BROMINATIONS WITH N-BROMOSUCCINIMIDE AND RELATED COMPOUNDS

THE WOHL–ZIEGLER REACTION

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Received January 16, 1948

CONTENTS

I. HISTORICAL

In contrast to the well-known addition of halogen to the double bond, it was only in 1919 that the first report by Wohl (99) appeared on an apparently general method for the direct introduction of a halogen atom (bromine) in the "allyl position" of an olefin.

$$-CH{=}CH-CH_2- \rightarrow -CH{=}CH-CHX-$$

rather than

$$-CHX-CHX-CH_2-$$

Wohl's papers (99, 100), although unusual, did not attract much attention, partly because the reagent used, *N*-bromoacetamide, was not too readily available, but chiefly because in his work the theoretical rather than practical aspects of this reaction were emphasized. The same result, i.e., substitution of the methylene group rather than addition of halogen to the double bond, has been accomplished by direct halogenation of simple low-molecular-weight olefins (31), particularly at high temperatures, but this method is only of very limited general applicability and will not be discussed in this review. In 1942, Ziegler and his collaborators (103) published their extensive research on the allylic bromination of olefins, in which they introduced the unique brominating agent *N*-bromosuccinimide. Their findings, which emphasized the preparative nature of this reaction, were employed almost immediately by organic chemists, as demonstrated by the relatively large literature which has already accumulated on the subject during the past five years.

In the meantime, a number of workers have introduced the use of catalysts in conjunction with *N*-bromoimides and have applied these reagents to brominations of aromatic and ketonic substances, thus extending appreciably the scope of the reaction as envisaged originally by Wohl and Ziegler. This review of the Wohl–Ziegler reaction, as the bromination with *N*-bromoimides will be referred to, has been written primarily with its synthetic applications in mind and to direct attention to those aspects of the reaction which still have to be investigated.

II. The Scope and Present Limitations of the Wohl–Ziegler Reaction

A. Introduction

Wohl (99, 100) showed that *N*-bromoacetamide[1] reacted in the cold in ether or acetone solution over a period of several hours or days with olefins (such as with 2,3-dimethyl-2-butene to give about 16 per cent of 1-bromo-2,3-dimethyl-2-butene), with anisole to yield 75 per cent of *p*-bromoanisole, and with ethyl acetoacetate to give a 45 per cent yield of the corresponding α-bromo derivative. In the latter case, *N*-bromophthalimide could be substituted for *N*-bromoacetamide. During the next twenty-three years only isolated examples (89, 95, 101) of the use of *N*-bromoacetamide in anhydrous media[1] were reported.

Ziegler and coworkers (103), in connection with their work on cantharidin (102), carried out an extensive search for a halogenating agent for olefins which would not attack the double bond but would substitute in the α-methylenic or "allyl position." The feasibility of such a reaction had already been demonstrated by Wohl's earlier work, as well as by other examples in which attack in the allyl position had been observed, as in the case of various oxidizing agents, dienophiles, etc. (summarized in references 1, 25, 103). However, it was necessary to find a reagent which would fulfill all or most of the following requirements: (*a*) it should be stable and readily available; (*b*) it should effect "allylic halogena-

[1] Reactions of *N*-bromoacetamide in aqueous solution usually involve the formation of hypobromous acid and do not fall within the scope of this review (for leading references see 85 and 103).

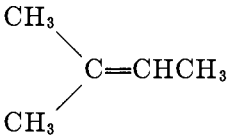
tion" with a minimum of side reactions; (*c*) the halogen carrier should be of relatively low molecular weight and recoverable (it was obvious that with few exceptions (31) free halogens could not be employed); (*d*) preferably, it should react in an inert solvent.

In 1942, in a detailed empirical study, Ziegler *et al.* (103) reported that *N*-bromosuccinimide met practically all the requirements enumerated above. *N*-Bromophthalimide, already employed by Wohl (100), was fairly satisfactory, while *N*-chlorosuccinimide, *N*-bromoglutarimide, and *N*-bromohexahydrophthalimide could not be used in this type of reaction. Certain *N*-chloroacylanilides and *N*-chloroamides (but not sulfonamides or imides) showed some promise as chlorinating agents, but were not studied in detail and have not found any general applicability, since they were inferior to *N*-bromosuccinimide as halogenating agents. The experimental conditions are considered in detail in Section IV, but in general with *N*-bromosuccinimide, the reagent is refluxed in carbon tetrachloride with the substance to be brominated until all the reagent has been consumed.

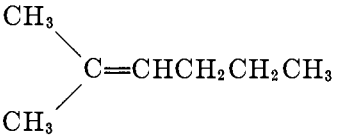
B. MONOÖLEFINS

1. Aliphatic and alicyclic olefins

As mentioned above, Wohl (99) studied the bromination with *N*-bromoacetamide of a few simple olefins, such as 2,3-dimethyl-2-butene. Ziegler (103), in a more extensive study, found that with few exceptions *N*-bromosuccinimide reacted much more readily with a methylene than a methyl group and that tertiary hydrogen atoms in general were not attacked. Thus, 2-methyl-2-butene (I) required 16 hr. for completion of the reaction, while with 2-methyl-2-hexene (II) the reaction was finished after 10 min. A similar relationship was observed with the diphenylolefins III and IV.



I



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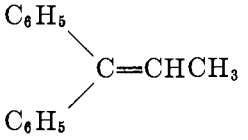

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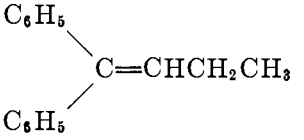
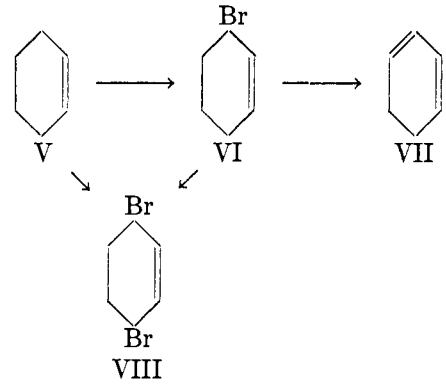


IV

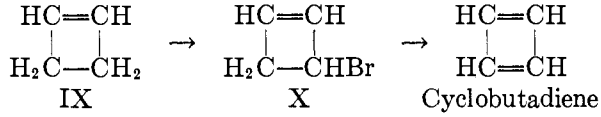
With cyclohexene (V), the 3-bromo derivative (VI) was obtained in high yield in about 20 min. and on dehydrobromination with quinoline it afforded 80–90 per cent of 1,3-cyclohexadiene (VII), undoubtedly the simplest method for preparing this compound.



With *N*-bromophthalimide instead of *N*-bromosuccinimide, the yield of VI was lowered to about 50 per cent and appreciable amounts of the adduct of cyclohexene and *N*-bromophthalimide were isolated. The dibromination of cyclohexene to VIII proceeded very unsatisfactorily when an excess of *N*-bromosuccinimide was treated with cyclohexene, but much more readily when 1 mole of *N*-bromosuccinimide was allowed to act upon the monobromo compound (VI). Ziegler's explanation for this difference is given below in Section III. More recently, Howton (36) made a detailed study of this reaction in the presence of peroxide and has isolated, in addition to VI, small amounts of VIII and of 1,2-dibromocyclohexane. The latter possibly arose from the reaction of free bromine, formed from *N*-bromosuccinimide and hydrogen bromide (probably liberated by spontaneous dehydrobromination of VI). With an excess of *N*-bromosuccinimide, V yields brominated benzene derivatives (5).

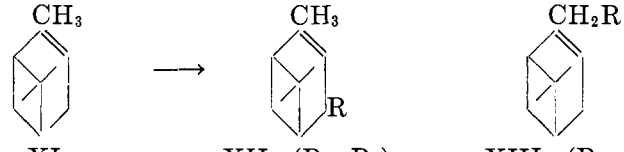
While only one monosubstitution product is possible in the case of cyclohexene, several products could be formed with substituted cyclohexenes. Mousseron *et al.* (61) examined the action of *N*-bromosuccinimide on several substituted cyclohexenes and cyclopentenes. Whereas 1-alkyl-1-cyclohexenes yielded predominantly the 6-bromo derivative, the corresponding 1-chloro derivative gave the 3-isomer. All the possible methylcyclohexenes as well as a few other compounds were studied, and the results are given in table 1. Cyclopentenes seem to react similarly.

Baker (3) in his Tilden lecture suggested that a promising approach to the solution of the cyclobutadiene problem would be the application of the Wohl–Ziegler reaction to cyclobutene (IX) affording the 3-bromo derivative (X), which on removal of hydrogen bromide, either directly or by treating X with dimethylamine and applying the exhaustive methylation procedure, should lead to cyclobutadiene. This suggestion has been tested experimentally by Howton and Buchman (37), who obtained traces of the desired 3-bromocyclobutene (X), the major product being 1,2-dibromocyclobutane. Results with methylenecyclobutane are shown in table 1.



2. *Isoprenoids*

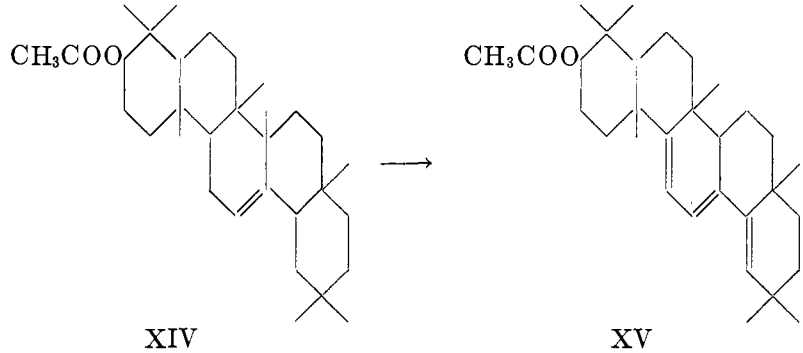
Ziegler (103) reported the successful bromination of α-pinene (XI) with *N*-bromosuccinimide to give an unknown monobromopinene. The reaction has recently been reinvestigated by Buu-Hoï and coworkers (14), who assigned to the product the structure XIIa rather than the alternate XIIIa, since it was not identical with the product formed in the reaction of *l*-myrtenol (XIIIb) with phosphorus tribromide. It should be pointed out that an authentic sample of bromopinene from *l*-verbenol (XIIb) was not prepared.



XI XIIa (R = Br) XIIb (R = OH) XIIIa (R = Br) XIIIb (R = OH)

Apparently, this reaction follows Ziegler's rule in that a methylene group is attacked in preference to a methyl group.

Ruzicka and Plattner (63, 79, 80) have employed the Wohl–Ziegler reaction extensively in their work on steroids and terpenes. Among the reactions studied, this has led to an improved procedure for norcedrenedicarboxylic acid (63), as well as to the introduction of double bonds into the amyrin molecule (79). Thus when β-amyrin acetate (XIV) was refluxed in carbon tetrachloride solution with an excess of *N*-bromosuccinimide for 2 hr., dibromination occurred followed by loss of hydrogen bromide, resulting in an excellent yield of β-amyratrienol acetate (XV). The corresponding reaction with the benzoate gave poorer results (62). Other examples of mono-unsaturated isoprenoids are considered in table 1.



XIV XV

β-Amyrin acetate β-Amyratrienol acetate

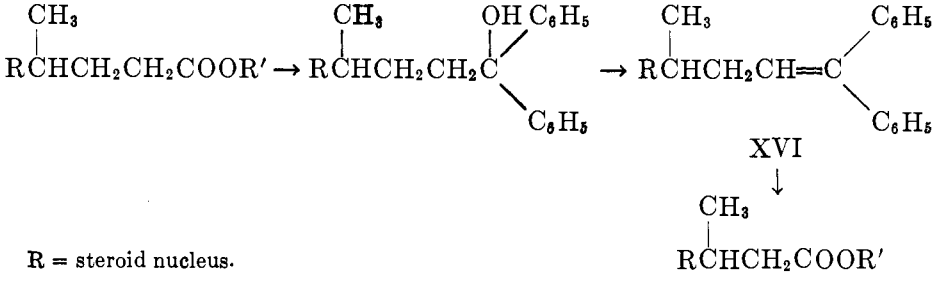
Roberts and Trumbull (124) studied the reaction of camphene and norbornylene, where allylic bromination is possible only at the bridge-head positions. Camphene gave predominantly the vinyl bromide (ω-bromocamphene), while norbornylene yielded the 7-bromo derivative (*cf.* table 1).

3. *Steroids*

The application of the Wohl–Ziegler reaction to steroid chemistry has been

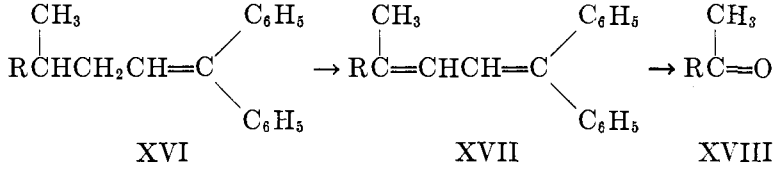
one of the most striking examples of its usefulness and is mainly due to Meystre, Miescher, Wettstein, and their coworkers (49–58, 96, 97).

An important problem in steroid chemistry has been the degradation of the bile acid side chain to the "methyl ketone," "etio acid," and "17-ketone" stages, which in turn represent intermediates for the synthesis of the progestational, cortical, and androgenic hormones. The conventional and very tedious method has been the classical Barbier–Wieland degradation, which removed one carbon atom at a time by formation of the diphenylcarbinol, followed by dehydration and oxidation.



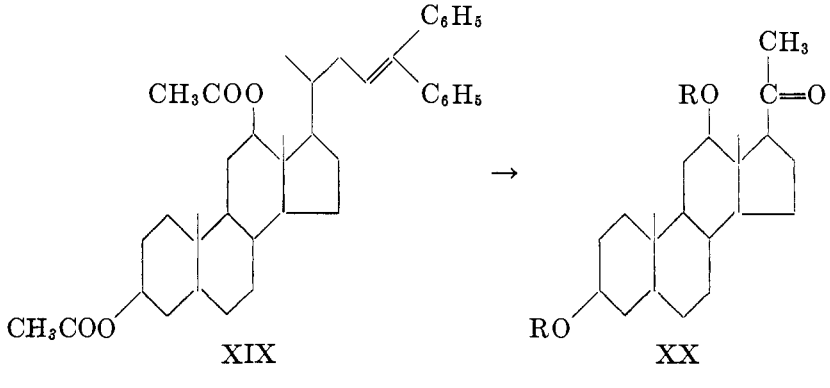
R = steroid nucleus.

Meystre and coworkers (49), and independently Ettlinger and Fieser (24), found that the diphenylethylene derivative (XVI) could be brominated with *N*-bromosuccinimide, the elements of hydrogen bromide eliminated, and the resulting crude diene (XVII) oxidized to remove three carbon atoms in essentially one step, leading directly to the "methyl ketone" stage (XVIII).



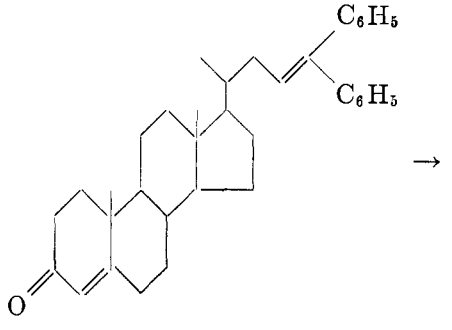
XVI XVII XVIII

The initial attempts were carried out in the usual manner with Δ^{23}-3(α),12(α)-diacetoxy-24,24-diphenylcholene (XIX) and gave about 25 per cent of the methyl ketone XX without isolation of intermediates. This represented already a major advance over the corresponding Barbier–Wieland degradation, which required seventeen steps and afforded the methyl ketone in 7 per cent overall yield.

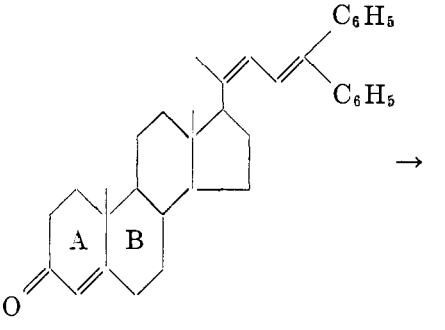


XIX XX

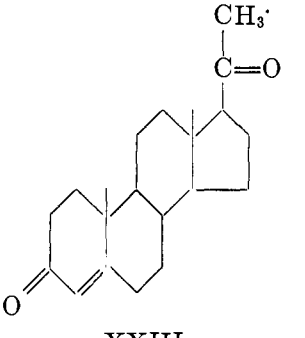
The Swiss workers soon discovered (50) that exposure to strong light had a powerful catalytic effect and that yields of 82 per cent of pure diene could be realized with either *N*-bromosuccinimide or *N*-bromophthalimide. The bromination was complete after about 15 min., but refluxing was continued for 4 hr., hydrogen bromide being eliminated during that period. The recognition of photocatalysis in the Wohl–Ziegler reaction extended appreciably the scope of the reaction, as will become apparent from the succeeding sections. The same investigators in a series of papers (51, 52, 53, 56) applied their photocatalytic method to a number of bile acids with various substituents in the steroid nucleus. Starting from 3(β)-hydroxycholenic acid, they developed six synthetic routes, all involving the Wohl–Ziegler reaction, which led to the important hormone progesterone (XXIII). Perhaps the most interesting method from the standpoint of the selectivity of the Wohl–Ziegler reaction involves as the starting material the unsaturated ketone XXI (56). In the presence of light, XXI reacted with *N*-bromosuccinimide almost exclusively in the side chain to give the intermediate XXII (after dehydrobromination with dimethylaniline) without attack in ring A or B (see Section D below; also 19, 54). After oxidative removal of the side chain, progesterone (XXIII) was obtained in 32 per cent over-all yield based on XXI without isolation of intermediates.



XXI



XXII



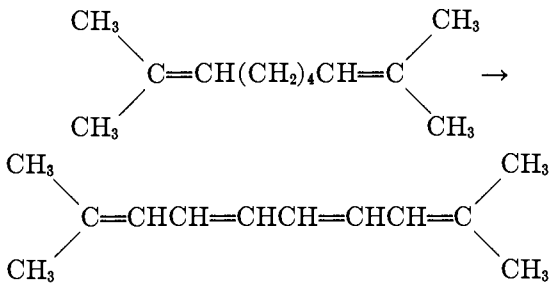
XXIII

Moffett and coworkers (59) employed this method for the degradation of hyodesoxycholic acid.

C. POLYOLEFINS (SEE TABLE 2)

1. Non-conjugated

In the single case studied by Ziegler (103), 2,9-dimethyl-2,8-decadiene reacted nearly quantitatively with 2 moles of *N*-bromosuccinimide, but the dehydrobromination product, the tetraene, was obtained only in an impure state.



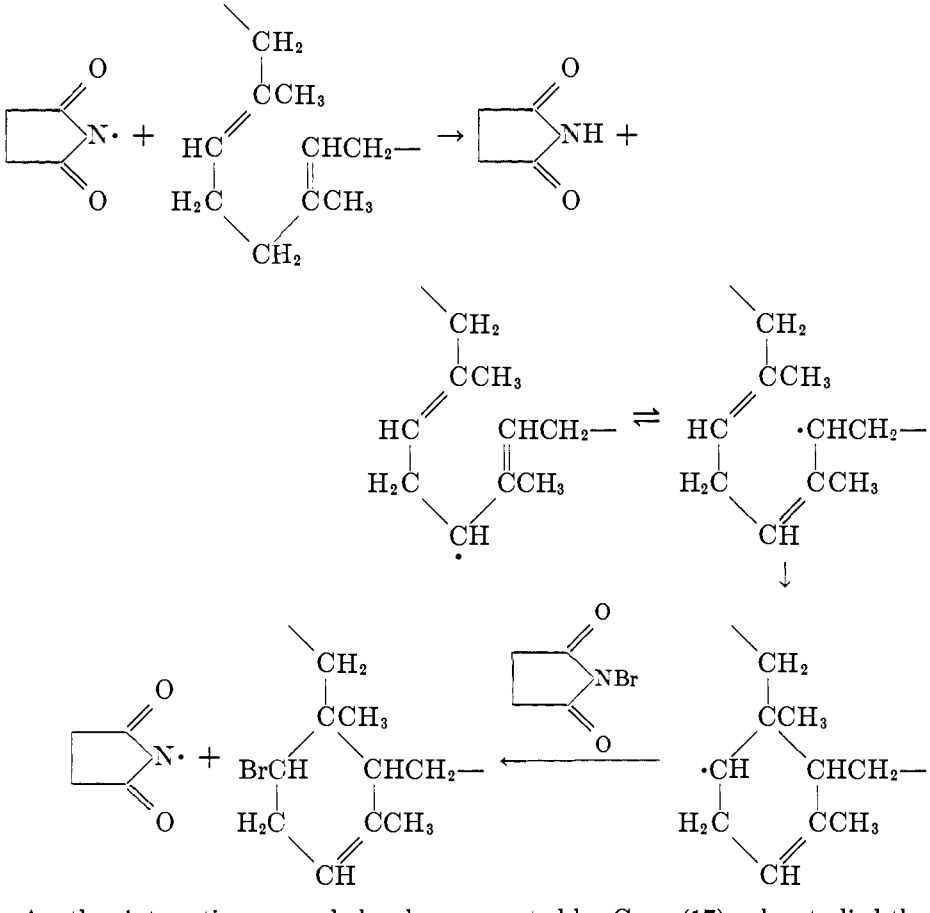
Recent work by Schmid and Karrer (86), who have introduced the use of dibenzoyl peroxide as catalyst in the Wohl–Ziegler reaction, still further extended the scope of the method which Ziegler thought to have reached in the case of the decadiene. These workers have shown that a number of brominations, previously unsuccessful with *N*-bromosuccinimide (such as the bromination of tertiary hydrogen atoms, the side chain of toluene, conjugated dienes), could be accomplished readily when a small amount of peroxide was added to the reaction mixture, often in conjunction with strong light.

Using this new extension, Karrer and Ringli (43) have studied the bromination of diallyl (XXIV) with *N*-bromosuccinimide. In the presence of peroxide and light, after refluxing for about 8 hr., diallyl (1,5-hexadiene) gave a monobromo compound to which was assigned the structure XXV and which readily reacted with silver acetate or alcoholic alkali. Further bromination of the monobromo compound with *N*-bromosuccinimide led to a dibromo compound, considered to be 3,4-dibromo-1,5-hexadiene, which was convertible to a diacetate and similar derivatives. More recent work (44) has shown, however, that the dibromo compound possessed the isomeric structure XXVI resulting from two allylic rearrangements, and that the monobromo compound (117) should be represented by XXV as believed originally, rather than by one of the other two possible allylic structures. Reaction of XXV with silver acetate was shown to be accompanied by rearrangement.

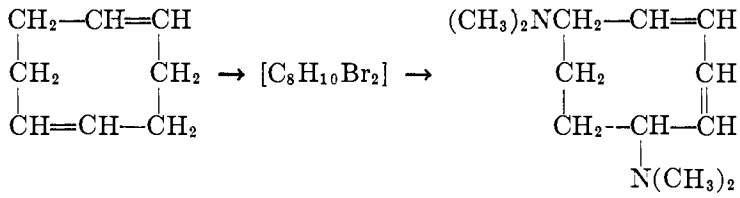
$$\underset{\text{XXIV}}{CH_2{=}CHCH_2CH_2CH{=}CH_2} \rightarrow \underset{\text{XXV}}{CH_2{=}CHCHBrCH_2CH{=}CH_2} \rightarrow \underset{\text{XXVI}}{BrCH_2CH{=}CHCH{=}CHCH_2Br}$$

The possibility of allylic rearrangements in the Wohl–Ziegler reaction should never be overlooked. This has been noted by Ziegler in the dibromination of dodecylene (103) and by others (17, 37, 97).

Bloomfield (7), who observed that dihydromyrcene (2,6-dimethyl-2,6-octadiene) easily gave a monobromo compound with *N*-bromosuccinimide, applied the Wohl–Ziegler reaction to acetone-extracted crepe rubber and obtained bromo-rubber of the empirical formula $(C_{10}H_{15}Br)_x$. Since the iodine number of this bromo-rubber was far below the calculated amount and on the assumption that bromination occurred only in the allyl position, Bloomfield postulated that cyclization occurred during the reaction as depicted below, employing a free-radical mechanism (see also Section III on mechanism).



Another interesting example has been reported by Cope (17), who studied the action of *N*-bromosuccinimide in the presence of peroxide (light had no effect) on 1,5-cycloöctadiene (XXVII), which was obtained from chloroprene dimer. Depending on the molar ratio, a mono or dibromo compound or both were formed. In view of the ample opportunity for allylic rearrangements, definite structures have not yet been assigned to these compounds, but on treatment with dimethylamine the dibromo derivative gave 5,8-bis(dimethylamino)-1,3-cycloöctadiene (XXVIII), an intermediate in the Willstätter synthesis of cyclooctatetraene.

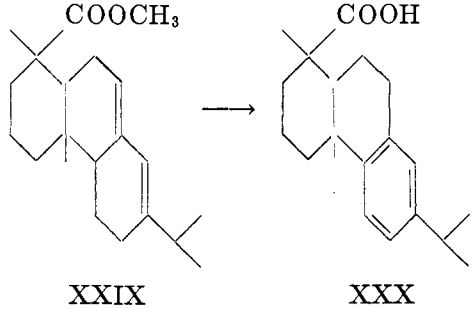


XXVII XXVIII

In the field of carotenoids, Karrer and Rutschmann (39) prepared dehydrolycopene, which possesses fifteen conjugated double bonds, by treating lycopene with 2 moles of *N*-bromosuccinimide, the intermediate dibromo compound losing hydrogen bromide spontaneously. The bromination is formulated as occurring on the methylene groups adjacent to the isolated double bonds rather than to the conjugated system.

2. Conjugated

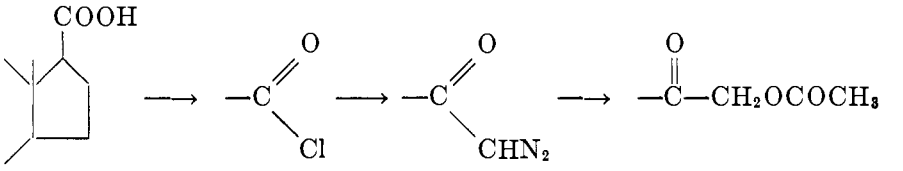
Ziegler (103) was unable to isolate any definite product on treating 1,3-cyclohexadiene with *N*-bromosuccinimide and believed that substitution of a methylene group adjacent to a conjugated system of double bonds was beyond the scope of his reaction. This has since been shown to be incorrect (see also Section II,E). For instance, using *N*-bromosuccinimide without catalysts, a new and simplified method for the preparation of dehydroabietic acid (XXX) from methyl abietate (XXIX) in one operation has been reported by Jeger *et al.* (38). The previous synthesis (26) of this interesting compound involved catalytic dehydrogenation and purification through the sulfonic acid.



XXIX XXX

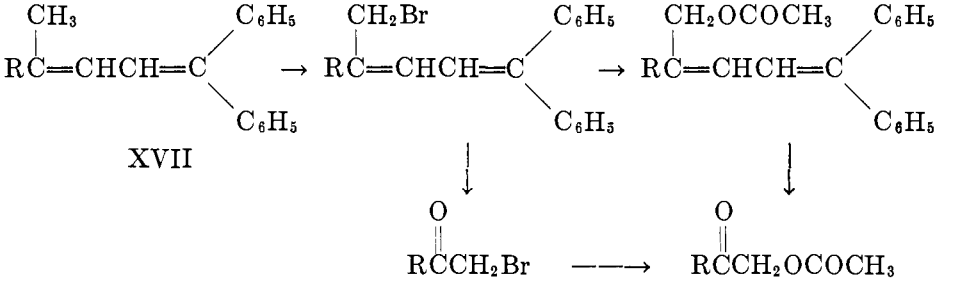
Methyl abietate Dehydroabietic acid

An important application of the Wohl–Ziegler reaction has been reported by Meystre and Wettstein (55, 57, 58, 96), who succeeded in adapting their bile acid degradation method to the introduction of the ketol side chain characteristic of the cortical hormones. Prior to their work, the method employed most commonly involved degradation of the sterol side chain to the "etio acid" (XXXI), conversion to the diazo ketone, and reaction with acetic acid. The pertinent literature on this and related methods has been reviewed elsewhere (55).



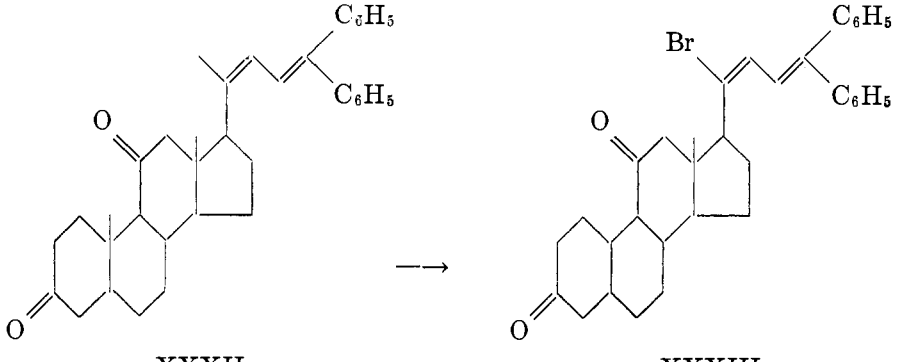
XXXI

These investigators found that preferably, but not necessarily, in the presence of strong light the steroid dienes (XVII) which they had prepared in connection with their work on bile acid degradation, using the Wohl–Ziegler reaction, could be brominated with an additional mole of *N*-bromosuccinimide, the bromine entering in position 21. The bromo compound could then be oxidized, followed by treatment with potassium acetate, or the process could be reversed. It was thus possible to introduce the cortical hormone side chain directly and to eliminate the complete degradation of the sterol or bile acid side chain to the etio acid stage (XXXI).



XVII

The yields of bromo compound were in the neighborhood of 70 per cent in several instances and furthermore, as in the bromination of the steroid ethylenes (Section II,B), the presence of certain reactive groups in the steroid nucleus did not interfere. This led to a new synthesis for 11-desoxycorticosterone (58). An unusual example was $\Delta^{20(23)}$-3,11-diketo-24,24-diphenylcholadiene (XXXII), where bromination to XXXIII was accomplished in 62 per cent yield (96). The latter was then converted to the valuable 11-dehydrocorticosterone acetate.

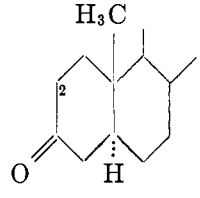


XXXII XXXIII

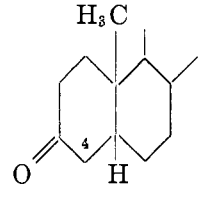
D. CARBONYL COMPOUNDS

Except for the early work of Wohl[2] on the bromination of ethyl acetoacetate with *N*-bromoacetamide (99) and *N*-bromophthalimide (100), it was not until 1946 that publications appeared in which *N*-bromoimides had been employed for the bromination of ketones. The special application of the Wohl–Ziegler reaction to carbonyl compounds will be illustrated below with several examples.

Schmid and Karrer (86) showed that cyclohexanone and certain ketopelargonic acid derivatives readily afforded the corresponding α-bromoketones. Employing strong light and either *N*-bromosuccinimide or *N*-bromophthalimide, it was found recently (19) that saturated 3-ketosteroids of the allo (XXXIV) and normal (XXXV) series reacted in a few minutes to form the 2-bromo and 4-bromo compounds, respectively.

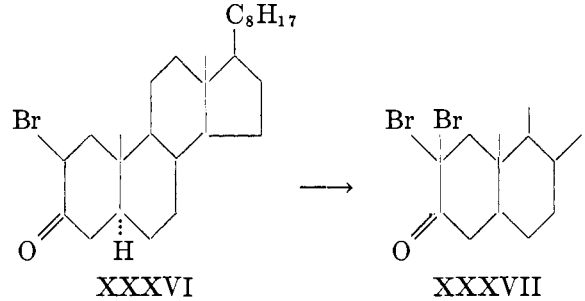


XXXIV



XXXV

Free hydroxyl and carbomethoxyl groups did not seem to interfere. It is apparent, therefore, that the same stereochemical factors are involved with *N*-bromosuccinimide as with bromine in acetic acid. This method may have special application in cases where groups sensitive to bromine or hydrogen bromide are present. For instance, the further bromination of 2-bromocholestanone (XXXVI) with *N*-bromosuccinimide was shown to result in the formation of the 2,2-dibromo compound XXXVII, while with bromine in acetic acid, hydrogen bromide had to be removed to obtain the same results (20).



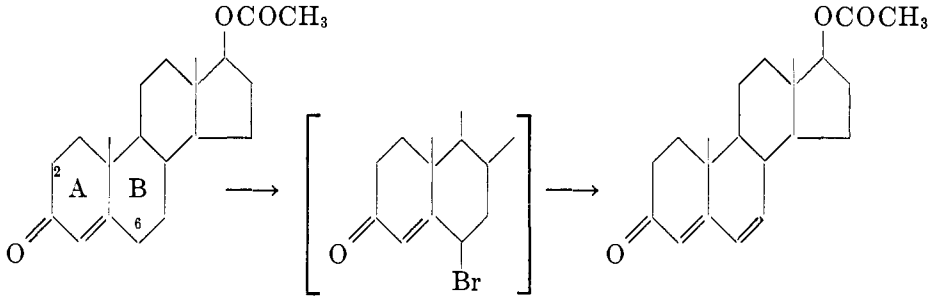
XXXVI XXXVII

Preliminary experiments (21) on 1-keto-1,2,3,4-tetrahydrophenanthrene demonstrated that it could be converted to 1-phenanthrol by reaction with

[2] As pointed out by Stork (90), the conversion of cinchotoxine to cinchoninone by Rabe (70) in 1911 [and later of quinotoxine to quininone (71)] may well represent the earliest example of the bromination of a ketone by an *N*-bromo compound, although it was not formulated as such by Rabe.

N-bromosuccinimide followed by dehydrobromination, but no advantages over the conventional method using bromine seemed apparent.

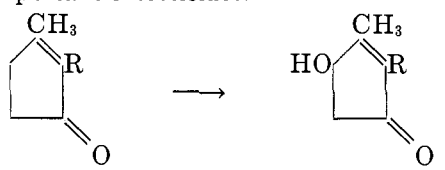
Meystre and Wettstein (54) have examined the action of *N*-bromosuccinimide on α,β-unsaturated steroid ketones, such as testosterone acetate (XXXVIII), where reaction could occur either alpha to the ketone group in position 2 or in the "allyl position" in ring B. The latter was found to be the case; after dehydrobromination 80 per cent of 6-dehydrotestosterone acetate (XXXIX) was obtained by a method of synthesis which was superior to those described earlier for compounds of type XXXIX. It should be noted that in this case, better yields were obtained when the reaction was carried out in the dark with excess *N*-bromosuccinimide for a longer time rather than with strong light, possibly suppressing the competing ketone bromination.



XXXVIII XXXIX

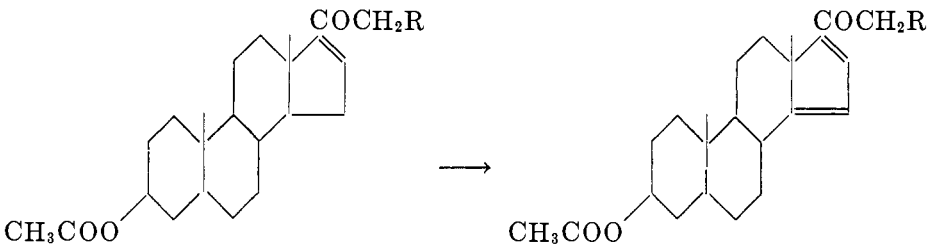
As mentioned before (Sections II,B and II,C), in certain ketones where a reactive double bond or diene structure is present in another part of the same molecule, in the presence of light the methylenic group of the latter can be brominated with *N*-bromosuccinimide without attacking the ketone (see, e.g., compounds XXI and XXXII). Other examples of this specificity are listed in table 3.

The reaction of *N*-bromosuccinimide with α,β-unsaturated ketones has recently been used in the synthesis of dihydrocinerolone (XLIa) (88) and tetrahydropyrethrolone (XLIb) (18) from dihydrocinerone (XLa) and tetrahydropyrethrone (XLb), the intermediate bromo compounds having been converted with carbonate or acetate to the alcohols. The course of the Wohl–Ziegler reaction in this case was used as further evidence for the presently accepted structures of these important insecticides.



XLa: R = C_4H_9 XLIa: R = C_4H_9
XLb: R = C_5H_{11} XLIb: R = C_5H_{11}

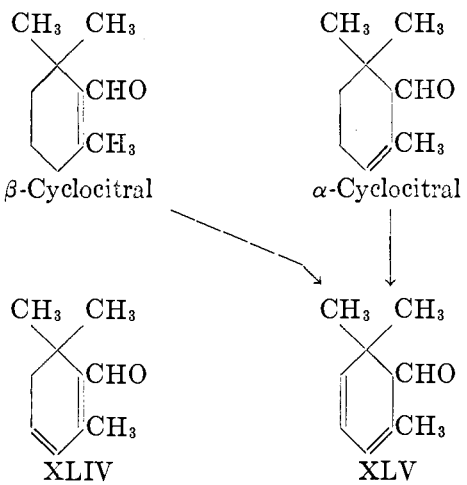
Similar results have been obtained by Plattner and coworkers (66, 67) in certain steroid ketones (XLII), which furnished the doubly unsaturated ring D intermediates (XLIII) of importance for the synthesis of steroid aglucones.



XLII (R = H; $OCOCH_3$) XLIII (R = H; $OCOCH_3$)

With the exception of a preliminary report by Buu-Hoï (12), in which it was claimed[3] that certain ketones of the mesityl oxide type gave the α-bromoketone rather than the allyl bromide, it seems that in general in α,β-unsaturated ketones where bromination of a methylene group alpha to the ketone and alpha to the double bond is possible, the latter reaction occurs.

Aldehydes, in contrast to ketones, have hardly been investigated. Crotonaldehyde and related aldehydes have been reported to lead to decomposition products only (12, 103) when treated with *N*-bromosuccinimide in the usual manner. This could probably be circumvented by using either derivatives such as the acetal (*cf.* 103) or by employing conditions milder than are customary in the Wohl–Ziegler reaction. A very recent publication illustrates this point. Karrer and Ochsner (45a) attempted to prepare safranal (XLIV) from β-cyclocitral and found that the reaction was carried out best by adding *N*-bromosuccinimide in portions while cooling, the reaction being complete in about 5 min. The crude bromination product was dehydrobrominated with collidine to yield an aldehyde isomeric with safranal. Evidence was presented in favor of structure XLV for the product, which was also obtained in the Wohl–Ziegler reaction of α-cyclocitral. It was clear that in the case of β-cyclocitral, migration

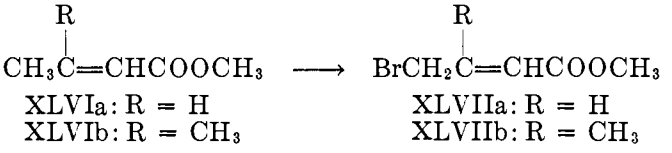


[3] No experimental details were given and the evidence presented in favor of the α-bromoketone structure was equivocal, particularly since the possibility of allylic rearrangements was not considered.

of the double bond must have occurred at some stage of the reaction, but the structure of the intermediates was not determined. This example again emphasizes the need for considering the possibility of rearrangements in the Wohl–Ziegler reaction.

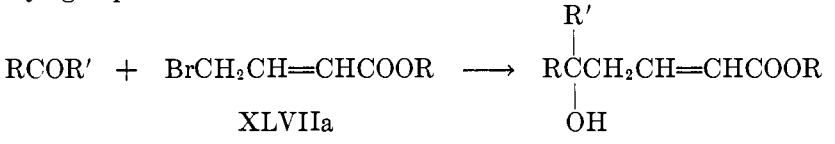
E. COMPOUNDS WITH FUNCTIONAL GROUPS (OTHER THAN CARBONYL) ALPHA OR BETA TO A DOUBLE BOND

One of the most important examples of this type was reported first by Ziegler (103)—namely, the allylic bromination of methyl crotonate (XLVIa) and senecioate (XLVIb)—leading to the very important γ-bromo derivatives (XLVII) in excellent yield.



XLVIa: R = H; XLVIb: R = CH_3 — XLVIIa: R = H; XLVIIb: R = CH_3

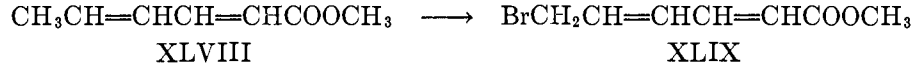
To appreciate the simplicity of this reaction, one need only examine the many steps which were necessary to prepare these compounds prior to Ziegler's publication (8, 29, 30). As shown by several workers (22, 28, 29, 104), γ-bromocrotonates readily undergo the Reformatsky condensation and the synthesis of these esters through the Wohl–Ziegler reaction has made possible a very useful extension, whereby a four-carbon-atom chain may be introduced at the site of a carbonyl group.



XLVIIa

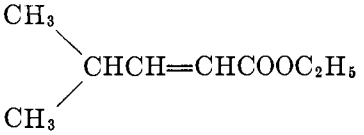
Among the more noteworthy recent applications of the γ-bromocrotonic esters, there should be mentioned the synthesis of compounds related to vitamin A (2, 33, 41, 114), of six-membered rings (16), and of tropinone (45).

The bromination of the next higher homolog, methyl sorbate (XLVIII), also could be accomplished, either in the presence of peroxide (42) or at higher temperature (33) to yield the ε-bromo derivative (XLIX), but unfortunately this compound did not undergo the Reformatsky reaction (33, 42).



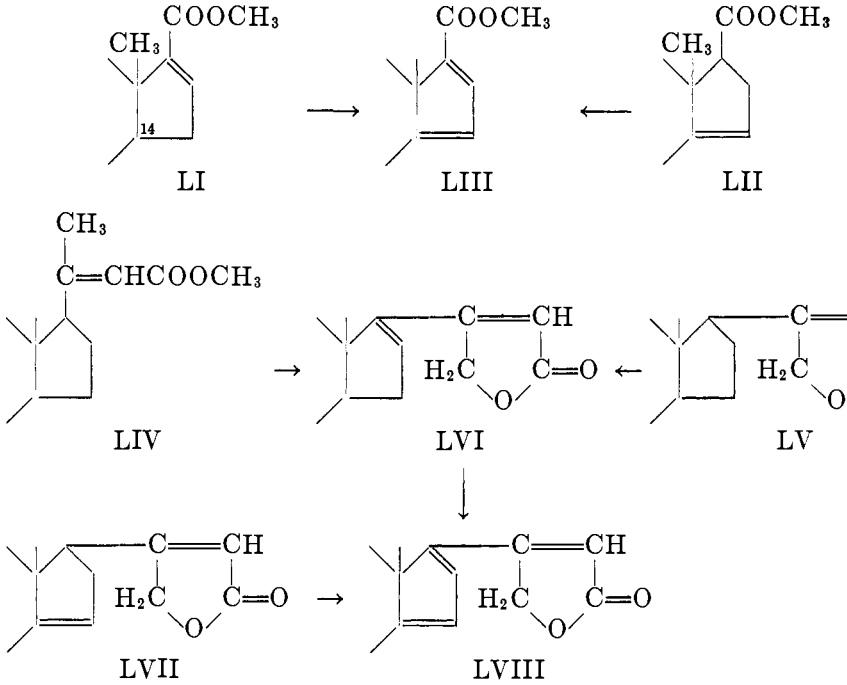
XLVIII — XLIX

Using peroxide, Schmid and Karrer (86) were able to effect substitution of the tertiary hydrogen of ethyl 4-methyl-2-pentenoate (L), a reaction which was not possible under Ziegler's original conditions.

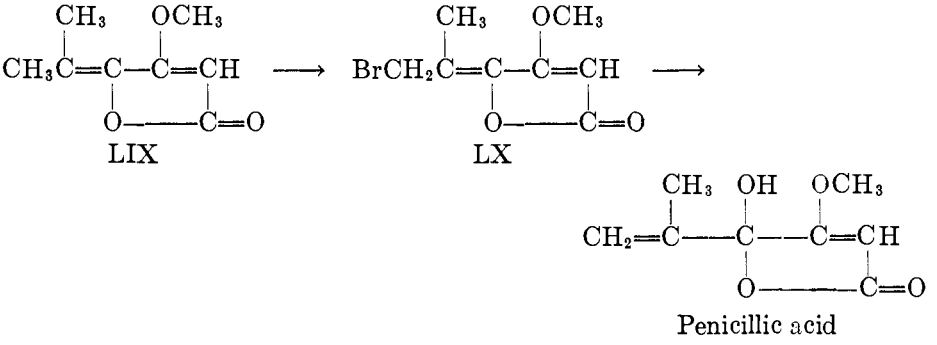


L

Ruzicka, Plattner, and their coworkers have used the photocatalyzed Wohl-Ziegler reaction in the bromination of α,β-unsaturated esters (LI, LIV) (81, 83), nitriles (68, 84), and lactones (LV, LVI) (64, 82) of the steroid series which has made possible the introduction of a hydroxyl group into position 14 and thus the partial synthesis of compounds of the steroid aglucone type. Starting with the corresponding 14,15-unsaturated derivatives, e.g., LII and LVII, the same type of compound was obtained (64, 65).

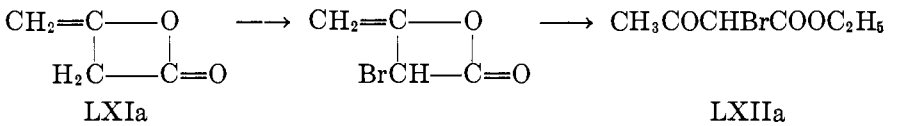


Recently Raphael (72) treated the unsaturated lactone LIX with *N*-bromosuccinimide and obtained the ϵ-bromo derivative LX in excellent yield, which in turn could be converted to penicillic acid.



Among the numerous formulations postulated for ketene dimer, the isomeric β-lactone structures (LXIa and LXIb) have been considered seriously on the

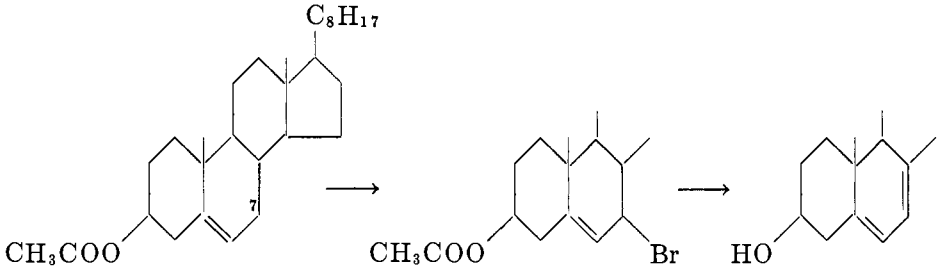
basis of physicochemical evidence. Blomquist and Baldwin (6a) pointed out that reaction with *N*-bromosuccinimide should lead in each case to a different bromo compound, which on alcoholysis should produce ethyl α-bromoacetoacetate (LXIIa) in the case of the ketene dimer with an exocyclic double bond (LXIa) or the γ-bromo derivative (LXIIb) if the isomeric structure LXIb were the correct one. When tested experimentally, only ethyl α-bromoacetoacetate (LXIIa) was isolated, and this was considered chemical evidence in favor of structure LXIa for ketene dimer. The possibility of an allylic rearrangement should not be discounted however, particularly in view of the resemblance to methylenecyclobutane (37). Furthermore, it has been pointed out recently (120) that ketene dimer probably represents an equilibrium mixture of LXIa and LXIb and it is conceivable that one form (LXIa) reacts preferentially with *N*-bromosuccinimide.



LXIa LXIIa

LXIb LXIIb

Ziegler (103) reported without giving details that cholesterol acetate reacted with *N*-bromosuccinimide. Henbest and coworkers (32) and independently Buisman *et al.* (10) have studied this reaction and reported that bromination occurred in position 7 and that the bromo compound LXIII could be dehydrobrominated to lead to 7-dehydrocholesterol (LXIV) in about 30 per cent over-all yield, thus affording a new and improved synthesis of provitamin D_3. Other cholesterol esters have given similar results (116).



Cholesterol acetate LXIII LXIV

F. AROMATIC HYDROCARBONS

1. Nuclear bromination

Benzene was believed to be unattacked by *N*-bromosuccinimide (11, 25), and it has been used as solvent in the Wohl–Ziegler reaction even in peroxide-catalyzed reactions (see Section IV,B), but Schmid (87) discovered that in the presence of equimolar amounts of certain metal chlorides (aluminum, zinc, and

ferric) or sulfuric acid, nuclear bromination of benzene or toluene could be achieved readily. In spite of the large amount of chloride necessary, these compounds are claimed to act as catalysts.

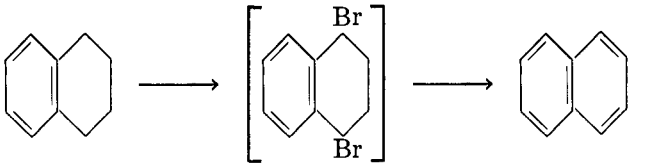
In the case of polynuclear aromatic hydrocarbons (11), catalysts were not necessary, naphthalene and phenanthrene reacting in about 6 hr. to give the 1- and 9-bromo derivatives, respectively; with acenaphthene and anthracene the reaction was complete in a matter of minutes, the corresponding 5- and 9-bromo derivatives being formed.

Already Wohl (99) had observed reaction of *N*-bromoacetamide with anisole, and Buu-Hoï (11) has studied the action of *N*-bromosuccinimide on a wide variety of benzene and naphthalene derivatives, notably ethers. No catalysts were used and the reactions with phenol ethers required several hours for completion, while ethers of α- and β-naphthol reacted in a few minutes.

2. "Side chain" bromination

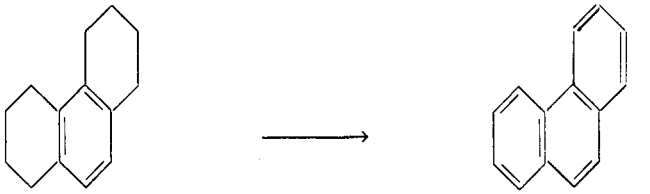
While toluene is not attacked by *N*-bromosuccinimide in the absence of catalysts (11; see, however, 9), Schmid and Karrer (86) demonstrated that benzyl bromide was formed in 64 per cent yield in the presence of peroxide. Thus, in analogy to the behavior of bromine with toluene, substitution can be effected in the nucleus or in the methyl group depending on the conditions employed. In the presence of electronegative groups, "side chain" substitution occurs without catalysts (4, 11). This holds true also for 1- and 2-methylnaphthalenes (11, 13), di- and tri-phenylmethanes (11), fluorene (98), and related compounds. In several dimethylnaphthalenes (13) one methyl group can be brominated selectively. An interesting case is 1-ethylnaphthalene, where "side chain" bromination is observed (13), vinylnaphthalene being obtained in 73 per cent yield in contrast to the closely related acenaphthene, where reaction occurred in the nucleus (11). In the presence of peroxide, the former reaction seemed to predominate (5) and acenaphthylene was isolated. It is quite probable that in a number of the examples studied by Buu-Hoï and coworkers (11, 13), the reaction time could be diminished appreciably and possibly higher yields obtained with the use of catalysts, such as light or peroxide. However, even in the absence of catalysts the yields were quite good (see table 5) and the Wohl–Ziegler reaction is to be preferred in several instances to the classical methods of synthesis for such compounds.

Very recently, Barnes (5) has applied the peroxide-catalyzed Wohl–Ziegler reaction to a number of hydroaromatic hydrocarbons, thereby developing a novel low-temperature method for the dehydrogenation of tetralin types. The reaction was carried out by refluxing the hydrocarbon with the calculated amount of *N*-bromosuccinimide in carbon tetrachloride and dehydrobrominating after the completion of the bromination with acetate. Under those conditions, tetralin (LXV) afforded naphthalene (LXVI) in 74 per cent yield, *sym*-octahydrophenanthrene (LXVII) gave phenanthrene (LXVIII) in 63 per cent yield, and bibenzyl (LXIX) yielded 56 per cent of stilbene (LXX). Other examples of this elegant method are given in table 5.



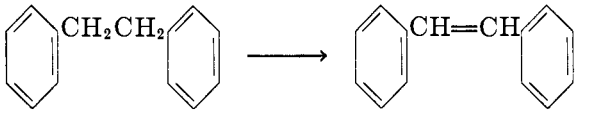
LXV
Tetralin

LXVI
Naphthalene



LXVII
sym-Octahydrophenanthrene

LXVIII
Phenanthrene



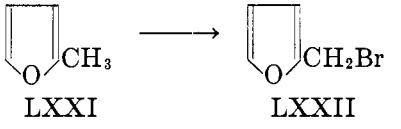
LXIX
Bibenzyl

LXX
Stilbene

G. HETEROCYCLIC COMPOUNDS

A considerable amount of work needs to be done in investigating the full applicability of the Wohl–Ziegler reaction to heterocyclic compounds. A start in this direction where oxygen is the heteroatom has been made, particularly in France.

Buu-Hoï and Lecocq (15) observed that 2-methylfuran (LXXI) reacted very vigorously to form 2-bromomethylfuran (LXXII) in excellent yield. With 2,5-dimethylfuran (LXXIII) and 2,6-dimethyl-γ-pyrone (LXXIV) one methyl group could be brominated selectively. In the case of LXXIV, with bromine only nuclear bromination has been observed.



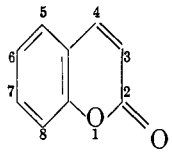
LXXI

LXXII

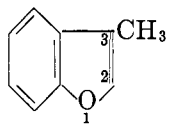
LXXIII

LXXIV

Coumarin (LXXV) derivatives have been studied by Molho and Mentzer (60) and also by Lecocq and Buu-Hoï (47), who noted that a 4-methyl group was never attacked,[4] in contrast to the 3-methyl or ethyl substituents in which case "side chain" bromination was observed. Methyl groups attached to the aromatic ring were substituted with ease.



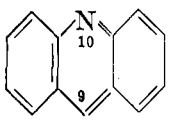
LXXV



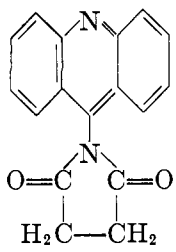
LXXVI

Erlenmeyer and Grubenmann (23) have demonstrated that in the presence of peroxide, reaction with 1 mole of *N*-bromosuccinimide resulted in nuclear substitution of 3-methylbenzofuran (LXXVI) to give the 2-bromo derivative, while 2 moles of *N*-bromosuccinimide led to the 2-bromo-3-bromomethyl compound.

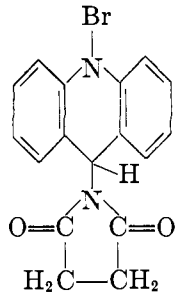
A very detailed study of the reaction of *N*-bromosuccinimide with acridine (LXXVII) has been recorded by Schmid and Leutenegger (87a), who isolated from the complex reaction mixture two monobromoacridines, two dibromoacridines, *N*-(9-acridyl)succinimide (LXXVIII), several brominated derivatives of the latter, acridine hydrobromide, acridone, and three unidentified compounds.



LXXVII
Acridine



LXXVIII



LXXIX

The positions of the bromine atoms were not established, but substitution at position 9 was excluded. To explain the formation of such a variety of products, two reactions of *N*-bromosuccinimide were postulated: (*a*) direct substitution as in other aromatic compounds (see Section II,F) and (*b*) addition of *N*-bromosuccinimide across the 9,10-positions, yielding the hypothetical intermediate LXXIX which loses hydrogen bromide, resulting in the formation of LXXVIII. A combination of both reactions (a and b) would account for the isolation of brominated derivatives of LXXVIII. The hydrogen bromide lost from the hypothetical intermediate LXXIX forms acridine hydrobromide (insoluble in

[4] The influence of catalysts, however, has not been examined.

carbon tetrachloride), thus removing some acridine from the reaction mixture, which in turn offers an explanation for the isolation of the dibromo compounds even though only 1 mole of *N*-bromosuccinimide was employed.

Only a few isolated experiments have been recorded with other nitrogen and sulfur heterocyclics, none approaching in thoroughness the above-mentioned work on acridine. "Side chain" bromination has been reported for α- and γ-picolines, quinaldine (11), and 2,5-dimethylthiophene (15). Nuclear bromination of thiophene has been accomplished with both *N*-bromoacetamide (89) and *N*-bromosuccinimide (11). A few other examples are given in table 6.

III. Mechanism of the Reaction

In his first paper Wohl (99) suggested a mechanism for the allylic bromination of olefins with *N*-bromoacetamide in which he postulated the formation of an intermediate complex between the two compounds.

$$R_2C{=}CR\overset{\displaystyle H}{\overset{|}{C}}H{\rightleftarrows}Br\cdots NHCOCH_3 \rightarrow R_2C{=}CRCH_2Br + CH_3CONH_2$$

A difference in the stability of such hypothetical addition complexes was employed by Ziegler and coworkers (103) to account for the observation that the preparation of 3,5-dibromocyclohexene was accomplished readily on treating 3-bromocyclohexene with 1 mole of *N*-bromosuccinimide, but proceeded only with difficulty when 2 moles of the reagent were allowed to react with cyclohexene.

A somewhat similar mechanism in terms of ion-radicals has been used recently by Ettlinger (25), who assumed that after closely approaching each other, the unsaturated compound and *N*-bromoimide underwent electron transfer, resulting in the formation of two unstable ion-radicals "which exchange hydrogen and bromine in a continuous process."

Photocatalysis, peroxide catalysis, and the fact that the point of attack of *N*-bromosuccinimide in olefins usually coincides with that of reagents generally believed to react through free radicals (e.g., benzoyl peroxide, benzenediazonium chloride), all suggest the presence of neutral free radicals (extensive review in reference 25) and such a mechanism is favored at present (34, 35). Already in 1937 Waters (92), in postulating a free-radical mechanism for certain reactions of benzenediazonium chloride, tentatively extended it to positive halogen compounds in general, and its specific applicability to the Wohl–Ziegler reaction has been pointed out recently (93). Bloomfield (7) also favored a neutral, free-radical chain mechanism and depicted the reaction as proceeding through a thermal, homolytic dissociation of *N*-bromosuccinimide (a), followed by abstraction of hydrogen from the methylene group by the free radical (b), and involving chain termination (c) as well as propagation (d).

(a) $(C_4H_4O_2)N\cdot Br \rightarrow (C_4H_4O_2)N\cdot + Br\cdot$

(b) $-CH_2-C{=}C- + (C_4H_4O_2)N\cdot \rightarrow -\dot{C}H-C{=}C- + (C_4H_4O_2)NH$

(c) $-\dot{C}H-C=C + Br\cdot \rightarrow -CHBr-C=C-$ (or $-C=C-CHBr$)

(d) $-\dot{C}H-C=C- + (C_4H_4O_2)N\cdot Br \rightarrow CHBr-C=C-$ (or $-C=C-CHBr$) $+ (C_4H_4O_2)N\cdot$

This treatment also has been applied to explain the reaction of decalin (5) and of rubber (7) with *N*-bromosuccinimide (see Section II,C). A recent attempt to demonstrate the homolytic dissociation of positive halogen compounds has been recorded by Robertson and Waters (73), who measured the catalytic effect (presumably due to the formation of free radicals) of such substances on the autoöxidation of tetralin. *N*-Bromosuccinimide was found to be a very potent catalyst, in contrast to *N*-bromophthalimide. The analogy of allylic bromination by means of *N*-bromosuccinimide to the free-radical vapor-phase allylic halogenation studied by Rust and Vaughan (78) also has been mentioned (91, 94).

Ettlinger (25) has pointed out that the free radicals formed by thermal dissociation of *N*-bromosuccinimide must possess rather low reactivity, since attack on the solvent (carbon tetrachloride) has not been observed (see also 93) in contrast to the behavior of free radicals produced, for instance, from benzoyl peroxide. Ettlinger (25) reviewed the pertinent literature and also examined the stability of *N*-bromosuccinimide in various solvents, notably dioxane, where decomposition was catalyzed by dioxane peroxide and inhibited by tetrabromohydroquinone. It should be noted that a small amount of *N*-phenylsuccinimide has been isolated (36, 37) in a reaction where benzene was the solvent (see also reference 87a on a similar reaction with acridine).

A report (69) favoring the O—Br rather than N—Br structure for bromophthalimide was written before Ziegler's work (103) became available in Russia.

In conclusion, it can be seen that various investigators have presented indirect evidence to favor a free-radical mechanism for the Wohl–Ziegler reaction with *N*-bromosuccinimide. In the case of *N*-bromophthalimide, it is believed that an ionic mechanism also enters (25), since Ziegler *et al.* (103) observed addition of *N*-bromophthalimide to cyclohexene as well as substitution by halogen. In the case of steroid ethylenes (50) or ketones (19), *N*-bromosuccinimide and *N*-bromophthalimide seem to be equally effective when employed in conjunction with photocatalysis. It should be pointed out that satisfactory mechanisms[5] will have to explain the bromination of olefins in the allyl position, the "side chain bromination" of toluene types, the nuclear bromination of aromatic compounds, and the α-bromination of ketones. Any such mechanism also should account for the amazing reactivity of *N*-bromosuccinimide, the apparently lowered reactivity of *N*-bromophthalimide and, most important, the complete

[5] The plural "mechanisms" is used purposely, since it is likely that *N*-bromosuccinimide (and *N*-bromophthalimide) may react by several mechanisms, resulting from homolytic as well as heterolytic dissociation of the reagent. It is highly questionable that the bromination of the methylthiophenes (107), which proceeds in different directions depending on the presence of peroxide, or the addition of bromine to double bonds with *N*-bromosuccinimide (36, 37, 102, 124), as compared to allylic bromination, should all occur by the same mechanism.

ineffectiveness (103) of *N*-bromoglutarimide, *N*-bromohexahydrophthalimide, and *N*-chlorosuccinimide in the allylic type of reaction. This last observation should be confirmed and repeated, using peroxide and light. It is essential that a sound study of mechanism should be based on comparative data on the effect of variations of experimental conditions (catalysts, temperature, time, etc.) on representative examples of the three major types of reaction, i.e., allylic, nuclear, and ketone bromination. It is unfortunate that some of the speculations on the mechanism of the Wohl–Ziegler reaction are based on isolated examples which are not always comparable from an experimental standpoint.

IV. Experimental Conditions

A. *N*-Bromoimides

N-Bromosuccinimide is prepared in 75–81 per cent yield by brominating quickly an ice-cold, alkaline solution of succinimide (103). It is desirable to employ *N*-bromosuccinimide of 97 per cent purity or better in the Wohl–Ziegler reaction and for that purpose, the reagent is best recrystallized *quickly* from hot water. Preferably the purity of the product is determined iodometrically (103) rather than relying on the melting point. In the absence of light and moisture, the reagent is stable for many months (25). *N*-Bromosuccinimide is available commercially.

N-Bromophthalimide is synthesized by a nearly identical method (9) from phthalimide.

N-Bromoacetamide can be prepared in 40–55 per cent yield by treating equimolar quantities of acetamide and bromine with a concentrated solution of potassium hydroxide and separating the *N*-bromoacetamide by extraction with hot benzene (6). It has been recommended to store the reagent in the ice box and to use only colorless material melting at 108°C. (99).

B. Solvents

By far the most widely used solvent has been carbon tetrachloride, which was employed almost exclusively by Ziegler in his original studies. In certain cases (7, 24, 25, 36, 37) benzene has added advantages, particularly since *N*-bromosuccinimide is appreciably more soluble in benzene than in carbon tetrachloride. Benzene is not attacked by *N*-bromosuccinimide in the presence of peroxide under ordinary circumstances (87; see, however, 36), but it cannot be used in the presence of catalysts such as aluminum chloride (87; see also Section II,F). Petroleum ether (10, 116) and heptane (37) have been used occasionally, but do not seem to offer any obvious advantages. Although reported only very recently (6a, 121), chloroform has given excellent results particularly in large-scale runs (*cf.* table 4), since it is a more general solvent for organic compounds than carbon tetrachloride and succinimide is soluble in hot chloroform, thus yielding a homogeneous solution. Carbon disulfide (87) gave only poor results in the bromination of toluene. Ethanol has been employed with *N*-bromosuccinimide (27) and *N*-bromoacetamide (101), and ether and acetone have been used with *N*-bromoacetamide (99, 100). Acetic anhydride has been suggested (103) as a

possible solvent, but *N*-bromosuccinimide seems to be unstable in it as well as in ethyl acetate, dioxane, and tri-*n*-butylamine (25). *N*-Bromosuccinimide did not attack nitrobenzene in the absence of catalysts (25), but that solvent was useless in the single case tried (bromination of XIX). Ether has been suggested (103) as a possible solvent in the bromination of very reactive methylene groups, but no actual experiments have been described. In many instances (e.g., 11, 33, 89, 103) no solvent is used and the reaction is carried out in an excess of the reactant.

C. MOLAR PROPORTIONS

An excess of olefin was recommended by Ziegler (103) in the bromination of several olefins (table 1), such as cyclohexene to avoid side reactions due to polybromination (see, for instance, the reaction of cyclohexene with 6 moles of *N*-bromosuccinimide (5)). An excess of reactant is used generally in the bromination of aromatic hydrocarbons (11, 87), phenol ethers (11), and related compounds. In steroid brominations, either equimolar amounts or an excess of *N*-bromosuccinimide is employed. Thus, for the bromination of steroid ethylenes and steroid dienes (*cf.* 50, 51, 57) equimolar amounts are suggested and in certain brominations of unsaturated steroid esters and derivatives (68, 83, 84), in contrast to crotonic acid esters (15a, 48, 103), an excess of *N*-bromosuccinimide is used. For steroid ketones equimolar amounts have been employed in conjunction with photocatalysis (19), but an excess may be added without catalysts (54). For dehydrogenations of tetralin types, the calculated amount of *N*-bromosuccinimide is recommended (5). In general, no definite rules can be established and the optimum proportions vary often with the specific example at hand.

D. TEMPERATURE

In most instances, the reactions are carried out at the boiling point of the solvent. In certain unusually reactive compounds, the temperature may be lowered by using a solvent such as ether (103) or by cooling (15, 27, 45a). On the other hand, it has sometimes been found advantageous to operate at higher temperatures. Thus, while the bromination of 1-phenyl-1-propene (103) required about 15 hr. in refluxing carbon tetrachloride solution, the reaction was complete almost instantaneously and without appreciable diminution in yield when carried out at 140°C. A similar observation was made in the bromination of methyl crotonate (103). Reactions at higher temperatures generally are carried out in the absence of a solvent (33, 102, 113). Reactions with *N*-bromoacetamide are performed at room temperature or in an ice bath for prolonged periods of time (99, 100, 101).

E. CATALYSTS

For reactions where photocatalysis is employed, such as in the bromination of steroid ethylenes (50), it has been found useful to combine the sources of heat and light by placing a General Electric reflector drying lamp (250 watts, 115 volts) below the flask. In large batches, several lamps are used to produce refluxing. For peroxide-catalyzed reactions, 5–10 mole per cent of freshly pre-

pared dibenzoyl peroxide has been recommended (86), although sometimes peroxide-containing substances (36) have been used. Mixing the peroxide with *N*-bromosuccinimide in the dry state and using the powdered material subsequently may be advantageous (5). To effect nuclear brominations of aromatic hydrocarbons, such as benzene or toluene, 1 mole of aluminum, zinc, or ferric chloride or sulfuric acid has to be used, since smaller amounts give poor results (87).

F. GENERAL PROCEDURE

Dry reagents are essential to avoid hydrolysis of the *N*-bromoimide. In general, the reactant is dissolved in carbon tetrachloride or another suitable solvent, *N*-bromosuccinimide or *N*-bromophthalimide is added, and the mixture is refluxed. The disappearance of the insoluble *N*-bromoimide on the bottom with the simultaneous formation of the insoluble imide floating on top indicates the completion of the reaction. This can be confirmed by testing for the absence of bromine (starch–iodide test). Quite often, e.g., in the case of ketones (19), a color develops in the beginning which disappears suddenly when the reaction is complete. This has also been observed in other instances (5, 86). After the completion of the reaction, the insoluble imide is filtered, washed with solvent, and the filtrate is worked up in a suitable manner (removal of solvent, followed by crystallization, distillation, etc.) to isolate the product. The proper conditions will have to be chosen for each particular case, taking into consideration the remarks made in Section III, A to E. In general the reaction is carried out first without catalysts and if unsuccessful (owing to incomplete reaction or other reasons), peroxide or light or both (43) can be employed as catalysts. A combination of several variables may be considered to achieve selectivity or minimize side reactions (*cf.* 54). The wide variety of experimental conditions which can be used are rather obvious and represent a particularly attractive feature of the Wohl–Ziegler reaction.

In many instances, the resulting bromo compound is unstable and loses the elements of hydrogen bromide spontaneously on longer refluxing (*cf.* 50, 51, 53). In those cases where loss of hydrogen bromide is only partial, the succinimide is filtered at the end of the reaction (negative potassium iodide test, absence of heavy precipitate on the bottom), the solvent is removed and a base is added to complete dehydrobromination; potassium or sodium acetate (5, 38), sodium carbonate (13), dimethylaniline (49, 51, 56), pyridine (*cf.* 19, 64, 82), collidine (10, 21, 45a, 54), alumina (81), and similar reagents have been used. It should be noted that in particularly unstable bromo compounds, where dehydrobromination occurs before bromination is complete, hydrogen bromide can liberate free bromine from *N*-bromosuccinimide and give rise to side reactions (97).

V. Conclusion

It is evident that although a considerable amount of ground has been covered, much work remains to be done to determine the full scope of the Wohl–Ziegler reaction. The fairly recent introduction of catalysts—light, peroxide, metal

chlorides—necessitates the repetition of many of the earlier experiments, particularly unsuccessful ones, in which catalysts have not been used, in order to demonstrate the feasibility of the Wohl–Ziegler reaction in those cases.

A great deal of work still is to be done in the field of heterocyclics, where promising results may be expected. With one questionable exception (100), acetylenic compounds have not yet been examined. More definite evidence also will be needed to put the reaction mechanism on a strong footing.

VI. Tables

Practically all compounds which have been investigated in the Wohl–Ziegler reaction up to January 1, 1948 are given in tables 1 to 7. A few arbitrary classifications have been made; for instance, XXI is given under monoölefins rather than polyolefins, since the reaction only involves the isolated double bond in the side chain, but the compound is also classified under carbonyl compounds. Under reaction conditions, the time given denotes the period at reflux temperature, unless stated otherwise; dehydrobrominating agents are usually not specified.

The author is indebted to Dr. David R. Howton, California Institute of Technology, Dr. Roderick A. Barnes, Rutgers University, Dr. H. B. Henbest, Imperial College of Science and Technology, Dr. John D. Roberts, Massachusetts Institute of Technology, and Dr. Karl Dittmer, University of Colorado, for furnishing unpublished material, and to Dr. Gilbert Stork, Harvard University, for stimulating correspondence. The helpful suggestions of Dr. C. R. Scholz of this laboratory are gratefully acknowledged.

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TABLE 1

Wohl–Ziegler reaction of monoölefins

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(*1*) *Aliphatic and alicyclic olefins:*			
Propylene	NBA,* ether, 19 days, room temperature	29% dibromo derivative	(100)
2-Methyl-2-butene	2NBA, acetone, cold	50% dibromo derivative	(99)
	1/2NBS, CCl_4, 16 hr.	40% monobromoamylene	(103)
2,3-Dimethyl-2-butene	NBA, ether, 12 hr.	16% 1-bromo-2,3-dimethyl-2-butene	(99)
2-Bromo-3-methyl-2-butene	NBA, acetone, 24 hr., room temperature	13–22% dibromo derivative	(99)
2-Methyl-2-hexene	1/2NBS, CCl_4, 10 min.	40% 4(?)-bromo-2-methyl-2-hexene	(103)
2-Octene	1/3NBS, CCl_4, 1 hr.	70% monobromoöctene	(103)
Diisobutylene	1/3NBS, CCl_4, 5 hr.	68% monobromoisobutylene	(103)
4-Nonene	NBS, CCl_4, 40 min.	65% monobromononene	(103)
1-Dodecylene	1/2NBS, CCl_4, 5 min.	77% monobromododecylene	(103)
	2NBS, CCl_4, 32 min.	33% 1,4(?)-dibromo-2-dodecylene	(103)
3-Bromo-1-dodecylene	NBS, 4 hr.	40% 1,4(?)-dibromo-2-dodecylene	(103)
Ethyl undecylate	1/3NBS, CCl_4, 30 min.	46% monobromo derivative	(103)
Methyl oleate	NBS, CCl_4, 40 min.	Quantitative yield of monobromo derivative	(103)
Cyclobutene	NBS, C_6H_6, 6 hr., peroxide	67% 1,2-dibromocyclobutane, trace 3-bromocyclobutene	(37)
Methylenecyclobutane	NBS, C_6H_6, 6 hr., peroxide	13.5% 2-bromo-1-methylenecyclobutane, 1.5% 1-bromomethyl-1-cyclobutene, 57% methylenecyclobutane dibromide, 15% *N*-phenylsuccinimide	(37)
1-Methylcyclopentene	"Ziegler's conditions"	Unstable bromo derivative	(61)
1-Chlorocyclopentene	"Ziegler's conditions"	3-Bromo-1-chloro-1-cyclopentene	(61)
Cyclohexene	NBP, CCl_4, 1 hr.	50% 3-bromo-1-cyclohexene, 21% *N*-(2-bromocyclohexyl)phthalimide	(103)
	1/5NBS, (CCl_4), 20 min.	82–87% 3-bromocyclohexene	(103)
	NBS, C_6H_6, 32 min., peroxide	50% 3-bromo-1-cyclohexene, 6.4% 1,2-dibromocyclohexane, 2% 3,6-dibromo-1-cyclohexene, 1% *N*-phenylsuccinimide	(36, 110)
	6NBS, CCl_4, 12 hr., peroxide	58% *m*- and *p*-dibromobenzenes	(5)

TABLE 1—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
1-Methyl-1-cyclohexene	"Ziegler's conditions"	Chiefly 6-bromo-1-methyl-1-cyclohexene, trace of 3-bromo isomer	(61)
1-Methyl-2-cyclohexene	"Ziegler's conditions"	4-Bromo-1-methyl-2-cyclohexene	(61)
1-Methyl-3-cyclohexene	"Ziegler's conditions"	5-Bromo-1-methyl-3-cyclohexene	(61)
Methylenecyclohexane	"Ziegler's conditions" (long heating)	2-Bromo-1-methylenecyclohexane, polybromo compounds	(61)
1-Ethylcyclohexene	"Ziegler's conditions"	6-Bromo-1-ethylcyclohexene	(61)
1,3-Dimethyl-3-cyclohexene	"Ziegler's conditions"	2-Bromo-1,3-dimethyl-3-cyclohexene	(61)
1-Chlorocyclohexene	"Ziegler's conditions"	3-Bromo-1-chloro-1-cyclohexene	(61)
3-Bromo-1-cyclohexene	1/3NBS, CCl_4, 1 min.	31% 3,6-dibromo-1-cyclohexene	(103)
Cycloöctene	NBS	1,3-Cycloöctadiene	(103)
9,10-Octalin	4NBS, CCl_4, peroxide	30% *x*-tetrabromoöctalin	(5)
Styrene	NBS	No reaction	(46)
α-Methylstyrene	NBS	Reacts	(103)
1-Phenyl-1-propene	1/2NBS, CCl_4, 15.5 hr.	75% cinnamyl bromide; 67% when carried out at 140°C. (instantaneous reaction)	(103)
1,1-Diphenyl-1-propene	NBS, CCl_4, 18 hr.	86% γ,γ-diphenylallyl bromide	(103)
1,1-Diphenyl-1-butene	NBS, CCl_4, 95 min.	3-Bromo-1,1-diphenyl-1-butene	(103)
1, 1-Diphenyl-4-methyl-1-pentene	NBS, CCl_4, light, then dehydrobrominate	1,1-Diphenyl-4-methyl-1, 3-pentadiene	(58a)
Diethylstilbestrol dipropionate	2NBS, CCl_4, 30 min.	64% 3,4-bis(*p*-propionoxyphenyl)-2,5-dibromo-3-hexene	(111)
(*2*) *Isoprenoids:*			
α-Pinene	2/5NBS, CCl_4, 1 hr.	60% monobromopinene (XIIa)	(14, 103)
Camphene	1/2NBS, CCl_4, 24 hr., peroxide, light	24% ω-bromocamphene, 9% alkyl bromide, 7% allyl bromide	(124)

TABLE 1—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Norbornylene	1/2NBS, 2.5 hr., peroxide, light (21% yield in presence of HBr or absence of catalyst)	41% 7-bromonorbornylene	(124)
Cedrene	NBS, CCl_4, 10 min.	(Bromocedrene) oxidized in 35% yield to norcedrenedicarboxylic acid	(63)
$\Delta^{6,7}$-23-Nor-α-amyrene	NBS (70%), CCl_4, 4 hr.	65% $\Delta^{6,7;8,9}$-23-nor-α-amyradiene, 10% hexabromo derivative	(80)
$\Delta^{6,7}$-23-Nor-2-keto-α-amyrene	NBS, CCl_4, 4 hr., $BaCO_3$	$\Delta^{6,7;8,9}$-23-Nor-2-keto-α-amyradiene	(80)
β-Amyrin acetate	NBS (65%), CCl_4, 2 hr.	80% β-amyratrienol acetate (XV)	(79)
β-Amyrin benzoate	NBS, CCl_4, 3 hr.	2% β-amyratrienol benzoate, 9% bromo-β-amyratrienol benzoate	(62)
α-Amyrin acetate	NBS (65%), CCl_4, 2 hr.	80% α-amyradienol acetate	(79)
Methyl acetylursolate	NBS (65%), CCl_4, 2 hr.	70–75% methyl acetyldehydroursolate	(79)
(3) *Steroids:*			
Δ^{23}-24,24-Diphenylallocholene	NBS, CCl_4, 12 min., light, then dehydrobrominate	21% pure diene; 44% over-all to 17-methyl ketone	(51)
Δ^{23}-3(β)-Acetoxy-24,24-diphenylallocholene	NBS, CCl_4, 15 min., light, then dehydrobrominate	70% diene	(52, 97)
Δ^{23}-3(α)-Acetoxy-24,24-diphenylcholene	NBS, CCl_4, 15 min., light, then dehydrobrominate	*ca.* 50% diene	(52)
$\Delta^{4,23}$-3-Keto-24,24-diphenylcholadiene	NBS, CCl_4, 15 min., light, then dehydrobrominate	$\Delta^{4,20,23}$-3-Keto-24,24-diphenylcholatriene (XXII)	(56)
Δ^{23}-3(α),6(β)-Diacetoxy-24,24-diphenylcholene	NBS, CCl_4, 15 min., light, then dehydrobrominate	(Crude diene) 37% over-all to 17-methyl ketone (crude)	(59)
Δ^{23}-3(α),12(α)-Diacetoxy-24,24-diphenylcholene	NBS, C_6H_6, 2 hr., then dehydrobrominate	(Crude diene) 23% over-all to 17-methyl ketone	(24)
	NBS, CCl_4, 10 min., then dehydrobrominate	(Crude diene), 25% over-all to 17-methyl ketone	(49)
	NBS, CCl_4, 15 min., light, then dehydrobrominate	82% diene (same with NBP)	(50)

TABLE 1—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Δ^{23}-3(α),12(α)-Diacetoxy-23,23-diphenylnorcholene	NBS, CCl_4, light	No reaction	(50)
Δ^{23}-3(β)-Acetoxy-5-chloro-24,24-diphenylcholene	NBS, CCl_4, 20 min., light, then dehydrobrominate	56% diene	(53)
Δ^{23}-3(α)-Acetoxy-11-keto-24,24-diphenylcholene	NBS, CCl_4, 15 min., light, then dehydrobrominate	*ca.* 60% diene	(96)
Δ^{23}-3(α),7(α),12(α)-Triacetoxy-24,24-diphenylcholene	NBS, CCl_4, 15 min., light, then dehydrobrominate	Quantitative yield of crude diene; 39% overall to 17-methyl ketone	(51)

* NBA = *N*-bromoacetamide.
NBS = *N*-bromosuccinimide.
NBP = *N*-bromophthalimide.

TABLE 2

Wohl–Ziegler reaction of polyolefins

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(*1*) *Non-conjugated:*			
1,5-Hexadiene	4/5NBS,* CCl_4, 8 hr., light, peroxide	45% 3-bromo-1,5-hexadiene	(43, 44, 117)
3-Bromo-1,5-hexadiene	NBS, CCl_4, 6 hr., light, peroxide	52% 1,6-dibromo-2,4-hexadiene	(43, 44)
1,5-Cycloöctadiene	NBS, CCl_4, 1 hr, peroxide	57% monobromo derivative	(17)
	2NBS, CCl_4, 1 hr, peroxide, then $(CH_3)_2NH$	34% 5,8-bis(dimethylamino)-1,3-cycloöctadiene	(17)
Dihydromyrcene	NBS, CCl_4, N_2	Monobromo derivative	(7)
Rubber	NBS, $C_6H_5(CCl_4)$, 1/2 hr.	Bromo-rubber	(7)
2,9-Dimethyl-2,8-decadiene	2NBS, CCl_4, 1/2 hr.	Dibromo derivative	(103)
Lycopene	2NBS, CCl_4, 2 hr.	20% dehydrolycopene	(39)
(*2*) *Conjugated:*			
1,3-Cyclohexadiene	1/3NBS, CCl_4, 6 hr.	No definite product	(103)
1,3(?)-Dodecadiene	2/3NBS, CCl_4, 10 hr.	28% (crude) bromododecadiene	(103)
Methyl abietate	NBS, CCl_4, 3 hr., $BaCO_3$, then CH_3COONa	32% dehydroabietic acid	(38)

TABLE 2—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
1,1,4a-Trimethyl-7-isopropyl-1,2,3,4,4a,5,6,9,10,10a-decahydrophenanthrene	NBS, CCl_4, 1 hr., $BaCO_3$, then CH_3COONa	23% dehydroabietane	(38)
β-Amyradienol-II acetate	NBS, CCl_4, 3 hr.	β-Amyratrienol acetate	(62)
β-Amyradienol-I acetate	NBS (80%), CCl_4, 2 hr.	β-Amyratrienol acetate	(62)
$\Delta^{4;20;23}$-3-Keto-24,24-diphenylcholatriene	NBS, CCl_4, 10 min., light	$\Delta^{4;20;23}$-3-Keto-21-bromo-24,24-diphenylcholatriene	(58)
$\Delta^{20;23}$-3,11-Diketo-24,24-diphenylcholadiene	NBS, CCl_4, 15 min., light	62% $\Delta^{20;23}$-3,11-diketo-21-bromo-24,24-diphenylcholadiene	(96)
$\Delta^{20;23}$-3-Keto-12(α)-acetoxy-24,24-diphenylcholadiene	NBS, CCl_4, 15 min., light	69% $\Delta^{20;23}$-3-keto-12(α)-acetoxy-21-bromo-24,24-diphenylcholadiene	(57)
$\Delta^{20;23}$-3(α),12(α)-Diacetoxy-24,24-diphenylcholadiene	NBS, CCl_4, 10 min., light (1 hr. without light)	71% $\Delta^{20;23}$-3(α),12(α)-diacetoxy-21-bromo-24,24-diphenylcholadiene	(57)
$\Delta^{20;23}$-3(β)-Acetoxy-5-chloro-24,24-diphenylcholadiene	NBS, CCl_4, 20 min., light	74% $\Delta^{20;23}$-3(β)-acetoxy-5-chloro-21-bromo-24,24-diphenylcholadiene	(58)

* NBS = *N*-bromosuccinimide.

TABLE 3

Wohl–Ziegler reaction of carbonyl compounds

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(1) Non-conjugated:			
Ethyl acetoacetate	NBP* or NBA, ether, cold	45% ethyl α-bromoacetoacetate	(99, 100)
2-Methyl-2-hepten-6-one	NBS, CCl_4	Bromination alpha to keto group	(12)
Cyclohexanone	NBS, CCl_4, 40 min.	2-Bromocyclohexanone	(86)
Tetrahydro-γ-pyrone	NBS, CCl_4, 25 min., light	50% 3,5-dibromo derivative	(125)

TABLE 3—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
α-Cyclocitral	NBS, CCl_4, 5 min., 30°C., then dehydrobrominate	2,2,6-Trimethyl-3,5-cyclohexadien-1-aldehyde	(45a)
Methyl 2-keto-3-phenylhydrazono-8-octanecarboxylate	NBS, CCl_4, few minutes	Methyl 1-bromo-2-keto-3-phenylhydrazono-8-octanecarboxylate	(86)
	2NBS, CCl_4, 20 min.	53% methyl 1-bromo-2-keto-3-(*p*-bromophenylhydrazono)-8-octanecarboxylate, 19% 3-bromo isomer	(86)
1-Keto-1,2,3,4-tetrahydrophenanthrene	NBS, CCl_4, 4 min., light, then dehydrobrominate (collidine)	57% 1-phenanthrol	(21)
Cholestan-3-one	NBS or NBP, CCl_4, 1 min., light (30 min., no light)	66% 2-bromocholestanone	(19)
2-Bromocholestan-3-one	NBS, CCl_4, 1 min., light	52% (crude) 2,2-dibromocholestanone	(19)
Dihydrotestosterone hexahydrobenzoate	NBS, CCl_4, 4 min., light	50% 2-bromo derivative	(19)
Methyl 3-ketoalloetiocholanate	NBS, CCl_4, 2 min., light	54% 2-bromo derivative	(19)
Coprostan-3-one	NBP, CCl_4, light	33% 4-bromocoprostanone	(19)
Methyl 3-keto-12-hydroxycholanate	NBS, CCl_4, 4 min., light, then dehydrobrominate	30% Δ^4-3-keto-12-hydroxycholenate	(19)
$\Delta^{6,7}$-23-Nor-2-keto-α-amyrene	NBS, CCl_4, 4 hr., $BaCO_3$	Bromination α to double bond (see table 1)	(80)
Δ^{23}-3(α)-Acetoxy-11-keto-24,24-diphenylcholene	NBS, CCl_4, 15 min., light	Bromination in position 22 (see table 1)	(96)
$\Delta^{20,23}$-3,11-Diketo-24,24-diphenylcholadiene	NBS, CCl_4, 15 min., light	Bromination in position 21 (see table 2)	(96)
(2) *α,β-Conjugated:*			
Crotonaldehyde	NBS	Black decomposition product	(12, 103)
Crotonaldehyde diethylacetal	NBS	Reacts	(103)
3-Penten-2-one	NBS, CCl_4	1-Bromo-3-penten-2-one	(12)
4-Methyl-3-penten-2-one	NBS, CCl_4	1-Bromo-4-methyl-3-penten-2-one	(12)

TABLE 3—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Dihydrocinerone (XLa)	NBS, CCl_4, 18 hr.	2-Butyl-3-methyl-4-bromo-2-cyclopenten-1-one	(88)
Tetrahydropyrethrone (XLb)	NBS, CCl_4, 1/2 hr.	67% 2-amyl-3-methyl-4-bromo-2-cyclopenten-1-one	(18)
2,5-Diphenyl-4-cyclopentene-1,3-dione	NBS, CCl_4, 48 hr.	70% 2-bromo-2,5-diphenyl-4-cyclopentene-1,3-dione	(76)
Triphenylcyclopentenone	NBS, CCl_4, 14 hr.	Monobromo derivative	(77)
β-Cyclocitral	NBS, CCl_4, 5 min., 30°C., then dehydrobrominate	15–20% 2,2,6-trimethyl-3,5-cyclohexadien-1-aldehyde	(45a)
Progesterone	3NBS, CCl_4, 1½ hr., dark	6-Bromoprogesterone	(54)
Testosterone acetate	3NBS, CCl_4, 5 hr., dark, then dehydrobrominate	80% 6-dehydrotestosterone acetate	(54)
$\Delta^{4;23}$-3-Keto-24,24-diphenylcholadiene	NBS, CCl_4, 15 min., light	Bromination in position 22 (table 1)	(56)
$\Delta^{4;20;23}$-3-Keto-24,24-diphenylcholatriene	NBS, CCl_4, 10 min., light	Bromination in position 21 (table 2)	(58)
Δ^{16}-3(β)-Acetoxy-20-keto-5-allopregnene	NBS, CCl_4, 15 min., light, then dehydrobrominate	55% $\Delta^{14;16}$-3(β)-acetoxy-20-keto-5-allopregnadiene	(66)
Δ^{16}-3(β),21-Diacetoxy-20-keto-5-allopregnene	NBS, CCl_4, 1/2 hr., light, then dehydrobrominate	49% $\Delta^{14;16}$-3(β), 21-diacetoxy-20-keto-5-allopregnadiene (35% with peroxide)	(67)
β-Ionone	NBS, CCl_4, then dehydrobrominate	Dehydro-β-ionone	(115)
1,3-Diacetyl-4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone	NBS, CCl_4, 1 hr.	85–92% 1,3-diacetyl-4-bromomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone	(108, 109)
1,3-Dipropionyl-4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone	NBS, CCl_4, 1 hr.	53% 4-bromomethyl derivative	(109)

* NBP = *N*-bromophthalimide.
NBA = *N*-bromoacetamide.
NBS = *N*-bromosuccinimide.

TABLE 4

Wohl–Ziegler reaction with compounds possessing functional groups (other than carbonyl) alpha or beta to a double bond

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(1) Functional group alpha to double bond:			
Allyl alcohol	NBA,* ether, 4 days, cold	Mono- and di-bromo derivatives	(100)
Crotonic acid	2NBA, acetone, 40 hr., cold	Monobromo derivative	(100)
Methyl crotonate	1/2NBS, CCl_4, 13 hr.	86% methyl γ-bromocrotonate	(103)
Methyl crotonate ($2\frac{3}{4}$ moles)	2NBS, 300 cc. $CHCl_3$, 5 min. (peroxide)	80% methyl γ-bromocrotonate	(121)
Ethyl crotonate	1/2NBS, CCl_4, 6 hr. (peroxide)	82% ethyl γ-bromocrotonate	(22, 48)
Methyl senecioate	1/4NBS, 8 min.	60–80% methyl γ-bromosenecioate	(103)
Diethyl mesaconate	2/3NBS, CCl_4, 1 hr., peroxide	68% diethyl γ-bromomesaconate	(15a)
Ethyl β-ethoxycrotonate	NBA, ether, 2 days, cold	Ethyl γ-bromo-β-ethoxycrotonate	(100)
1-Ethoxybutadiene	5NBS, ethanol, 2 hr., room temperature	64% γ-bromocrotonaldehyde diethyl acetal	(27)
Methyl sorbate	1/4NBS, stirred 120°C.	65% methyl ϵ-bromosorbate	(33)
	NBS, CCl_4, 20 min., 110°C., peroxide	39% crude, 6% pure	(42)
Ethyl 4-methyl-2-pentenoate	NBS, CCl_4, several hours, peroxide	67% ethyl 4-bromo-4-methyl-2-pentenoate	(86)
3-Acetoxycyclohexene	1/2NBS, CCl_4, 30 min.	58% 3-acetoxy-6-bromocyclohexene	(103)
3-Ethoxycyclohexene	NBS	Mixture of monobromo compounds	(103)
Isocantharic acid No. 2 methyl ester	NBS, 6 hr., 135°C.	36% x-(4,5?)-bromoisocantharic acid methyl ester	(102)
β-Cyclogeranic acid	NBA	3-Bromo-β-cyclogeranic acid	(95)
Ethyl β-ethoxycinnamate	NBA, ether, 5 days, cold	76% ethyl α-bromo-β-ethoxycinnamate	(100)
3-Methoxy-4-hydroxy-5-methyl-2,4-hexadienic acid lactone	NBS, CCl_4, peroxide	6-Bromo-3-methoxy-4-hydroxy-5-methyl-2,4-hexadienic acid lactone (good yield)	(72)

TABLE 4—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Methyl Δ^{16}-3(β)-acetoxyalloetiocholenate	1.13NBS, CCl_4, 10 min., light, then dehydrobrominate	77% methyl $\Delta^{14;16}$-3(β)-acetoxyalloetiocholadienate (50% without light)	(83)
Methyl $\Delta^{20;22}$-3(β)-acetoxyallonorcholenate	NBS, CCl_4, 20 hr., then alumina	Less than 10% β'-[Δ^{16}-3(β)-acetoxyalloetiocholenyl-(17)]-$\Delta^{\alpha'\beta'}$-butenolide	(81)
Δ^{16}-3(β)-Acetoxy-5-alloetiocholenenitrile	1.3NBS, CCl_4, 20 min., light, then dehydrobrominate	77% $\Delta^{14;16}$-3(β)-acetoxy-5-alloetiocholadienenitrile	(68)
Δ^{16}-3(β)-Acetoxyetiocholenenitrile	1.25NBS, CCl_4, 12 min., light, then dehydrobrominate	81% $\Delta^{14;16}$-3(β)-acetoxyetiocholadienenitrile	(84)
β'-[3(β)-Acetoxyalloetiocholanyl-(17)]-$\Delta^{\alpha'\beta'}$ butenolide	NBS, CCl_4, 20 min., light, then dehydrobrominate	63% β'-[Δ^{16}-3(β)-acetoxyalloetiocholenyl-(17)]-$\Delta^{\alpha'\beta'}$-butenolide	(82)
β'-[$\Delta^{16,17}$-3(β)-Acetoxyalloetiocholenyl-(17)]-$\Delta^{\alpha'\beta'}$-butenolide	NBS, CCl_4, 2 hr., light, then dehydrobrominate	13% β'-[$\Delta^{14,15;16,17}$-3(β)-acetoxyalloetiocholadienyl-(17)]-$\Delta^{\alpha'\beta'}$-butenolide	(64)
β-Anhydrodigoxigenin diacetate	NBS, CCl_4, 2 hr., light, then dehydrobrominate	58% anhydro-16,17-dehydrodigoxigenin diacetate	(64)
Δ^{16}-3(β)-Acetoxy-5,6-dibromoetiocholenenitrile	NBS, CCl_4, 8 min., light, then KI	80% $\Delta^{5;16}$-3(β)-acetoxy-15-bromoetiocholadienenitrile	(123)
(*2*) *Functional group beta to double bond:*			
Ketene dimer (LXIa)	NBS, $CHCl_3$, distill solvent, then ethanol + trimethylamine	43% ethyl α-bromoacetoacetate	(6a)
1,2-Dimethyl-1,2,3,6-tetrahydrophthalic anhydride	NBS, CCl_4, 5 hr.	Quantitative (crude) 6-bromo-1,2-dimethyl-1,2,3,6-tetrahydrophthalic anhydride	(102)

TABLE 4—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Methyl acetyl-β-boswellinate	NBS (70%), CCl_4, 3 hr.	Methyl $\Delta^{8,7;8,9}$-2-acetoxy-α-amyradiene-23-carboxylate	(80)
Methyl Δ^{14}-3(β)-acetoxy-5-alloetiocholenate	NBS, CCl_4, light, then dehydrobrominate	69% methyl $\Delta^{14;16}$-3(β)-acetoxy-5-alloetiocholadienate	(65)
Methyl Δ^{14}-3(β)-acetoxy-17-iso-5-alloetiocholenate	NBS, CCl_4, light, then dehydrobrominate	65% methyl $\Delta^{14;16}$-3(β)-acetoxy-5-alloetiocholadienate	(65)
Cholesterol acetate	NBS, petroleum ether, 7 min., light, then dehydrobrominate	29% 7-dehydrocholesterol acetate (bromo compound isolated)	(10, 32, 103)
Cholesterol benzoate	NBS, petroleum ether (80–100°C.)	35% 7(β)-bromo derivative	(116)
Cholesteryl chloride	NBS, petroleum ether	50% 7(β)-bromo derivative	(116)
Cholesteryl bromide	NBS, petroleum ether	50% 7(β)-bromo derivative	(116)

* NBA = *N*-bromoacetamide.
NBS = *N*-bromosuccinimide.

TABLE 5

Wohl–Ziegler reaction with aromatic hydrocarbons

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(1) Nuclear bromination:			
Benzene	NBS,* 1 hr., 95°C.	No reaction	(11, 25)
	NBS, 4–16 hr., depending on catalyst ($AlCl_3$, H_2SO_4, etc.)	41–67% bromobenzene, small amount of di- and tetra-bromobenzenes	(87)
Toluene	NBS, 1½–7 hr., depending on catalyst	21–71% *p*-bromotoluene, some polybromotoluene	(87)
1-Methyl-3,4-dihydronaphthalene	NBS with difficulty	Nuclear bromination	(122)
Naphthalene	1/3NBS, CCl_4, 6 hr.	77% α-bromonaphthalene	(11)
Biphenyl	NBS, CCl_4, $FeCl_3$, several days	4-Bromobiphenyl	(105)
Acenaphthene	1/2NBS, CCl_4, 10 min.	85% 5-bromoacenaphthene	(11)
Phenanthrene	NBS, CCl_4, 5 hr.	46% 9-bromophenanthrene	(11)
Anthracene	NBS, CCl_4, few minutes	58% 9-bromoanthracene	(11)
Benz[*a*]anthracene	NBS, CCl_4	Good yield of 7-bromo derivative	(105)

TABLE 5—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Chrysene	NBS, CCl_4	6-Bromochrysene	(105)
Pyrene	NBS, CCl_4	Excellent yield of 1-bromopyrene	(105)
Phenol	NBA, ether, 12 hr., cold	*p*-Bromophenol	(99)
Anisole	1/3NBS, 16 hr.	32% *p*-bromoanisole	(11)
	NBA, acetone, 24 hr., room temperature	75% *p*-bromoanisole	(99)
Phenetole	1/2NBS, 16 hr.	20% *p*-bromophenetole	(11)
3-Methoxytoluene	1/2NBS	49% 6-bromo-3-methoxytoluene	(11)
1,4-Dimethoxybenzene	1/2NBS, CCl_4, 12 hr.	73% 2-bromo-1,4-dimethoxybenzene	(11)
1,2-Dimethoxybenzene	1/2NBS, CCl_4, 6 hr.	62% 4-bromo-1,2-dimethoxybenzene	(11)
1,3-Dimethoxybenzene	1/2NBS, CCl_4, 6 hr.	82% 4-bromo-1,3-dimethoxybenzene	(11)
1-Methoxynaphthalene	2/3NBS, CCl_4	79% 4-bromo-1-methoxynaphthalene	(11)
2-Methoxynaphthalene	2/3NBS, CCl_4, 15 min.	94% 1-bromo-2-methoxynaphthalene	(11)
2-Ethoxynaphthalene	NBS, CCl_4, 15 min.	79–88% 1-bromo-2-ethoxynaphthalene	(11)
2-Methoxy-6-methylnaphthalene	NBS, CCl_4, 4–5 hr.	71% 1-bromo-2-methoxy-6-methylnaphthalene	(74, 75)
Methyl phenyl sulfide	NBS, CCl_4	Poor yield of methyl *p*-bromophenyl sulfide	(11)
Phenyl acetate	1/2NBS, vigorous reaction	37% *p*-bromophenyl acetate, considerable amount of *o*-bromo isomer	(11)
Acetanilide	NBS, CCl_4, 1 hr.	Quantitative yield of *p*-bromoacetanilide	(11)
Dimethylaniline	1/3NBS, CCl_4, 15 min.	71% *p*-bromodimethylaniline	(11)
Estradiol	2NBA, ethanol, 18 hr., room temperature	94% 2,4-dibromoestradiol	(101)
(*2*) *"Side chain" bromination:*			
Toluene	NBP	Benzyl bromide	(9)
	NBS, CCl_4, 45 min., peroxide	64% benzyl bromide	(86)
o-Chlorotoluene	1/2NBS, CCl_4, 2½ hr.	83% *o*-chlorobenzyl bromide	(4)
p-Nitrotoluene	*ca.* 1/2NBS, CCl_4, 12 hr.	50% *p*-nitrobenzyl bromide	(11)
Indene	1/2NBS, CCl_4, 24 hr.	51% 1-bromoindene	(11)
Tetralin	2NBS, CCl_4, 1/2 hr., peroxide, then CH_3COOK	74% naphthalene	(5, 122)
1,2-Dihydronaphthalene	NBS, CCl_4	Naphthalene and 15% 1,2-dibromotetralin	(122)

TABLE 5—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
1,4-Dihydronaphthalene	NBS, CCl_4	Naphthalene and 15% 2,3-dibromotetralin	(122)
1-Methylnaphthalene	NBS, CCl_4, 12 hr.	58% 1-naphthylmethyl bromide	(13)
2-Methylnaphthalene	1/2NBS, CCl_4, 6 hr.	80% 2-naphthylmethyl bromide	(11)
2-Methyl-3,4-dihydronaphthalene	NBS, then dehydrobrominate	2-Methylnaphthalene	(122)
1-Ethylnaphthalene	NBS, CCl_4, 12 hr., then dehydrobrominate	73% 1-vinylnaphthalene	(13)
1,2-Dimethylnaphthalene	NBS, CCl_4	Mixture of both monobromo compounds	(105)
1,6-Dimethylnaphthalene	NBS, CCl_4	Mixture	(105)
2,3-Dimethylnaphthalene	NBS	2-Bromomethyl-3-methylnaphthalene	(119)
2,6-Dimethylnaphthalene	NBS, CCl_4, 12 hr.	52% 6-bromomethyl-2-methylnaphthalene	(13)
2,7-Dimethylnaphthalene	NBS, CCl_4, 12 hr.	41% 7-bromomethyl-2-methylnaphthalene	(13)
1-Chloro-3,4-dihydronaphthalene	NBS, then dehydrobrominate	1-Chloronaphthalene	(122)
Acenapthene	NBS, CCl_4, peroxide, then CH_3COOK	20% acenapthylene	(5)
Diphenylmethane	NBS, (NBA), CCl_4, 1 hr.	81% diphenylmethyl bromide	(11)
Bibenzyl	NBS, CCl_4, peroxide, then CH_3COOK	56% stilbene, 10% stilbene dibromide	(5, 122)
p-Methylstilbene	NBS, CCl_4, 3 hr., peroxide	49% *p*-bromomethylstilbene	(118)
Triphenylmethane	NBS, CCl_4, vigorous reaction	55–62% triphenylmethyl bromide	(11)
Fluorene	NBS, CCl_4, 3 hr.	61% 9-bromofluorene	(98, 105, 112)
2-Nitrofluorene	NBS, CCl_4	9-Bromo-2-nitrofluorene	(105)
9-Phenylfluorene	NBS, CCl_4	9-Bromo-9-phenylfluorene	(11)
1,2,3,4-Tetrahydrophenanthrene	2 NBS, CCl_4, peroxide, then CH_3COOK	79% phenanthrene	(5)
as-Octahydrophenanthrene	4NBS, CCl_4, peroxide, then CH_3COOK	21% phenanthrene, 12% 1-bromophenanthrene (with 5.5NBS)	(5)

TABLE 5—*Concluded*

COMPOUND	REACTION CONDITIONS	PIECD OF PRODUCT	REFERENCES
sym-Octahydrophenanthrene	NBS, CCl_4, peroxide, then CH_3COOK	63% phenanthrene	(5)
sym-Octahydroanthracene	NBS, CCl_4, peroxide, then CH_3COOK	69% anthracene	(5)
Retene	NBS, CCl_4	1-Bromomethyl-7-isopropylphenanthrene	(105)

* NBS = *N*-bromosuccinimide.
NBA = *N*-bromoacetamide.
NBP = *N*-bromophthalimide.

TABLE 6

Wohl–Ziegler reaction with heterocyclic compounds

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(1) Oxygen heterocyclics:			
2-Methylfuran	NBS,* CCl_4, 1/2 hr., cold	2-Bromomethylfuran (excellent yield)	(15)
2,5-Dimethylfuran	NBS, CCl_4, cold	2-Bromomethyl-5-methylfuran	(15)
Aucubin hexaacetate (2,3-disubstituted furan)	NBS, CCl_4, 1 hr., peroxide	Poor yield of monobromo derivative (substitution in 4- or 5-position)	(40)
Tetrahydro-γ-pyrone	NBS, CCl_4, 25 min., light	50% 3,5-dibromo derivative	(124)
2,6-Dimethyl-γ-pyrone	NBS, CCl_4, 1/2 hr.	2-Bromomethyl-6-methyl-γ-pyrone	(15)
3-Methylbenzofuran	NBS, CCl_4 (peroxide)	2-Bromo-3-methylbenzofuran	(23, 113)
	2NBS, CCl_4, 2 hr., peroxide	64% 2-bromo-3-bromomethylbenzofuran	(23)
2-Bromo-3-methylbenzofuran	NBS, CCl_4, peroxide	2-Bromo-3-bromomethylbenzofuran	(113)
2-Carbethoxy-3-methylbenzofuran	NBS, 130°C., 5 min.	65% 2-carbethoxy-3-bromobenzofuran	(113)
3-Methylcoumarin	NBS, CCl_4	3-Bromomethylcoumarin	(60)
4-Methylcoumarin	NBS, CCl_4	No reaction	(47)
6-Methylcoumarin	NBS, CCl_4	6-Bromomethylcoumarin (good yield)	(47)
4,6-Dimethylcoumarin	NBS, CCl_4	6-Bromomethyl-4-methylcoumarin	(47)
4,7-Dimethylcoumarin	NBS, CCl_4	7-Bromomethyl-4-methylcoumarin	(47)

TABLE 6—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
7-Methoxy-4-methylcoumarin	NBS, CCl_4	3-Bromo-7-methoxy-4-methylcoumarin	(60)
3-Ethyl-7-methoxy-4-methylcoumarin	NBS, CCl_4	60% 3-(α-bromoethyl)-7-methoxy-4-methylcoumarin, 15% 6-bromo-3-ethyl-7-methoxy-4-methylcoumarin	(60, 120a)
3-Propyl-7-methoxy-4-methylcoumarin	NBS, CCl_4	3-(α-Bromopropyl)-7-methoxy-4-methylcoumarin	(120a)
(*2*) *Nitrogen heterocyclics:*			
α-Picoline	NBS	Easy bromination in side chain	(11)
γ-Picoline	NBS		(11)
Quinaldine	NBS		(11)
N-Benzoylindole	NBS	3-Bromo-*N*-benzoylindole	(11)
Carbazole	NBS, CCl_4, 7 min., peroxide	55% 3-bromocarbazole	(86)
Acridine	NBS, CCl_4, 5 hr., peroxide (8 hr. without peroxide)	Mono- and di-bromoacridines, *N*-(9-acridyl)-succinimide, several brominated derivatives of *N*-(9-acridyl)-succinimide, acridine hydrobromide, etc.	(87a)
1,3-Diacetyl-4-methyl-2-imidazolone	NBS, CCl_4, 20 min.	70% 1,3-diacetyl-4-bromomethyl-2-imidazolone	(109)
1,3-Diacetyl-4,5-dimethyl-2-imidazolone	NBS, CCl_4, 15 min.	82% 1,3-diacetyl-4-bromomethyl-5-methyl-2-imidazolone	(109)
	2NBS, CCl_4	50% 1,3-diacetyl-4,5-bis(bromomethyl)-2-imidazolone	
1,3-Diacetyl-4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone		See table 3	(108, 109)
(*3*) *Sulfur heterocyclics:*			
Thiophene	NBA, 45 min.	52% 2-bromothiophene	(89)
	2.5NBA, 45 min., then 5 hr., room temperature	65% 2,5-dibromothiophene	(89)
	1/6NBS, 24 hr.	77% 2-bromothiophene	(11)

TABLE 6—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
2-Methylthiophene.....	NBS, CCl_4, 5 hr.	66% 2-methyl-5-bromothiophene, 24% 2-bromomethylthiophene	(107)
	NBS, CCl_4, 5 hr., peroxide	84% 2-bromomethylthiophene, 16% 2-methyl-5-bromothiophene	
	2NBS, CCl_4, 5 hr., with or without peroxide	2-Bromomethyl-5-bromothiophene	
3-Methylthiophene.....	NBS, CCl_4, 5 hr.	90% 2-Bromo-3-methylthiophene	(106. 107)
	NBS, CCl_4, 6 hr., peroxide	65–90% 3-bromomethylthiophene, small amount of 2-bromo-3-methylthiophene	(106, 107)
	2NBS, CCl_4, 5 hr.	Chiefly 2, 5-dibromo-3-methylthiophene	(107)
	2NBS, CCl_4, 5 hr., peroxide	Chiefly 2-bromo-3-bromomethylthiophene	(107)
2,5-Dimethylthiophene.	NBS, CCl_4, few minutes, 60°C.	37% 2-bromomethyl-5-methylthiophene	(15)
3-Bromo-2,5-dimethylthiophene.....	NBS	3-Bromo-2-bromomethyl-5-methylthiophene and 3-bromo-5-bromomethyl-2-methylthiophene	(119)
Thianaphthene.....	NBS, CCl_4, 36 hr.	3-Bromothianaphthene	(15)

* NBS = *N*-bromosuccinimide.
NBA = *N*-bromoacetamide.

TABLE 7

Wohl–Ziegler reaction with miscellaneous compounds

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Malonic ester half-amide..	NBA,* acetone, 24 hr., cold	Monobromo derivative	(99)
tert-Butyl bromide.....	NBA, ether, cold	15% isobutylene bromide	(99)
1-Phenyl-1-propyne.....	NBA, ether, 24 days, room temperature	45% dibromo derivative	(100)
Decalin.....	NBS, CCl_4, 20 min., peroxide	*x*-Tetrabromoöctalin	(5)
	4NBS	14% *x*-tetrabromoöctalin, 9% 1,5-dibromonaphthalene	

* NBA = *N*-bromoacetamide.
NBS = *N*-bromosuccinimide.

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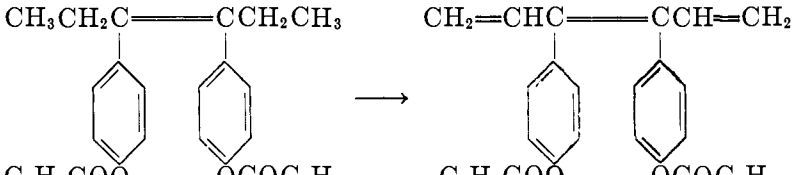
VIII. APPENDIX

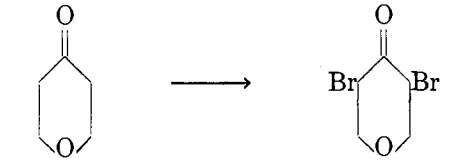
The appendix covers the literature up to June 1, 1948 and the additional material has also been incorporated into the tables.

Freiman (111) showed that diethylstilbestrol dipropionate (LXXX) reacted with 2 moles of *N*-bromosuccinimide to yield a dibromo compound which could be dehydrobrominated to the corresponding hexatriene derivative (LXXXI).



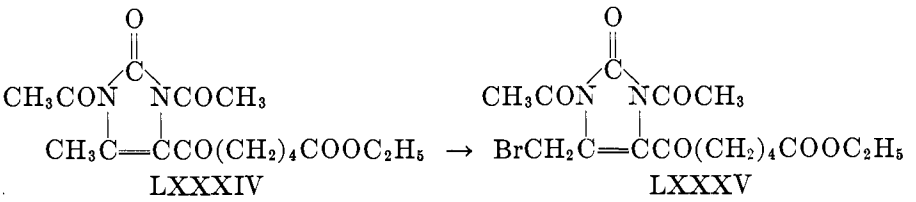
LXXX LXXXI

The bromination of tetrahydro-γ-pyrone (LXXXII) represents another example of the bromination of a saturated ketone with *N*-bromosuccinimide and is reported to lead to the 3,5-dibromoketone LXXXIII (125), which could be converted to γ-pyrone on treatment with pyridine. Free bromine gave only traces of the desired product.

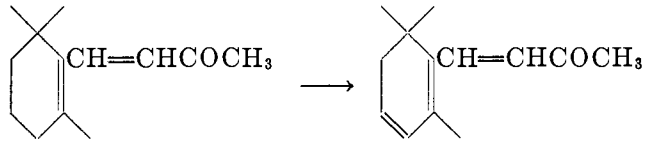


LXXXII LXXXIII

Further confirmation of the statement that bromination of α,β-unsaturated ketones occurs in the allyl position, unless blocked, is afforded by reports on the reaction of *N*-bromosuccinimide with the imidazolone LXXXIV which gave LXXXV (108, 109) and β-ionone (LXXXVI) (115), which after dehydrobromination yielded dehydro-β-ionone (LXXXVII). The latter represents a promising starting material for the synthesis of dehydrovitamin A_1 (114, 115), which is of considerable interest since it may be identical with vitamin A_2.

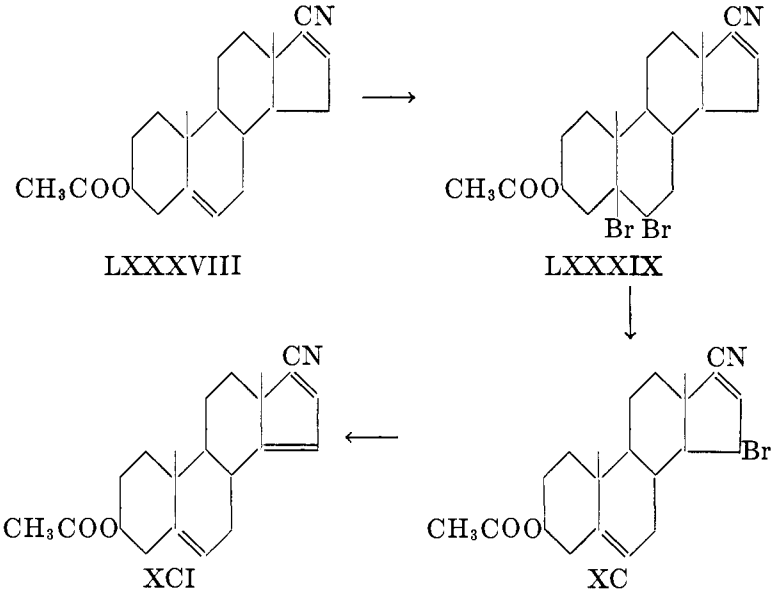


LXXXIV LXXXV



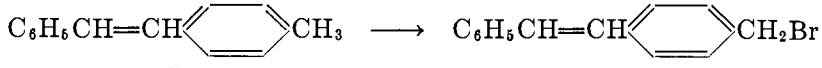
LXXXVI LXXXVII

Plattner and coworkers (123) described an apparently general method for the introduction of the 14,15-double bond into steroids which contain also unsaturation in ring B. The procedure was illustrated with the choladienenitrile LXXXVIII, in which the 5,6-double bond was protected with bromine and LXXXIX was treated with *N*-bromosuccinimide to afford after debromination the 15-bromo derivative (XC). Dehydrobromination of the latter in the usual manner gave an 80 per cent over-all yield (based on LXXXVIII) of the desired triene XCI.



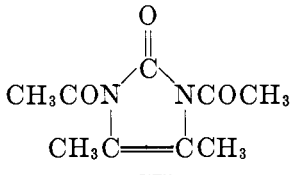
LXXXVIII LXXXIX XCI XC

In continuation of earlier work, Buu-Hoï and Lecocq (105) showed that higher polycyclic hydrocarbons such as pyrene and chrysene were readily monobrominated with *N*-bromosuccinimide. Mousseron and coworkers (122) investigated the action of *N*-bromosuccinimide on hydroaromatic compounds and obtained essentially the same results as Barnes (5). Their report, however, that fluorene does not react with *N*-bromosuccinimide is incorrect (98, 105, 112). As a route to 4-styrylbenzylamines, Kon (118) investigated the action of *N*-bromosuccinimide on *p*-methylstilbene (XCII) and observed side-chain bromination (XCIII) in the presence of peroxide.

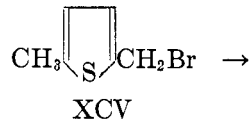


XCII XCIII

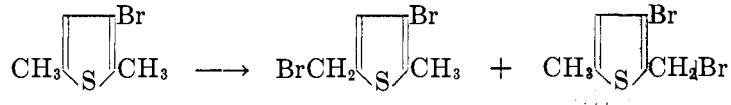
Interesting experiments have been reported with heterocyclics. Imidazolones such as XCIV could readily be mono- or di-brominated in the methyl groups (109). Lecocq and Buu-Hoï (119) observed that 2-bromomethyl-5-methylthiophene (XCV) on treatment with cyanide underwent a rearrangement to the 3-bromo-2,5-dimethylthiophene (XCVI). Carbonation of the Grignard reagent of XCV led to similar results, and so did the higher substituted thiophene derivative XCVII. The latter as well as XCVIII (which did not rearrange, the 3-position being blocked in this instance) were obtained from XCVI and *N*-bromosuccinimide.



XCIV

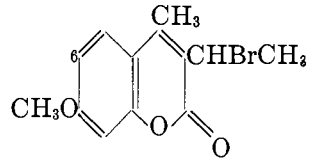


XCV



XCVI XCVII XCVIII

Similarly, 3-methylthiophene reacted with *N*-bromosuccinimide in the methyl group (106, 107), especially when peroxide was used. The resulting 3-thenyl bromide also seemed to undergo a partial rearrangement to 2-bromo-3-methylthiophene (106). In the absence of peroxide, 2- and 3-methylthiophenes underwent predominantly nuclear bromination (107). An unusual rearrangement of a bromine atom from the 3-ethyl group of the coumarin derivative IC to the 6-position has been reported (120a). No explanation was advanced and the structure of the product was not demonstrated unequivocally.



IC

The reaction of 3-methylbenzofuran (LXXVII) with *N*-bromosuccinimide has been investigated further by Grubenmann and Erlenmeyer (113), who showed that bromination in the methyl group was achieved readily when the 2-position was blocked.

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