH_2C_6H_5$	C_6H_6			$p\text{-}BrC_6H_4N(CH_3)CH_2C_6H_5$	104
N-Benzylcarbazole	CCl_4	C_6H_5CHO		Carbazole + 3-bromocarbazole	161
$HOCH_2CH_2N(C_2H_5)_2$	CCl_4	$(CHO)_2$		$(C_2H_5)_2NH$	161
$o\text{-}C_6H_4(CO)_2NCH_2C_6H_5$	CCl_4	C_6H_5CHO		$o\text{-}C_6H_4(CO)_2NCHBrC_6H_5$	161
$o\text{-}C_6H_4(CO)_2NCH_2OCH_3$	CCl_4			$o\text{-}C_6H_4(CO)_2NH$	161

The study of the mechanisms of these cleavage reactions has received little attention to date.

2. *Carbon–Nitrogen Bonds*

a. Amines

Carbon-nitrogen bond scission in tertiary amines by NBS occurs readily with the formation of aldehydes and secondary amines, frequently in good yields. The results indicate that a methyl or methylene group attached to nitrogen is required and given a choice, the $N\text{–}CH_2$ linkage is cleaved preferentially. The method should be extremely useful in degradative work. The reaction has been carried out in aqueous dioxane (58), benzene (104), and in refluxing carbon tetrachloride or, at lower temperatures, by irradiation with ultraviolet light or in the presence of benzoyl peroxide (161). Aryl groups, attached directly to nitrogen, are brominated readily, exclusively in the *para* position (104). The mechanism of such cleavages has not been clearly established.

In contrast, the dealkylation of cyclic tertiary amines by NBS and N,2′,4′,6′-tetrachlorobenzanilide, has been reported (52) to occur only to a slight extent. Thus, with N-methylpiperidine only 1–2% of the N-methyl content of the amine was converted to formaldehyde. Instead, non-selective halogenation and some dehydrohalogenation to aromatic compounds was observed.

Some typical dealkylations of tertiary amines are shown in Table VI.

It has been reported that primary amines react vigorously with NBS in aqueous medium at room temperature to form the corresponding aldehydes and that this reagent may be employed as a means for distinguishing among primary, secondary, and tertiary aromatic amines using color tests (10, 14).

b. Amino Acids and Peptides

The facile oxidative degradation of α-amino acids to aldehydes by NBS and N-bromophthalimide in aqueous medium involves both carbon–carbon and carbon–nitrogen bond cleavage.

For example, alanine was oxidized to acetaldehyde in 50% yield by NBS and in 25–35% yield by NBP (194). Phenylglycine was similarly cleaved by both reagents to give 25–40% yields of benzaldehyde.

Recently, a qualitative and quantitative study was made of the gases evolved in the bromodecarboxylation of amino acids and derivatives by NBS (120). The effects of pH, added palladium chloride, and concentration of NBS were examined. Except for certain special cases, all compounds studied evolved one mole of carbon dioxide per mole of amino acid and pH did not appreciably affect the rate of evolution.

The only gases evolved by aqueous solutions of amino acids treated with NBS at ambient temperatures were carbon dioxide and nitrogen (198). In addition, nitriles and aldehydes corresponding to the decarboxylated parent amino acids were found. The yield of nitrile was greatest from amino acids with long carbon chains, whereas shorter chains gave greater yields of aldehyde. The formation of aldehyde was accompanied by the liberation of an equal amount of ammonia, which subsequently was oxidized to nitrogen by NBS.

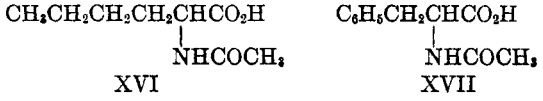
A minimum of two moles of NBS is consumed per mole of amino acid. Higher consumptions were attributed to the presence of other functional groups in the molecule. Tryptophan and tyrosine required appreciably more NBS than any other amino acids (*vide infra*).

Carbon–nitrogen bond breaking also occurs when β-amino acids react with NBS in water to form bromine-containing intermediates and then molecules having two fewer carbon atoms. Thus, $C_6H_5CH(NH_2)CH_2\text{-}CO_2H$, on heating with NBS–water at 150–170°, formed a residue which, on treatment with dilute alkali and subsequent acidification, gave an 81% yield of benzoic acid (21). The bromine-containing intermediate was shown to be $C_6H_5CH(NHBr)CBr_3$. This

substance was converted to benzoate ion by 30% KOH and to $C_6H_5COCBr_3$ by concentrated HCl.

Under the same bromination conditions, β-aminobutyric acid gave 1,1,1-tribromoacetone, which, in turn, formed acetamide on treatment with methanolic ammonia. The conversion of $C_6H_5CH_2CH(NH_2)CH_2CO_2H$ to *p*-bromophenylacetic acid provides another illustration of these oxidative cleavages.

There has been a considerable amount of recent work on peptide bond cleavages by NBS. Heyns and Stange (98) observed that N-acetylnorleucine (XVI) and N-acetylphenylalanine (XVII) failed to react with NBS, but that their silver salts gave 40–55% yields of *n*-valeraldehyde and phenylacetaldehyde, respectively,



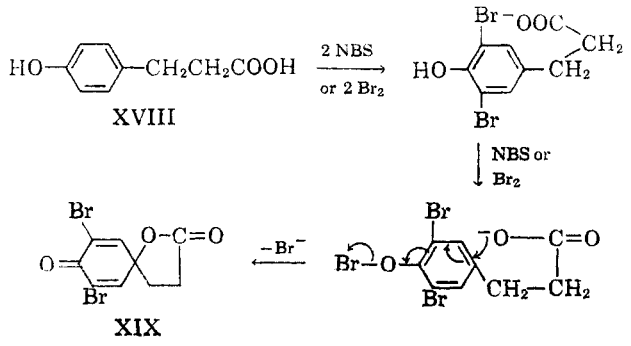
XVI XVII

However, α-aminoisobutyric acid, $(CH_3)_2CH(NH_2)CO_2H$, formed acetone on NBS oxidation and N,N-dimethyl-α-aminocaproic acid gave *n*-valeraldehyde and dimethylamine (99).

The following di- and tripeptides and their silver salts have been degraded by NBS (100), the products giving on hydrolysis the indicated amino acids, identified with ninhydrin on paper chromatograms: alanylleucine → leucine; leucylalanine → alanine + leucine (weak); glycylphenylalanine → phenylalanine; leucylphenylalanine → phenylalanine + leucine (weak); leucylglycylglycine → glycine; and alanylglycylphenylalanine → glycine + phenylalanine.

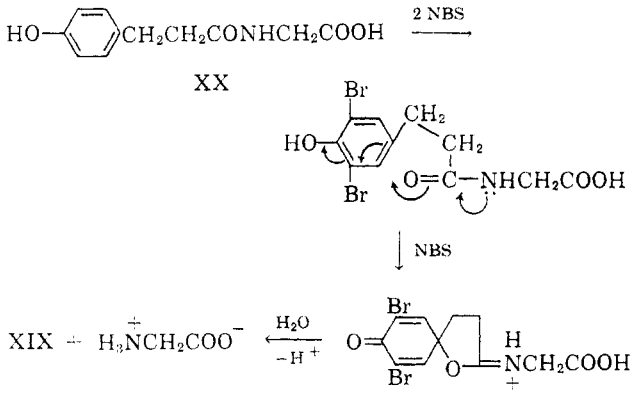
The major contribution in the study of peptide cleavages by NBS has been the work of Witkop and his colleagues (166, 167, 168, 173, 193). Their elegant studies represent an important advance in peptide structure determination for it affords a specific method for rupturing peptide chains at linkages involving the carboxyl group of tyrosine and tryptophan.

Thus, these workers found that phloretic acid (XVIII) reacted with 3 moles of NBS or bromine at pH 4.6 (acetonitrile–acetate buffer) to give the spirodienone lactone (XIX) by oxidative bromination (193). It has been postulated that the reaction involves an oxidative participation between the phenolic ring and the carboxylate anion, leading to the lactone



XVIII XIX

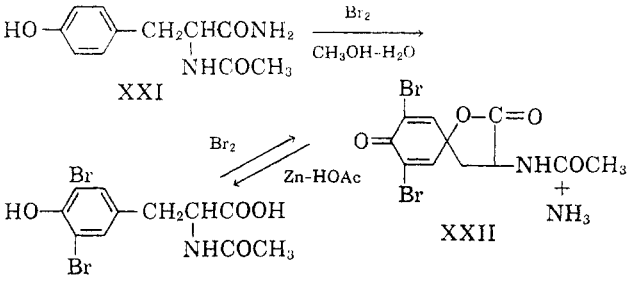
The ability of peptide bonds to participate in the lactonization reaction was demonstrated by the conversion of N-phloretylglycine (XX), a tyrosyl-peptide model, to the lactone XIX with cleavage and release of glycine in 80% yield. The correspondence between dienone formation and release of glycine was shown by measuring the ultraviolet absorption at 260 mμ and by quantitative ninhydrin assay after addition of varying amounts of NBS. The highest yields are obtained in aqueous acetic or dilute mineral acid (192).



XX XIX

Corey and Haefele (51) also showed that N-benzyl-3,5-dibromophloretamide was similarly degraded to compound XIX.

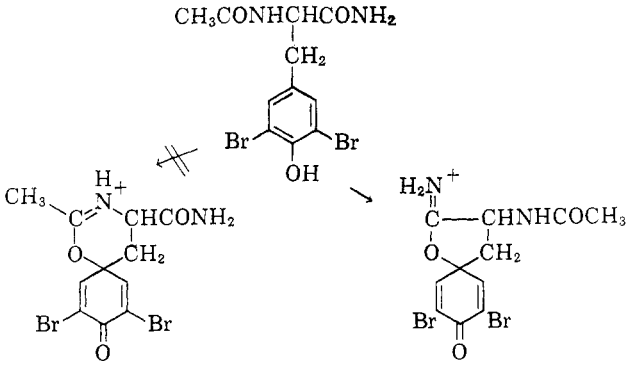
In analogous fashion, N-acetyltyrosine amide (XXI) reacted with bromine in aqueous methanol to liberate ammonia and form the spirodienone lactone XXII, which also was obtained directly from N-acetyl 3,5-dibromotyrosine and bromine, as shown below (51)



XXI XXII

Thus, the attachment of the α-acylamino substituent to the simple phloretic acid system, which simulates the peptide structure, does not alter the course of the cleavage reaction. It is of particular interest that cleavage involves the tyrosyl–nitrogen bond instead of the acetyl–nitrogen linkage, in agreement with previous observations that *aryl participation to form a five-membered ring is favored over that leading to a six-membered spiro ring* (49, 89, 90).

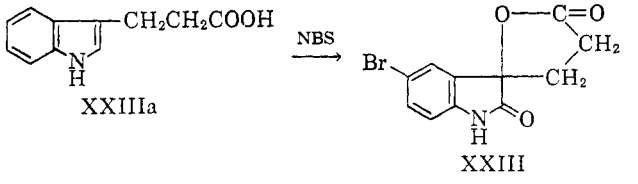
The oxidative bromination of the tripeptide derivative N-carbobenzyloxy-S-benzyl-L-cysteinyl-L-tyrosyl-L-isoleucine gave a 40% yield of ninhydrin-reactive material, solely *isoleucine*, thus demonstrating the specific and facile cleavage of the tyrosylisoleucine peptide bond. In a strongly acidic medium, cleavage



yields of 68–82% are obtained with a variety of N-acylated tyrosyl peptides (192).

It is very probable that the unusual cleavage of oxytocin and vasopressin by bromine water (175, 176) is of the type just described.

A novel, mild, selective use of positive halogen for degradation of tryptophyl peptides was suggested by the *intramolecular participation* reaction which occurs in the transformation of indole-3-propionic acid (XXIIIa) to the lactone of 5-bromodioxindole-3-propionic acid (a spirolactone) (XXIII) during oxidative bromination with N-bromosuccinimide (129, 168).

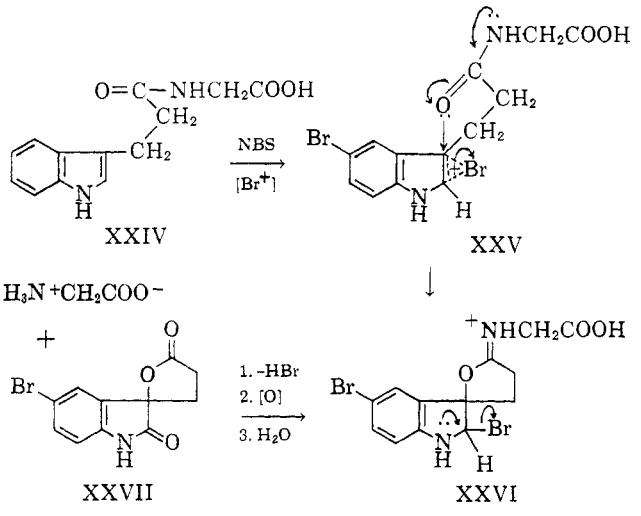


XXIIIa XXIII

The ability of peptide bonds to participate in this lactonization reaction was demonstrated with N-carbobenzyloxy-L-tryptophylglycine. In an alcoholic aqueous acetate buffer of pH 4.0, glycine was liberated in 39% yield. The carbobenzyloxy group apparently adversely affects the cleavage (the benzyl–oxygen bond is broken readily by NBS (144)), since benzoyltryptophylglycine and indole-3-propionylglycine (XXIV) liberated glycine to the extent of 55%. After complete oxidation of tryptophan, excess NBS degraded glycine. Addition of formate to the buffer solution to some extent protected the liberated glycine from degradation, even in the presence of large amounts of NBS. Similar yields (47–60%) were obtained for other model peptides.

Variation of the length of the indole chain showed that maximum cleavage occurs when 1,5-interaction is possible. The yields for 1,5, 1,6, and 1,4-interaction decreased in the order: 53% (ethyl indole-3-propionylglycinate), 17% (ethyl indole-3-butyrylglycinate) and 3% (ethyl indole-3-acetylglycinate).

This peptide cleavage probably proceeds by a mechanism analogous to that proposed for formation of XXIII from XXIIIa. In the case of a peptide, such as the simple model XXIV, interaction of the amide carbonyl group with the 3-position of the hypothetical bromonium ion intermediate XXV, leads to a salt of an iminolactone XXVI, which, after further oxidation of an intermediate indolenine and hydrolysis of the unstable iminolactone, gives the lactone XXVII and glycine.



XXIV XXV XXVII XXVI

Since ethyl carbobenzyloxy-L-oxytryptophylglycinate is cleaved only to the extent of 13%, while ethyl carbobenzyloxy-L-tryptophylglycinate gives 39% scission product, the former is not an important intermediate in the cleavage reaction. An N-bromoindole intermediate is also ruled out, since NBS converted N-methylindole-3-propionylglycine to glycine in good yield. It also has been shown that secondary amino acids, such as proline, participate in this reaction, presumably *via* the intermediate formation of quaternary iminolactones.

Substituents at the amide nitrogen bearing strong electron-attracting groups influence the amide $\rightleftarrows$ imidol tautomerism and prevent intramolecular participation and elimination. Thus, the *p*-nitroanilide of indole-3-propionic acid was not cleaved by NBS.

N-Bromoacetamide, which reacts with indoles much more slowly than NBS, degrades peptides of indole-3-propionic acid and of acyltryptophans in yields comparable with those obtained with NBS.

In a medium of 10 *M* lithium acetate at pH 4, the extent of cleavage of model peptides using both NBS and NBA increased markedly. This probably is because of the greatly decreased activity of water in concentrated salt solutions and under these conditions ring opening of the bromonium ion intermediate by water does not effectively compete with intramolecular participation of the imidol group. While high cleavage yields were obtained for small peptides, there was a marked decrease in cleavage of tobacco mosaic virus protein and lysozyme. It is likely that lithium acetate enhances the formation of a maximum of intramolecular hydrogen bonds, which leads to more rigid packing or to a tightening of the helical screw. The resulting steric restraints make the 1,5-interaction of the trypto-

phyl side chains difficult or impossible. Steric inhibition of 1,5-interaction is particularly pronounced (as evidenced by low cleavage yields) in cyclic peptides, such as tyrocidin B.

The usefulness of the controlled cleavage of C-tryptophyl bonds by N-bromosuccinimide was demonstrated by the degradation of *glucagon* (166), the crystalline hyperglycemic-glycogenolytic polypeptide hormone from pancreas, which contains only one tryptophan molecule among 29 amino acids (31).

Glucagon, with a C-terminal sequence, tryptophan-leucine-methionine-aspartic acid-threonine, was selectively and rapidly (< one minute) cleaved to the tetrapeptide: Leu-Met-Asp-Thr, although the yield was low (6–14%). This tetrapeptide previously had been obtained by action of chymotrypsin (30) and trypsin (29) on glucagon, but the cleavage by NBS was more rapid and more selective than that by any known peptidase. It is noteworthy that with NBS there was *no cleavage* of the two tyrosyl-peptide bonds in glucagon. Competition studies have demonstrated that in a mixture of tyrosyl and tryptophyl peptides, the first 2–3 equivalents of NBS liberate exclusively the amino acid next to tryptophan (192).

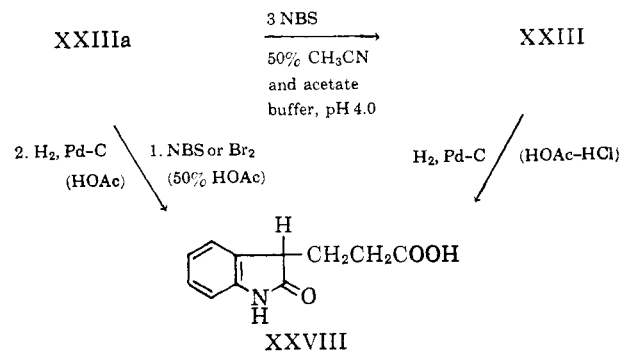
Although sulfur-containing amino acids (cystine and methionine) and the imidazole group (histidine) react rapidly with NBS, cleavage of tyrosyl-peptide bonds can be effected in their presence by using excess of reagent. The cleavage of the tyrosyl-valyl bond of hypertensin (containing a Val-His bond) has been demonstrated (192).

In summary, NBS or NBA offers a specific and rapid method for fragmenting high molecular weight peptides and proteins to smaller ones by cleaving peptide bonds attached to the tryptophyl and tyrosyl carboxyl groups and this selective chemical method is a most useful supplement to enzymatic degradative methods.

It has been shown recently that 2,2-diphenyl-4-pentenoic acid, as well as the previously mentioned indole-3-propionic and phloretic acids, may serve as acceptable blocking groups for synthesis of peptides that contain no functional groups whose rate of reaction with NBS or NBA is faster than that of the blocking group (130). These experiments have served as a guide in developing groups which may be removed both by positive bromine and by controlled action of acid.

Finally, it is of interest to note that indole-3-propionic acid (XXIIIa) may be converted readily in 50% yield to the bromine-free oxindole-3-propionic acid (XXVIII). The rapid reaction of NBS with indoles is difficult to arrest at the oxindole stage since further oxidation at position 3 and aromatic bromination at the 5-position readily occur. A one-step procedure has been developed in which excess brominating agent is used followed by simultaneous hydrogenolytic cleavage of the benzylic oxygen function and the aromatic bromine substituent (131).

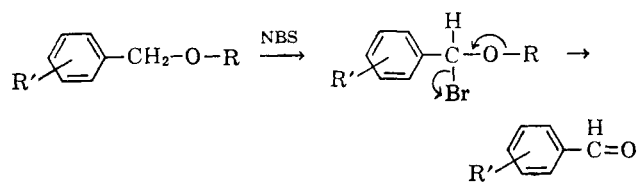
A study of the reaction of human and bovine serum albumin with NBS revealed the appearance of new N-terminal residues and splitting of the peptide chain at tryptophan carboxyl groups. Spectral changes suggested bromination and cyclization of tryptophan residues as in peptides (170).



Further details of these oxidative peptide cleavages may be found in a recent review (46).

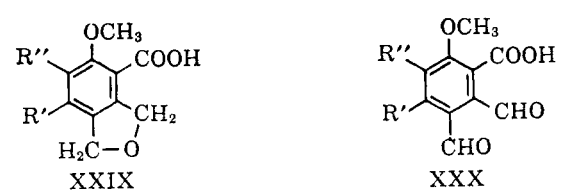
3. *Carbon–Oxygen Bonds*

Benzyl ethers react with N-bromosuccinimide in carbon tetrachloride under free radical conditions to give favorable yields of the corresponding benzaldehydes (160).



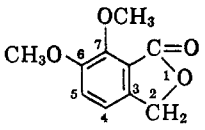
Allyl ethers failed to react under these conditions and phenyl ethers, *e.g.*, anisole, which do not possess benzylic hydrogens, give *ortho*- and *para*-bromophenyl ethers.

In a detailed study of substituted phthalaldehydes it was shown (22) that cyclic benzyl ethers (XXIX) were converted to the phthalaldehydes (XXX) by NBS in water.

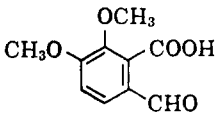


R′ = H, CH_3, OCH_3; R″ = CH_3, OCH_3

In a similar fashion, the γ-lactone meconin (XXXI), a substituted phthalide, was oxidized to opianic acid (XXXII) and 4-methylmeconin formed 3-methylopianic acid.



XXXI



XXXII

4. *Bonds Involving Sulfur*

Mercapto groups are oxidized by N-bromosuccinimide in carbon tetrachloride to disulfides (1).

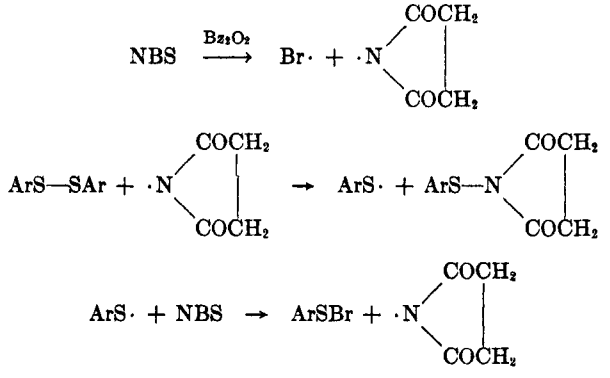
O,O-Dialkyldithiophosphoric acids are oxidized to bis-(O,O-dialkylthiophosphoryl) disulfides (XXXIII) by N-chlorosuccinimide in the presence of hydrochloric acid (206).

$$[(RO)_2PS_2]_2$$

XXXIII

R = C_2H_5, C_3H_7, *i*-C_3H_7, C_4H_9, *i*-C_4H_9, C_6H_{11}

The oxidative cleavage of aromatic disulfides by NBS in the presence of benzoyl peroxide to form N-arylmercaptosuccinimides has been reported recently (79). The cleavage of thioethers with NBS also has been described (78). The oxidative cleavage (chlorinolysis) of cystine esters to give sulfur-free chloroesters has been reported (6, 7).



F. INORGANIC APPLICATIONS

The oxidation of bromide and iodide ions to the free halogen by N-haloimides forms the basis of a convenient method for the qualitative and quantitative identification of these ions (71, 211, 214).

It has been shown recently (4) that N-chlorosuccinimide reacts with aqueous ammonia under strongly alkaline conditions to give hydrazine in 55–57% yields. The optimum mole ratio of ammonia to NCS is 100:1. It is postulated that chloramine (NH_2Cl) is the active intermediate which then reacts with excess ammonia to form hydrazine. Control of pH is essential (optimum range, 13.2-13.4), since at higher pH's chloramine decomposition becomes increasingly competitive and a second side reaction assumes greater importance

$$NH_2Cl + OH^- \rightleftarrows NH_3 + OCl^-$$

N-Chlorophthalimide and 1,3-dichloro-5,5-dimethylhydantoin ("Halane") react similarly.

It had been reported earlier (140, 101) that N-halogen compounds quantitatively oxidize hydrazine to nitrogen.

V. DEHYDROGENATION

A. INTRODUCTION OF SUPPLEMENTARY DOUBLE BONDS

1. *Bromination–Dehydrobromination*

The ability of N-bromosuccinimide to act as a specific reagent for allylic brominations has been used to great advantage for the introduction of supplementary double bonds, particularly in cyclic systems. In this way, a large number of monounsaturated compounds have been converted to conjugated dienes and trienes, including the aromatization of substituted cyclohexenes and cyclohexadienes.

The method involves a two-step bromination–dehydrobromination process. In many cases, the intermediate bromo compound is isolable and the second step proceeds only after treatment with a base. There are numerous examples, however, in which the bromo intermediate is unstable under the reaction conditions and spontaneously loses the elements of hydrogen bromide to form the final product. There appears to be no definite structural guide which can be used to predict in advance whether dehydrobromination will occur without the use of a base.

A variety of substances have been employed to effect the second step of the process. Tertiary amines, such as pyridine, quinoline, and γ-collidine, have found wide application, while potassium acetate, potassium carbonate, lithium carbonate, and even trialkylphosphites, have been used to a lesser extent.

In addition to NBS, other agents used occasionally for the bromination step are NBA and pyridinium bromide perbromide (PBP).

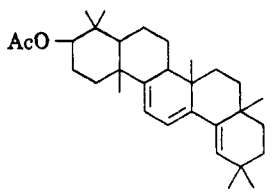
While a number of relatively simple olefins have been converted to dienes in this manner, the method has found particular application in a wide range of natural products, such as terpenes, steroids, alkaloids, flavanoids, and carotenes. As mentioned earlier, it has also been useful in effecting certain aromatizations.

An early indication of the potentialities of the method was the conversion of cycloöctene into 1,3-cyclooctadiene by NBS (227). Soon thereafter, the reaction was applied in the triterpene series by introducing supplementary double linkages into α- and β-amyrin type compounds (181). Thus, β-amyrin acetate was heated at 100° for two hours with NBS in carbon tetrachloride to give the halogen-free β-amyratrienol acetate (XXXIV). Similarly, α-amyrin acetate was converted to α-amyradienol acetate and methyl acetylursolate gave a 70–75% yield of methyl acetyldehydroursolate.

TABLE VII

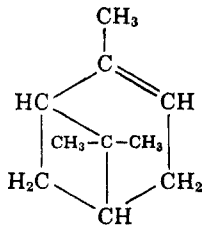
STEROIDAL DEHYDROGENATIONS

Starting material	Conditions	Product	References
Methyl $\Delta^{20,22}$-3β-acetoxynorallocholenate	NBS(CCl_4), 20 hr. chromatography (Al_2O_3)	$\Delta^{16,20}$-3β-Acetoxy-21-hydroxynorallocholadienic acid lactone	182, 183, 184
3-Acetoxy-21-hydroxy-$\Delta^{16,20}$-norallocholadienic acid lactone	NBS, light, C_5H_5N	3-Acetoxy-21-hydroxy-$\Delta^{14,16,20}$-norallocholatrienic acid lactone	42
3-Oxo-24,24-diphenyl-23-cholene 3-ethylene ketal	NBS (CCl_4), light, 12 hr. reflux, C_5H_5N (5 hr. reflux)	3-Oxo-24,24-diphenyl-20,23-choladiene	143
3,3'-Bicholesta-3,5,3',5'-tetraene	NBS	3,3'-Bicholesta-3,5,7,3',5',7'-hexaene	41
Cholesteryl benzoate	NBS, light, collidine	7-Dehydrocholesteryl benzoate + $\Delta^{4,6}$-cholestadienyl benzoate (?)	19, 116
Cholesteryl acetate	NBS, CCl_4; $PhNMe_2$	7-Dehydrocholesteryl acetate	75
$\Delta^{5,7}$-Cholestadiene	NBS, Bz_2O_2, CCl_4, heat	$\Delta^{5,8(9)}$-Cholestatriene	84
3β-Acetoxy-20-oxo-5-allo-Δ^{16}-pregnene	NBS, CCl_4, light, C_5H_5N	3β-Acetoxy-20-oxo-5-allo-$\Delta^{14,16}$-pregnadiene	172
1-Dehydrohydrocortisone 21-acylates	NBA, Me_2CO-H_2O, light, rm. temp., 3 hr.	1-Dehydrocortisone 21-acylates	85
9α-Fluoro-1,4-pregnadiene-11β,16α,17α,21-tetrol-3,20-dione diacetate	NBS, CCl_4, 2,4-lutidine	9α-Fluoro-1,4,6-pregnatriene-11β,16α,17α,-21-tetrol-3,20-dione diacetate	76
9β,11β-Oxido-1,4-pregnadiene 17α,21-diol-3,20-dione 21-acetate	NBS, light, CCl_4, C_6H_5COCl; collidine	9β,11β-Oxido-1,4,6-pregnatriene-17α,21-diol-3,20-dione 21-acetate	77
Δ^7-Cholestenyl acetates	NBS, Et_2O-MeOH	$\Delta^{7,9(11)}$-Cholestadienyl acetate (27%)	65
D-Homoetiocholan-3,11,17a-trione	PBP, HOAc-30% HBr, NaOAc; LiCl-$HCONMe_2$, heat, 2 hr.	D-Homo-4-androstene-3,11,17-trione	44
Pregnenolone benzoate	NBS, light, CCl_4, 10 min. reflux; collidine, 1 hr. reflux	7-Dehydropregnenolone benzoate	114
3-Acetoxy-7,22-ergostadiene	NBS, $CHCl_3$, −60°, $Br_2(CHCl_3)$; Zn + HOAc (debromination)	3-Acetoxy-7,9(11),22-ergostatriene	40
D-Homo-17a-isopregnan-17aβ-ol-3,11,20-trione	PBP(NaOAc), LiCl in $HCONMe_2$	D-Homo-17a-isopregn-4-en-17$^a\beta$-ol-3,11,20-trione (44%)	45
7,11-Dioxo-24,24-diphenyl-25,26,27-tris-norlanost-23-en-3β-ol	NBS (CCl_4)	7,11-Dioxo-24,24-diphenyl-25,26,27-tris-norlanost-20(22),23-dien-3β-ol	16

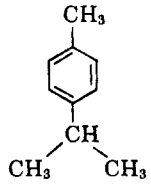


XXXIV

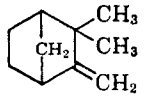
α-Pinene (XXXV) has been converted by NBS to p-cymene (XXXVI) and camphene (XXXVII) by way of an intermediate bromo compound, which was heated with quinoline (59).



XXXV



XXXVI



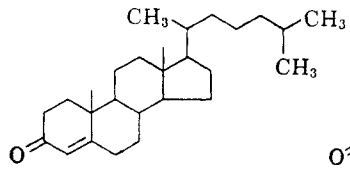
camphene

In an attempt to introduce one or two double bonds into the 4-membered ring of 1,2,3,4-tetraphenylcyclobutane, the sole product isolated, in 40% yield, was the ring-opened 1,2,3,4-tetraphenyl-1,3-butadiene (8).

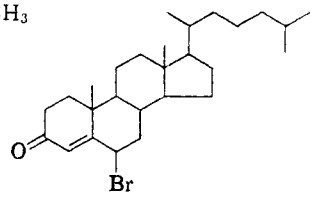
a. Steroidal Transformations

A large number of examples are available in both the journal and patent literature which illustrate the use of N-bromo compounds for the introduction of supplementary double bonds into the steroid nucleus. Some of these examples are collected in Table VII.

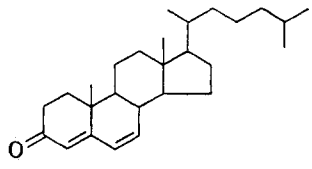
A few cases will serve to illustrate the scope of the method. Allylic bromination of Δ^4-cholesten-3-one (XXXVIII) by NBS gave the 6-bromo compound (XXXIX), which, on heating with collidine, readily formed $\Delta^{4,5;6,7}$-cholestadien-3-one (XL) (110).



XXXVIII



XXXIX

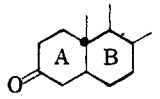


XL

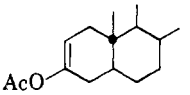
In a similar fashion $\Delta^{1,2;4,5}$-cholestadien-3-one was converted to $\Delta^{1,2;4,5;6,7}$-cholestatrien-3-one. It had been shown earlier (147) that treatment with NBS, then heating with collidine, converted testosterone acetate to 6-dehydrotestosterone acetate in 80% yield and progesterone to the 6-dehydro compound.

An interesting example of allylic bromination with subsequent spontaneous dehydrobromination is provided by the reaction of NBS with Δ^2-3-acetoxycholestene (XLI) (180). This enol acetate of choles-

tanone (XLII) (rings A/B *trans*) reacted with NBS in

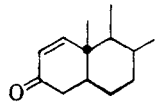


XLII

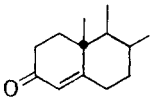


XLI

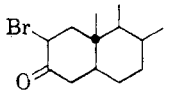
carbon tetrachloride to give a mixture of Δ^1 and Δ^4-cholesten-3-one (XLIII and XLIV) and 2-bromocholestan-3-one (XLV), the amount of which increased with reaction time at the expense of XLIII.



XLIII

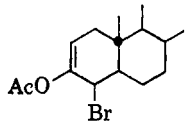


XLIV

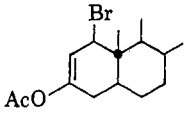


XLV

The origin of the reaction products has been attributed to the thermal and acid instability of the intermediate allylic bromination products, XLVI and XLVII. Spontaneous loss of hydrogen bromide from XLVI, then acid-catalyzed cleavage of the resulting enol acetate would yield compound XLIV. In contrast, XLVII might be expected to be comparatively stable



XLVI

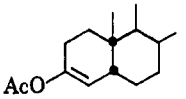


XLVII

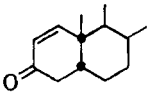
relative to XLVI, due to the absence of an available hydrogen for spontaneous dehydrohalogenation. However, the rapid formation of XLIII suggests the acid cleavage of XLVII and ketonization of the resulting enol to produce a β-bromoketone, which *does* possess a hydrogen atom on an adjacent carbon. Rapid loss of hydrogen bromide from this compound would afford compound XLIII. An alternative path for the formation of XLIII and XLIV based on primary elimination of acetyl bromide from XLVI and XLVII, has been discounted by a specially designed experiment. The quantitative distribution of the products indicated that the primary attack by NBS on XLI was at the C-1 position.

As time increased, the reaction became more complex. Hydrogen bromide in the reaction mixture catalyzed the regeneration of XLII from XLI and resulted in the formation of free bromine by reaction with NBS. Bromine and XLII reacted to form compound XLV (34). This compound was obtained from NBS and XLII (56).

The reaction of NBS with Δ^3-3-acetoxycoprostene (XLVIII) (rings A/B *cis*) was also investigated. The reaction was quenched one minute after initiation to give approximately equal amounts of compound XLIV and crude Δ^1-coprosten-3-one (XLIX). This indicated that in XLVIII the activation of both allylic positions (C_2 and C_5) was of a similar order of magnitude. The attack at the tertiary C_5 position was somewhat unexpected since it was anticipated that more vigorous activation would be required for this type of substitution by NBS.



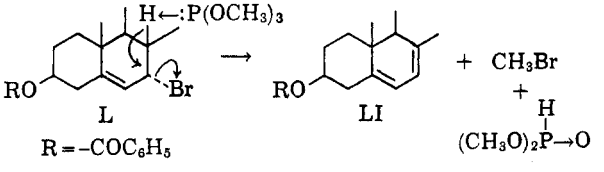
XLVIII



XLIX

It also has been observed (158) that 5-androsten-3β-ol-17-one isocaproate is converted to 5,7-androstadien-3β-ol-17-one isocaproate in 35% yield by the two-step procedure. It is of interest to note that under these conditions (NBS, light) no oxidation of the 3β-OH group (C–H *axial*) occurred whereas the 3α-OH (C–H equatorial) would be expected to be more susceptible to oxidation.

A novel variation for the dehydrobromination step is the use of trialkylphosphites instead of the conventional bases. Thus, cholesteryl benzoate reacted with 5,5-dibromohydantoin to give the 7-bromocholesteryl ester (L), which, on treatment with trimethyl- or triethylphosphite in refluxing xylene, gave a 52% yield of 7-dehydrocholesteryl benzoate (LI) (109). These reagents also have been used for debromination of vicinal dibromides to olefins (54).



L
R = -COC6H5
LI

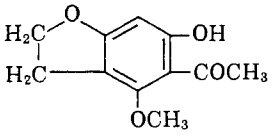
Another interesting variation is the selective dehydrobromination of 2,4-dibromo-3-oxo steroids in the presence of lithium carbonate in the solvent dimethylformamide. Under these conditions, the formation of pure 1,4-dienes is favored and the production of 4,6-dienes avoided (112, 113). Under milder conditions, the reaction may be stopped at the 1-dehydro-4-bromosteroid stage.

Mention may be made of the use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) for the introduction of a supplementary double bond in the A ring of steroidal 3-ketones (32).

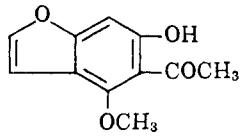
b. Conversion of Flavanones to Flavones

The dehydrogenation of derivatives of α- and γ-pyrone using NBS has received considerable attention. The attempted conversion of dihydrofurocoumarins into the corresponding furocoumarins was unsuccessful (105) because bromination occurred exclusively on the lactone ring. However, the dehydrogenation of certain coumaranes to coumarones, typified by the conversion of dihydrovisnaginone (LII) to visnaginone (LIII), was

accomplished in 59% yield by reaction with NBS, and then treatment with dimethylaniline and alcoholic alkali (74).



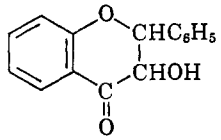
LII



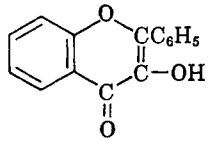
LIII

The dehydrogenation of flavanones and flavanone glycosides to the corresponding flavone compounds has been achieved in several instances (9, 23, 24, 106, 107, 137, 138).

For example, treatment of flavanone with NBS gave a mixture of flavone and 3-bromoflavanone. Flavanon-3-ol (LIV) was converted to flavon-3-ol (LV), with spontaneous dehydrobromination (24).



LIV



LV

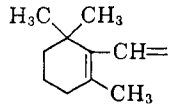
Similarly, naringenin (4′,5,7-trihydroxyflavanone) triacetate gave apigenin (4′,5,7-trihydroxyflavone) triacetate in 95% yield without the use of a base (9, 137). It was necessary, however, to remove the bromine, formed by oxidation of HBr by NBS, by distillation. Application of this procedure to hesperitin triacetate (4′-methoxy-3′,5,7-triacetoxyflavanone) gave diosmetin triacetate in 86% yield (137).

c. Carotenes

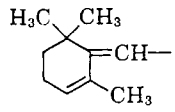
The action of NBS and NBA on α- and β-carotene has been studied in detail by Zechmeister and his coworkers (117, 171, 225, 226).

When β-carotene, $C_{40}H_{56}$ (LVI) (only one of the two rings shown, four middle isoprene units omitted), was heated under reflux with NBS in carbon tetrachloride, a complex pigment mixture was obtained, from which three substances were isolated in pure form: (1) dehydro-β-carotene, $C_{40}H_{54}$ (LVII), (2) the nonsymmetrical retrobisdehydrocarotene, $C_{40}H_{52}$ (LVIII), and (3) a pigment very probably identical with the symmetrical anhydroeschscholtzxanthin, $C_{40}H_{50}$ (LIX). Under the same conditions α-carotene gave only LVIII and LIX. Similar treatment with NBA produced LVII and LVIII in the case of β-carotene and only LVIII with α-carotene. Careful chromatographic separation of the pigment mixtures led to the isolation of three new crystalline "dehydrocarotenes."

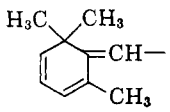
A markedly different mixture appeared when chloroform (containing about 1% ethanol) was used as the solvent. The products were mainly oxygenated (ketonic) pigments. Ethanol-free chloroform, however, gave results similar to those observed with carbon tetrachloride. The complex nature of these reaction mixtures has since been explored and amplified by Karrer (62, 63).



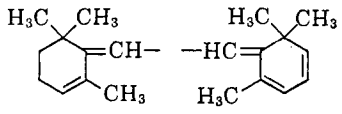
LVI



LVII



LIX



LVIII

It has been reported (53) that squalene is easily dehydrogenated with NBS in refluxing carbon tetrachloride to yield a mixture of carotenoid pigments, which may be separated by chromatography.

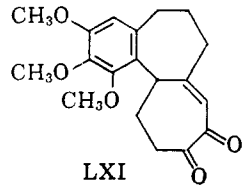
d. Applications to Other Natural Products

Steroid sapogenins containing the Δ^5-3-OH group and a spiroketal side chain in the 16,17-position, are selectively brominated in the 7-position with NBS under irradiation with artificial light. Dehydrobromination with collidine gives $\Delta^{5,7}$-sapogenins, useful as intermediates for synthetic hormones or, after irradiation, as products with antirachitic activity (179).

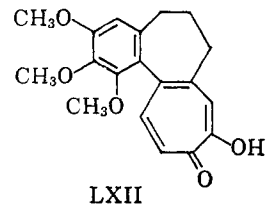
Dihydrodictamnine was converted to the furoquinoline alkaloid dictamnine by this two step procedure (47).

An important step in van Tamelen's brilliant total synthesis of the alkaloid *colchicine* (LX) (208, 209) was the dehydrogenation (aromatization) of the enedione (LXI) with NBS in refluxing chloroform to produce the tropolone ring of one of the key intermediates, desacetamidocholchiceine (LXII). Other aromatizations are discussed in Section (f).

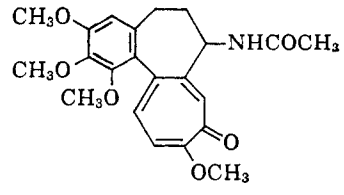
The method also has been used in structural studies of the triterpenoid Elatericin A (cucurbitacin D) (128). Similar action of NBS on friedelin and bromofriedelins also has been reported (115).



LXI



LXII



LX

TABLE VIII

DEHYDROGENATIONS WITH N-BROMOSUCCINIMIDE

Starting compound	Reaction conditions (all NBS)	Product	Reference
2,5-Dibenzylidenecyclopentanone	CCl_4, 12 hr., reflux	2,5-Dibenzylidene-3-cyclopentenone (60%)	224
2,6-Dibenzylidenecyclohexanone	CCl_4, 12 hr., reflux	2,6-Dibenzylidene-3-cyclohexenone (50%)	224
Polystyrene	Bz_2O_2, CCl_4, heat 2–7 hr.; C_6H_6, Na + C_4H_9OH, 10 hr., reflux	49% double bonds	188
1,4-Diphenylbutane	Bz_2O_2, CCl_4; C_5H_5N	1,4-Diphenyl-1,3-butadiene	111
$C_{10}H_{21}CH(CH_3)CO_2CH_3$	CCl_4, 45 min. reflux; quinoline, 2 hr., 140–160°	$C_9H_{19}CH{=}C(CH_3){-}CO_2CH_3$	36
Vanillin	$CHCl_3$, heat 14 hr.	5-Bromovanillin + 4% dehydrovanillin	221
1-Phenyl-2-isopropylcyclopropane	Bz_2O_2, CCl_4, 4 hr., reflux; $AgNO_3$ (C_2H_5OH)	$C_6H_5CH{=}CH{-}CH{=}C(CH_3)_2$ (low yield)	125
4-(2,6,6-Trimethyl-1-cyclohexenyl)-2-methyl-2-butenal	CH_2Cl_2, $NaHCO_3$-CaO; quinoline	4-(2,6,6-Trimethyl-2-cyclohexenylidene)-2-methyl-2-butenal	25
Dihydromuconic acid		Muconic acid	205
Cycloheptene	2 moles NBA; quinoline	Cycloheptatriene (20%)	57
Methyl 9α-acetoxydehydroabietate	CCl_4, u.v. light, N_2; KOAc (HOAc)	Methyl 9α-acetoxy-14(15)-dehydrodehydroabietate	200

TABLE IX

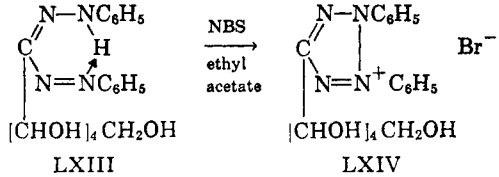
AROMATIZATIONS WITH N-BROMOSUCCINIMIDE (CCl_4) + BENZOYL PEROXIDE

Hydroaromatic compound	Products	Yield, %	References
Tetralin	Naphthalene	74	17, 152
1,4-Dihydronaphthalene	Naphthalene; 2,3-dibromo-1,2,3,4-tetrahydronaphthalene		152
sym-Octahydroanthracene	Anthracene	69	17
9,10-Dihydroanthracene	Anthracene		152
Tetrahydrophenanthrene	Phenanthrene	79	17
sym-Octahydrophenanthrene	Phenanthrene	63	17
asym-Octahydrophenanthrene	Phenanthrene; 1-bromophenanthrene	21, 12	17
1-Chloro-3,4-dihydronaphthalene	1-Chloronaphthalene		153
2-Methyl-3,4-dihydronaphthalene	2-Methylnaphthalene		153
Decalin	1,5-Dibromonaphthalene; x-tetrabromo-9,10-octalin	9 14	17
Acenaphthene	Acenaphthylene; dihydroxyacenaphthene	20 8	17
Bibenzyl	Stilbene, stilbene dibromide	56 10	17
1,1,6-Trimethyl-1,2-dihydronaphthalene	1,2,6-Trimethylnaphthalene (rearrangement)		18
d-Limonene	*p*-Cymene	80	18
Cyclohexene	*m*-Dibromobenzene; *p*-dibromobenzene (2:1)	58	17
1-(β-Phenylethyl)-1-cyclohexene	*trans*-Stilbene; stilbene dibromide; unkn. substance, m.p. 182–3° (lower yield of stilbene and more polybromo compounds if $CHCl_3$ replaced CCl_4)	48	18
1-Phenylcyclohexene	Biphenyl		152
1-Acetylcyclohexene	Acetophenone (after C_5H_5N treatment)		153
3-Ethoxycyclohexene	Phenol (after C_5H_5N)		153
3-Diethylaminocyclohexene	Diethylaniline (after C_5H_5N)	low	153

Conjugation in the methyl esters of fatty acids, *e.g.*, oleic, erucic, and stearolic acids, was introduced by treatment with NBS, then thermal dehydrobromination (156, 157). Yields of 30–40% of conjugated dienoic acid esters were obtained. When a three to four-fold excess of NBS was employed, some formation of trienes was observed, but attempts at separation were unsuccessful. Similar studies, including chemical dehydrobromination of allylic brominated unsaturated fatty acid esters also have been reported (108, 164, 165).

e. Miscellaneous Examples

Formazans are cyclized to tetrazolium salts in excellent yields by a variety of N-haloimides (especially NBP) and by NBA (124). This reaction has been extended to the direct conversion of sugar formazans, such as 1′,5′-diphenyl D-galactoformazan (LXIII) or its pentaacetate, to the corresponding tetrazolium salt (LXIV) in high yields (146). It is probable that the



LXIII LXIV

–NH– group is first converted to –NBr– and this is followed by stabilization (isomerization) to the salt. The method also has been applied successfully to the cyclization of 1-phenylazo-2-(arylamino)-naphthalenes and the *syn* forms of the phenylhydrazones of 2-pyridine and 2-quinolinecarboxaldehydes (124).

The wide variety of organic compounds which have been dehydrogenated with N-bromosuccinimide serves

TABLE X

DEHYDRATION OF HYDROXYSTEROIDS USING NBA OR NBS IN PYRIDINE

Steroid	Halogen compound	Product	References
6α,21-Difluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione	NBA	17α-Hydroxy-6α,21-difluoro-1,4,9(11)-pregnatriene-3,20-dione (70%)	197
6α-Methyl-11β-hydroxy-4-androstene-3,17-dione	NBA	6α-Methyl-4,9(11)-androstadiene-3,17-dione	93
6α,17α-Dimethyl-11β-hydroxytestosterone	NBA	6α,17α-Dimethyl-17β-hydroxy-4,9(11)-androstadien-3-one	92
6α-Methyl-11β-hydroxytestosterone	NBS	6α-Methyl-17β-hydroxy-4,9(11)-androstadien-3-one	94
6α-Fluoro-11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione	NBA	6α-Fluoro-17α-hydroxy-21-acetoxy-4,9(11)-pregnadiene-3,20-dione	141
2-Methyl-11β,17α-dihydroxy-20β,21-diacetoxy-4-pregnen-3-one	NBA	2-Methyl-17α-hydroxy-20β,21-diacetoxy-4,9(11)-pregnadien-3-one	190
6β-Fluoro-5α-hydroxyandrostane-3,17-dione	NBA, NBS	6β-Fluoro-4-androstene-3,17-dione	169, 5
6β-Fluoro-5α-hydroxy-19-norandrostane-3,17-dione	NBS	6β-Fluoro-19 nor-4-androstene-3,17-dione	5
1-Dehydro-6α-fluorohydrocortisone acetate	NBA	6α-Fluoro-17α-hydroxy-21-acetoxy-1,4,9(11)-pregnatriene-3,20-dione (50%)	196
6α-Fluorohydrocortisone acetate	NBA	6α-Fluoro-17α-hydroxy-21-acetoxy-4,9(11)-pregnadiene-3,20-dione (55%)	142
6α-Methyl-11β,17α-dihydroxy-4-pregnene-3,20-dione	NBA	6α-Methyl-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione	135
6α-Fluoro-11β-hydroxy-21-acetoxy-4-pregnene-3,20-dione	NBA	6α-Fluoro-21-acetoxy-4,9(11)-pregnadiene-3,20-dione	35

to demonstrate the scope and general utility of the method. This is further illustrated in Table VIII, in which a number of isolated examples from the recent literature are collected.

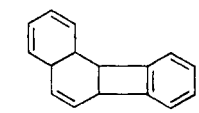
f. Aromatizations

Since many dehydrogenations of hydroaromatic compounds are accompanied by rearrangements, migrations, and ring closures, Barnes (17) studied the low temperature bromination-dehydrobromination procedure using NBS.

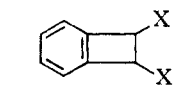
Tetralin reacted with NBS in carbon tetrachloride at reflux temperature in the presence of benzoyl peroxide to give a 74% yield of naphthalene. In other cases, shown in Table IX, the aromatic product often was accompanied by varying amounts of bromine-containing intermediates. Parallel results observed by Mousseron (153) are also tabulated.

It is of interest to note that under the reaction conditions cyclohexene gave a 58% yield of dibromobenzenes (2/3 *meta* and 1/3 *para*). Benzene does not react with NBS at an appreciable rate and, therefore, the intermediate must be a dibromocyclohexene or a dibromocyclohexadiene.

The proof of structure of benzocyclobutadiene dimer (LXV), prepared by zinc dehalogenation of compound LXVI, involved the aromatization of LXV by NBS in benzene to form benzo[a]biphenylene (LXVII) (37, 38). No bromo derivative of LXVII was isolated from the reaction mixture. Hence, the dimer was a dihydro derivative of LXVII. The position of the olefinic double bond in the dimer was confirmed by the observation that only one mole of bromine was absorbed to give a dibromide, LXVIII. Dehydrobromination with potassium *t*-butoxide produced the monobromide LXIX and dehydrogenation of LXIX by NBS in benzene gave 5-bromobenzo[a]biphenylene, LXX.

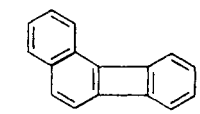


LXV

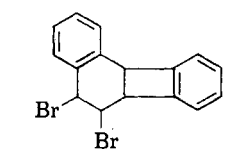


X = Br or I

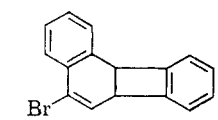
LXVI



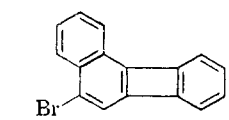
LXVII



LXVIII



LXIX



LXX

2. *Dehydrations Using N-Haloimides*

The use of NBA or NBS in pyridine at room temperature for the dehydration of 11β-hydroxysteroids represents a specific and important method for the introduction of the 9(11) double bond. The solution is often shaken with sulfur dioxide in order to remove the hydrogen bromide generated during the reaction. Under these conditions no oxidation of the 11β-hydroxy group has been observed. It is of interest to note that the first commercial application of NBS was in the dehydration of cholesterol. The examples listed in Table X have all been reported in the recent patent literature.

ADDENDUM

Covering pertinent literature through November, 1962

It has recently been shown (236) that the powerful reducing agent Cr(II) is quantitatively oxidized to Cr (III) in the presence of NBS in oxygen-free aqueous perchloric acid.

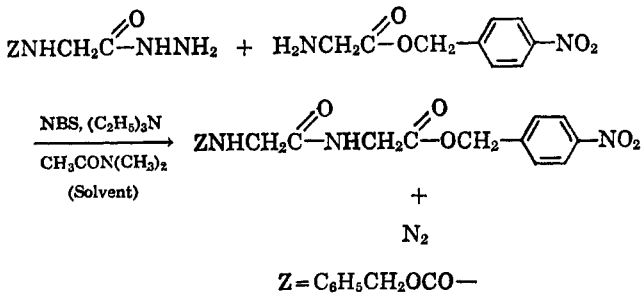
The oxidative cleavage of peptides of histidine, like

those of tryptophan and tyrosine, appears to proceed through intramolecular participation of the C-peptide bond in the ring opening of a labile bromonium intermediate (230).

Studies have been carried out on the participation of isolated carbon-carbon double bonds in the cleavage of peptides with NBS (228). The pH profiles of the cleavage reactions are diagnostic of the nature and location of the double bonds in peptides and amides derived from unsaturated amino acids, such as 2-amino-4-pentenoic acid ("allylglycine").

Recent reviews of the applications of non-enzymatic methods of peptide cleavage (229, 233) are of particular relevance to the role of NBS in this important field. A discussion of decarboxylation of α-amino acids, peptides, and proteins and selective cleavage of peptide bonds by NBS has been published (231).

A simple, rapid peptide synthesis *via* oxidative activation of acid hydrazides has been developed (234, 235). The procedure involves the reaction of N-substituted amino acid hydrazides with an amino acid ester in the presence of NBS.



The reaction is complete within five minutes with very high yields (80–86%). A desirable feature is that little racemization occurs so that the method can be applied to the synthesis of optically-active peptides containing side chains which are not sensitive to the oxidative conditions. The reaction probably involves the preferential oxidation of the acyl hydrazide in the presence of an amine to either an acyldiazonium salt or an acyl azo intermediate which then reacts with the nucleophilic amino group to form the peptide bond with nitrogen evolution.

By this method, a polymer (m.w. *ca.* 1400) derived from pro-gly-gly hydrazide, has been prepared (234).

The selective *in vitro* oxidation of the terminal double bonds in squalene, *via* bromohydrin and epoxide, has been accomplished by the use of NBS in aqueous ethylene glycol dimethyl ether ("glyme") (232).

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