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THE OXIDATION OF ACETALS WITH N-BROMOSUCCINIMIDE[1]

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A few cases of the conversion of acetals directly to esters with N-bromosuccinimide (NBS) have been reported.[3,4,5] The potential utility of this reaction has prompted us to investigate its generality, mechanism, and possible further usefulness. This paper reports our preliminary investigation.

As can be seen by the table summarizing our results, cyclic acetals in general are oxidized under mild conditions to esters with NBS in the presence of 2, 2'-azobisisobutyronitrile (AIBN). In contrast to the oxidation of open chain acetals with NBS, the esters resulting from cyclic acetals always contain bromine. This bromine is always found to be incorporated into the ester in such a way that it indicates where the cyclic acetal ring has been cleaved.

From our work thus far, the following general reaction can be written·

$R\text{-}\overset{O}{\overset{\|}{C}}OCH_2(CH_2)_nCH_2Br$ + succinimide

R= H, alkyl, or aryl

Theoretically n could be any number, but only the readily available structures where n = 0 or 1, have been demonstrated so far in our work.

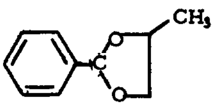
TABLE I

Oxidation of Cyclic Acetals with NBS and AIBN

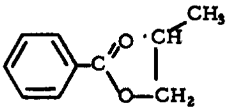
Cyclic Acetal	Product(s)	Solvent	Reaction Temp. Range	%Yield
2-n-Propyl-1,3-dioxolane	2-Bromoethyl butanoate*	CCl_4	35-40°	32
"	"	Benzene	"	67
2-Methyl-1,3-dioxolane	2-Bromoethyl acetate*	CCl_4	35-45°	40
"	"	Benzene	30-40°	66
1, 3-dioxolane	2-Bromoethyl formate*	CCl_4	reflux	22
"	"	Benzene	45-50°	30
Methylenebis-2-(1, 3) dioxolane)	2-Bromoethyl 2-(1,3-dioxolanyl)acetate *	CCl_4	35-40°	35
2-Phenyl-1,3-dioxolane	2-bromoethyl benzoate	CCl_4	30-40°	76
2-Phenyl-1, 3-dioxane	3-bromopropyl benzoate	CCl_4	35-40°	95
<u>cis</u>, <u>trans</u>-2-Phenyl-4-methyl-1, 3-dioxolane	1-methyl-2-bromoethyl benzoate and 2-methyl-2-bromoethyl benzoate	CCl_4	35-45°	92
1, 3-benzodioxole	4-Bromo-1,3-benzodioxole and 5-bromo-1,3-benzodioxole	CCl_4	reflux	

* contaminated with chloride

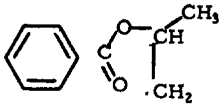
In a somewhat similar reaction, Huyser,[6] has studied the conversion of aromatic acetals to esters using t-butyl peroxide as a radical initiator. In another similar reaction Elad and Youssefyeh[7] have reported the conversion of cyclic aliphatic acetals to esters using light-excited acetone as the initiator. In Huyser's[6] study it was found that 2-phenyl-4-methyl-1, 3-dioxolane gave two esters, n-propyl benzoate and isopropyl benzoate, in a ratio of 5 to 1 respectively. This ratio was explained in terms of the



(A)



(B)

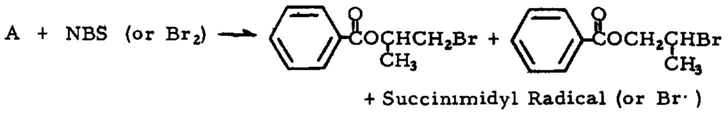


(C)

intermediate radical (A) uncoupling to give the primary radical (C) and the more stable secondary radical (B) which react further in a chain propagating step to give the two observed esters. It would be possible for a brominating reagent to react with the uncoupled radicals (B) and (C) proposed by Huyser propagate the chain and give brominated esters. However, in our system 2-phenyl-4-methyl-1,3-dioxolane reacted with N-bromosuccinimide and AIBN to give 1-methyl-2-bromoethyl benzoate and 2-methyl-2-bromoethyl benzoate in a ratio of 5 to 1 as determined by integration of the methyl signals in the nmr spectrum of the mixture.[8] This ratio does not reflect a predominance of product from the more stable uncoupled radical as in the system of Huyser, but rather the complete reversal of the ratio of brominated esters one might expect if radicals (B) and (C) were involved.[9] Thus in our system it seems quite likely that (A) does not uncouple and that radicals (B) and (C) are not intermediates.

A mechanism consistent with the data we have observed thus far is shown in equations 1 and 2. It is not certain whether NBS reacts directly in these radical brominations or by way of a very low concentration of free bromine released by a fast reaction of NBS with traces of HBr. Thus both species are shown.

(1)



(2) Succinimidyl Radical + 2-phenyl-4-methyl-1, 3-doxolane ⟶ A + Succinimide (or HBr)

In this mechanism the ratio of ester products would be determined by steric hindrance to attack of the brominating reagent. The details of reaction (1) will be the subject of a later publication.

Typical reaction conditions which we used are as follows One-half mole of the acetal was dissolved in 200 ml. of anhydrous benzene and maintained under a slow stream of nitrogen To this stirred solution was added slowly a mixture of one-half mole of NBS and 2 g of AIBN at such a rate that the reaction temperature was maintained between 30° and 40°. An ice bath may be needed to control the exothermic reaction After completion of the reaction, the mixture was cooled in an ice bath and the succinimide was filtered off. The filtrate was then fractionated at reduced pressure.

When CCl_4 was used as a solvent, chlorine was incorporated into the molecule in place of some of the bromine For example, the 2-bromoethyl butanoate derived from the reaction of 2-n-propyl-1 3-dioxolane and NBS in the presence of AIBN in CCl_4 solvent was shown by differential halogen analysis to contain 27. 27% by weight of the corresponding chlorocompound. The nmr spectrum of this sample and of all aliphatic esters produced where CCl_4 was the solvent showed signals due to the presence of the corresponding chlorocompound The chloride impurity disappeared when benzene was substituted for CCl_4 as the solvent. Although this phenomenon is not at all common, at least one other radical bromination reaction[10] carried out in CCl_4 has been shown to incorporate chloride from CCl_4 solvent.

It is interesting to note that without the radical initiator AIBN, the reaction conditions would be essentially the same as those of Marvel and Joncich,[11] but under their conditions the product is an α-bromoacetal presumably arising from an acid catalyzed reaction similar to the α-bromination of ketals. We were able to observe the radical and the acid catalyzed reactions in the same flask by allowing methylenebis-2-(1, 3-dioxolane) to react with bromine, in which case both bromomethylenebis-2-(1, 3-dioxolane) and 2-bromoethyl 2-(1, 3-dioxolanyl)acetate were products of the reaction.

From the reaction of tertiary amines with the bromo-ester products we have extended the utility of the reaction to give a general synthesis for derivatives of acetylcholine. To this end we have prepared as examples, acetylcholine bromide and 2-(1, 3-dioxolanyl)acetylcholine bromine in good yields, the latter compound being one which would be difficult to obtain by other methods.

References

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2. Fellow of the American Foundation for Pharmaceutical Education. 1962-1964, and Josiah Kirby Lilly Memorial Fellow, 1962-1964.

3. J. B. Wright, J. Am. Chem. Soc., 77, 4883 (1955).

4. D. G. Markees, J. Org. Chem., 23, 1490 (1958).

5. L. A. Cort and R. G. Pearson, J. Chem. Soc., London, 1682 (1960).

6. E. S. Huyser and Z. Garcia, J. Org. Chem., 27, 2716 (1962).

7. D. Elad and R. D. Youssefyeh, Tetrahedron Letters, No. 30, 2189 (1963).

8. The assignment of the two esters to their respective signals was verified by synthesis of the benzoates of a known 5 to 1 mixture of 1-chloro-2-propanol and 2-chloro-1-propanol.

9. It is possible that the less stable primary uncoupled radical (C) presumably in smaller concentration, reacts with the brominating reagent at a much greater rate than the more stable secondary uncoupled radical (B) thus giving the observed reversal of expected products. This mechanism although not very likely has not yet been rigorously eliminated.

10. F. W. Baker, H. D. Holtz and L. M. Stock, J. Org. Chem., 28, 514, (1963).

11. E. N. Marvel and M. J. Joncich, J. Am. Chem. Soc., 73, 973 (1951).