The Reaction of N-Bromophthalimide with Dihydropyran

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The major product of the reaction of N-bromophthalimide with 5,6-dihydro-4*H*-pyran is 2-phthalimidyl-3-bromotetrahydropyran (64%) consistent with a polar mechanism involving addition of a positive bromine at the 3-position of dihydropyran to form a carbonium ion intermediate which subsequently combines with a negative group. The substitution product predicted for free-radical attack on the α-methylene was not found, but 3-bromo-5,6-dihydro-4*H*-pyran was isolated (4.7%) and 2,3-dibromotetrahydropyran and related structures were detected by analytical methods (6 to 7.5%). Formation of these minor products can be explained by a competing free-radical reaction to form a substitution product which undergoes subsequent conversions with N-bromophthalimide by a polar mechanism.

The reaction most often observed with N-haloimides and simple olefins is an α-substitution of halogen by a free-radical mechanism.[2,3] Polar reactions are also observed, under favorable conditions, in which the N-haloimide supplies a positive halogen. For example, Ziegler[4] reports that N-bromophthalimide reacts with cyclohexene to give 21% of an adduct, N-(2-bromocyclohexyl)phthalimide, in addition to a 50% yield of the allylic substitution product.

The presence of an electron-releasing group adjacent to a double bond should increase the tendency toward reaction by a polar mechanism with an available positive halogen. Dihydropyran is an example of such a compound which also contains an α-methylene group.

The object of this investigation was thus to see whether N-bromophthalimide would react with 5,6-dihydro-4*H*-pyran (I) to give allylic bromination by a free-radical mechanism or attack on the double bond by a polar mechanism. It was also of interest to compare the reaction of N-bromophthalimide and I with that of N-bromosuccinimide and I, as previously reported from this laboratory,[5] as well as the reaction of N-bromophthalimide and cyclohexene.[4]

Previous study of the reaction of N-bromophthalimide with I has been reported by Hurd, Moffat, and Rosnati,[6] who isolated an 83.5% yield of an addition product. They proposed the product to be either 2-bromo-3-phthalimidotetrahydropyran formed by free-radical attack, or 2-phthalimido-3-bromotetrahydropyran, resulting from an ionic reaction.

Discussion

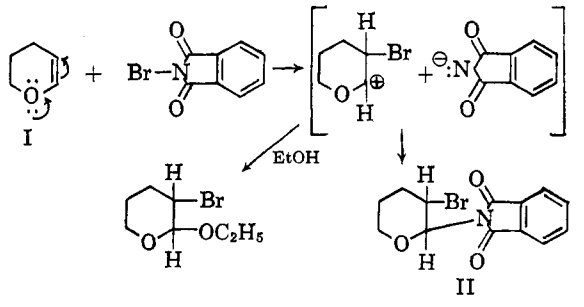
N-Bromophthalimide reacted with I in carbon tetrachloride to give a solution from which crystals of phthalimide separated, on cooling to room temperature, which accounted for 18% of the N-bromophthalimide used. The major product obtained when the solvent was removed, was the expected addition product of N-bromophthalimide and I (m.p. 144.5–145.0°) which was isolated in a 64% yield based on N-bromophthalimide.

The addition product reacted with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylosazone of 2,5-dihydroxpentanal. The same osazone was obtained from 2-ethoxy-3-bromotetrahydropyran. Although Woods and Temin[7] found that 2-ethoxy-3-bromo-5,6-dihydro-2*H*-pyran gave a 2,4-dinitrophenylhydrazone derivative of 2-bromo-5-hydroxy-2-pentenal, Shelton and Cialdella[5] found that under similar conditions the saturated 2-ethoxy-3-bromotetrahydropyran lost both the ethoxyl group and bromine to form the osazone. They also obtained the same osazone from 2-succimidyl-3-bromotetrahydropyran, 2-acetoxy-3-bromotetrahydropyran, and 2,3-dibromotetrahydropyran.

The addition product does not react with silver acetate, although 2,3-dibromotetrahydropyran, as an α-bromo ether, forms silver bromide quickly with silver acetate or silver nitrate. It thus appears that the addition product must be 2-phthalimidyl-3-bromotetrahydropyran (II) rather than the isomer, 2-bromo-3-phthalimidyltetrahydropyran, which also was regarded as possible by previous workers.[6] Their observation that, "the compound is dissolved slowly by hot, dilute alkali with liberation of bromide ion and nonformation of ammonia," is not inconsistent with structure II.

When II was refluxed with ethanol, it was recovered unchanged with no evidence of formation of either phthalimide or bromide ion. A similar stability was observed in the case of 2-succimidyl-3-bromotetrahydropyran.[5] However, reaction of N-bromophthalimide with I in absolute ethanol proceeded rapidly and smoothly to give a 44% yield of 2-ethoxy-3-bromotetrahydropyran, which was also obtained in 50% yield by the similar reaction of N-bromosuccinimide with I.

The formation of II as the major product provides strong support for a polar reaction in which a positive bromine adds at the double bond. When the reaction is carried out in absolute ethanol the intermediate carbonium ion can combine with ethanol rather than with the phthalimide anion.



Another reaction product isolated and identified was 3-bromo-5,6-dihydro-4*H*-pyran (III) obtained by dis-

(1) Based on the M. S. thesis of T. Kasuga.

(2) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

(3) L. Horner and E. H. Winkelmann, *Angew. Chem.*, **71**, 349 (1959).

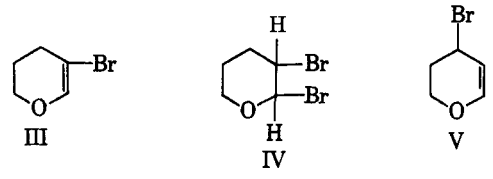
(4) K. Ziegler, A. Spath, E. Schaaf, W. Schumann, and E. Winkleman, *Ann.*, **551**, 80 (1942).

(5) J. R. Shelton and C. Cialdella, *J. Org. Chem.*, **23**, 1128 (1958).

(6) C. D. Hurd, J. Moffat, and L. Rosnati, *J. Am. Chem. Soc.*, **77**, 2793 (1955).

(7) G. Woods and S. Temin, *ibid.*, **72**, 139 (1950).

tillation in a 4.7% yield based on N-bromophthalimide. This product could be formed either by loss of a proton from the carbonium ion intermediate, or by dehydrohalogenation of 2,3-dibromotetrahydropyran (IV) in the process of isolation. The presence of IV was demonstrated in the similar reaction mixture of I and N-bromosuccinimide.[5]



III IV V

It was of particular interest to determine whether any allylic bromination occurred leading to the formation of the unknown 4-bromo-5,6-dihydro-4*H*-pyran (V) by a free-radical mechanism. A method of analysis was developed by Cialdella[5] based on the assumption that silver nitrate will react quantitatively with halogen alpha to a double bond (as in V) or alpha to the ether oxygen (as in IV) but not with a vinyl halide (as in III). The analytical results calculated from the solution of appropriate simultaneous equations are summarized in Table I. A 25–30% excess of dihydropyran was used, and subtraction of the excess gave small negative values in some cases.

TABLE I

ANALYSIS FOR ALLYLIC AND OTHER REACTIVE HALIDES

Reagent	NBS[d]	NBP[e]	NBP[f]
Reaction time (min.)[a]	39	24	18
Dihydropyran (I)[b]			
mmoles[c]	1.45	−0.56	−0.45
% yield[c]	14.5	−5.6	−4.5
4-Bromo-5,6-dihydro-4*H*-pyran (V)			
mmoles	0.04	0.02	−0.01
% yield	0.4	0.2	−0.1
Dibromides (IV, etc.)			
mmoles	0.93	0.74	0.58
% yield	9.3	7.4	5.8

[a] Time required for disappearance of the last particles of the reagent. [b] Dihydropyran corrected for excess initially present. [c] Based on the reagent N-bromosuccinimide or N-bromophthalimide. [d] N-Bromosuccinimide. [e] N-Bromophthalimide. [f] Traces of peroxide remaining in dihydropyran after distillation were removed by passing through chromatographic grade activated alumina just before use.

In all cases the calculated yield of V was essentially zero. The absence of the allylic-halogenated product suggests the possible absence of a free-radical reaction. Since Ziegler reported[4] that the reaction of cyclohexene with N-bromophthalimide in carbon tetrachloride formed 3-bromocyclohexene (presumably by a free-radical mechanism) as well as N-(2-bromocyclohexyl)-phthalimide (presumably by a polar mechanism), it is probable that both free-radical and polar reactions are involved in the present study.

A free-radical reaction would be expected to produce V. However, bromine substituted at an allylic position of I would be even more reactive than a bromine alpha to the double bond in cyclohexene, because of the additional activating effect of the oxygen conjugated with it. Consequently the N-bromoimides might react directly with V, or with hydrogen bromide produced by dehydrohalogenation of V, to give bromine. This bromine would then react with I to give IV which was formed as reported in Table I. Support for this interpretation is provided by the demonstration that N-bromosuccinimide reacts with allylic bromine in 3,6-dibromocyclohexene to form bromine and succinimide.[8] Bromine adducts have been observed in a wide variety of reactions of N-halo compounds, and both polar and free-radical additions have been suggested.[9]

It was found in this investigation that a known preparation of IV reacted with N-bromophthalimide to give a 30% yield of bromine and a 97% yield of phthalimide based on N-bromophthalimide. The rest of the bromine presumably reacted with III, formed in the dehydrohalogenation, to give 2,3,3-tribromotetrahydropyran. However, in the experiments in which an excess of I was present, the bromine would react with I to form more IV instead of reacting with III. The formation of III, at least in part, by the dehydrohalogenation of IV in the process of isolation, as well as in the course of the reaction of IV and N-bromophthalimide, appears probable.

Prolonged heating of N-bromophthalimide in carbon tetrachloride in the presence of azobisisobutyronitrile does not liberate free bromine. Accordingly the formation of bromine in the reaction of N-bromophthalimide with I probably involves a subsequent polar reaction on an intermediate formed by an initial reaction at the allylic position.

Dauben[10] has suggested that the different reactivities of N-bromides arise from alteration of ionic character in their N–Br bonds by structural features. From a knowledge of the dipole moment of the N–Br bonds and the acid dissociation constants, it was deduced that the bromine in N-bromosuccinimide is slightly negative, whereas the bromine in N-bromophthalimide has a partial positive charge. Thus N-bromophthalimide is more likely to give a positive halogen by a polar cleavage of the bond, while N-bromosuccinimide should participate more readily in a free-radical reaction. This is consistent with the results obtained in this investigation since more dibromide and less adduct was observed to be formed in the case of N-bromosuccinimide than in the case of N-bromophthalimide.

It is evident that N-bromoimides can react by either a polar or a free-radical mechanism depending upon reaction conditions, initiators, and the nature of the other reactants. Dihydropyran can lead to predominantly a polar reaction with N-bromophthalimide as a result of the polarizing effect of the oxygen alpha to the double bond, together with the favorable polarization of the N–Br bond in N-bromophthalimide. This accounts for the high yield of adduct obtained in the reaction of N-bromophthalimide with dihydropyran,[6] as compared to only 21% of adduct obtained in the reaction of N-bromophthalimide with cyclohexene.[4]

Experimental

Purification of Reactants.—Dihydropyran (I) was treated with dilute sodium hydrosulfite to remove peroxide and then redistilled [b.p. 84.5–84.7° (746 mm.)]. In some experiments it also was

(8) E. E. Borchert, M. S. thesis, Case Institute of Technology, 1961.

(9) R. E. Buckles, R. C. Johnson, and W. J. Probst, *J. Org. Chem.*, **22**, 55 (1957).

(10) H. J. Dauben, Abstracts, Division of Organic Chemistry, 136th National Meeting of the American Chemical Society, Atlantic City, N.J., September, 1959, pp. 52-3P.

passed through a column of chromatographic grade activated alumina just before use to completely remove any traces of peroxide.

N-Bromosuccinimide was recrystallized from water and dried over concentrated sulfuric acid in a vacuum desiccator (m.p. 174.5–178.5°).

N-Bromophthalimide was recrystallized from glacial acetic acid and melted at 204–206° after drying as for N-bromosuccinimide.

2,3-Dibromotetrahydropyran (IV) and 3-bromo-5,6-dihydro-4*H*-pyran (III) were prepared as previously described.[5]

Reaction Procedure.—A 120-ml. portion of a 0.25 *M* dihydropyran solution in carbon tetrachloride (0.03 mole) was combined with 0.024 moles of N-bromophthalimide (or N-bromosuccinimide) and heated in a water bath under a reflux condenser equipped with a drying tube. The reaction time was measured as the interval between the falling of the first drop from the condenser and the disappearance of the last particles of N-bromophthalimide (or N-bromosuccinimide). On cooling to room temperature, phthalimide (m.p. 234–238°) or succinimide (m.p. 123–124°) separated from the solution. The imides were identified by their infrared spectra and by mixture melting points with known samples.

Isolation of Reaction Products.—Additional phthalimide was obtained after removal of part of the solvent to give a total yield of 18% based on N-bromophthalimide. Most of the solvent and unchanged dihydropyran (I) were removed under reduced pressure. The distillate was collected in a receiver cooled with ice and followed by a Dry Ice–acetone trap. Titration of the distillate with bromine gave the values for unchanged I reported in Table I after correcting for the excess initially present.

The adduct II was obtained from the concentrated solution in a 64% yield after washing with carbon tetrachloride. It melted at 144–146° when recrystallized from either acetone–water or ethanol (lit.[6] m.p. 144°). This compound gave no evidence of reaction with silver acetate in acetic acid solution even after one month at room temperature. It also failed to show any evidence of reaction on refluxing overnight in absolute ethanol.

The liquid remaining after removal of II was stripped of residual solvent and distilled slowly at about 5 mm. until the residue began to resinify. The distillate was shown to be III (4.7% yield based on N-bromophthalimide) by comparison of the infrared spectrum with one from a known sample.

Analytical Procedure.—Reaction mixtures of N-bromophthalimide (or N-bromosuccinimide) and dihydropyran were prepared as described, and after cooling and filtration, identical 50-ml. aliquots were taken for analysis. The quantitative procedure for detecting allylic or other reactive halides in the reaction mixture has already been described.[5]

Reaction in Ethanol.—2-Ethoxy-3-bromotetrahydropyran was obtained by reaction of N-bromophthalimide with I in absolute ethanol by the procedure previously used for the corresponding reaction with N-bromosuccinimide.[5] A 44% yield of product was obtained (based on N-bromophthalimide) which was identified by infrared and by preparation of a 2,4-dinitrophenylosazone derivative identical to one prepared from the product of the same reaction with N-bromosuccinimide, and also from II, as described in the next section.

Preparation of Osazone Derivatives.—The addition product II was converted to the 2,4-dinitrophenylosazone of 2,5-dihydroxypentanal by the procedure used to obtain the identical derivative from the adduct of I with N-bromosuccinimide.[5] The osazone, as prepared from II, started to precipitate within 1 hr. After recrystallization from ethanol–ethyl acetate and then ethanol, the bright orange crystals melted at 240–241° with decomposition (lit.[11] m.p. 242°).

Reaction of 2,3-Dibromotetrahydropyran (IV) with N-Bromophthalimide.—A solution of 2,3-dibromotetrahydropyran (IV) made by titration of 10 ml. of 0.25 *M* I in carbon tetrachloride with 0.263 *M* bromine in carbon tetrachloride was added over a period of 20 min. to N-bromophthalimide (0.565 g., 0.0025 mole) in 50 ml. of carbon tetrachloride while refluxing. The solution was cooled to room temperature and filtered to remove the crystals of phthalimide (0.36 g., 97.6% yield based on N-bromophthalimide). Bromine was observed to be present in the filtrate, and comparison with the color of known amounts of bromine in carbon tetrachloride showed the presence of 28% based on N-bromophthalimide.

(11) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, **70**, 1484 (1948).

1,1-Azaspiro Compounds[1]

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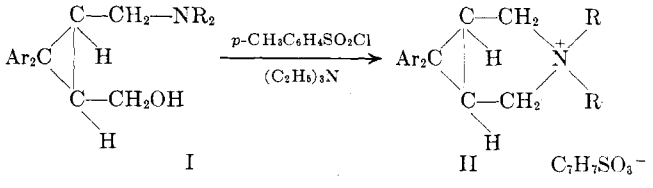
Syntheses of five-, six-, and seven-membered bicyclic 1,1-azaspiro systems have been rendered possible through the cyclization of suitable tertiary aminocarbinols using *p*-toluenesulfonyl chloride in the presence of tertiary bases (preferably triethylamine) as solvents.

The classical method for the synthesis of bicyclic azaspiro systems has been the reaction between a cyclic amine and α,ω-dihaloalkanes.[2] Several modifications of the same general procedure also have been employed. However, these require somewhat drastic conditions of fusion. The yields in most cases have not been reproducible and the 1,1-azaspiro compounds have not been the major product[3,4] of the reaction.

We wish to report a synthetic method for the formation of 1,1-azaspiro bi- and tricyclic compounds in excellent yields under mild conditions of reaction. The isolation and purification of the product of the reaction entails no ambiguity. By this procedure we have synthesized five-, six-, and seven-membered bi- and tricyclic 1,1-azaspiro systems.

In the course of the investigation of the aminoalcohols[5] of type I, when they were treated with *p*-toluenesulfonyl chloride in the presence of tertiary bases (pyridine or triethylamine) no sulfonic ester was isolated; either the starting aminoalcohol was recovered or the entire product had the properties of a quaternary salt.



When a cyclic amine was employed 1,1-azaspiro compounds were obtained.

(1) A portion of this material was presented before the Division of Organic Chemistry, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, Abstracts, p. 25Q.

(2) H. R. Ing, "Heterocyclic Compounds," Vol. III, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 426.

(3) D. M. Hall and F. Minhaj, *J. Chem. Soc.*, 4584 (1957).

(4) S. R. Ahmed and D. M. Hall, *ibid.*, 3043 (1958).

(5) R. Baltzly, N. B. Mehta, P. B. Russell, R. E. Brooks, E. M. Grivsky, and A. M. Steinberg, *J. Org. Chem.*, **27**, 213 (1962).