The above ester (5 g.) was hydrolyzed to 1-methylpentane-1,2,5-tricarboxylic acid (VIIa, R = H) by boiling with 60 ml. concentrated hydrochloric acid for 30 hr. The solution on evaporation produced an oil which solidified on keeping for some days and was finally crystallized twice from ethyl acetate, m.p. 145°.

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.42. Found: C, 49.61; H, 6.91.

2-Methyl-3-cyanocyclohexanone (IX). To an ethanolic solution of 2-methyl-2-cyclohexenone (16.7 g.) in a three necked flask fitted with a stirrer, a solution of sodium cyanide (6.4 g.) in water (20 ml.) was added with stirring. A reddish color developed which gradually intensified to wine red coloration. A slight rise in temperature was observed. After about 0.5 hr. a mixture of concentrated hydrochloric acid (6.9 ml.) and water (15 ml.) was added to this solution during 40 min., whereupon a light yellow oil separated. It was poured into a mixture of concd. hydrochloric acid (15 ml.) and water (200 ml.) and the oil was extracted with ether. The ether solution was dried and evaporated and the residual oil was distilled at 120°/3.5 mm. (5.2 g., 25%), n_D^{32} 1.4669.

Anal. Calcd. for $C_8H_{11}NO$: C, 70.07; H, 8.03. Found: C, 69.55; H, 8.36.

2-Methylcyclohexanone-3-carboxylic acid (VIa). The above nitrile (IX, 2.5 g.) was boiled first with concd. hydrochloric acid and then with a 20% solution of potassium hydroxide at 150–160° for 20 hr. The resultant solution was acidified and then extracted with ether. The ethereal solution after drying and evaporation gave an oil which on sublimation at 167°/0.2 mm. produced a solid acid, m.p. 97° (lit.[4] m.p. 97°).

The dinitrophenylhydrazone, crystallized from ethanol, m.p. 210°.

Anal. Calcd. for $C_{14}H_{16}N_4O_6$: N, 16.66. Found: N, 16.48.

Acknowledgment. We are grateful to Dr. P. C. Dutta, head of the Department of Organic Chemistry, Indian Association for the Cultivation of Science, for his active interest during the course of this investigation.

CALCUTTA 32, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

Reaction of *N*-Bromosuccinimide with Dihydropyran

J. REID SHELTON AND CATALDO CIALDELLA

Received January 14, 1958

Products identified from the reaction of *N*-bromosuccinimide with dihydropyran were 3-bromo-5,6-dihydro-4*H*-pyran, 2,3-dibromotetrahydropyran, and both geometrical isomers of 2-succinimidyl-3-bromotetrahydropyran. A polar mechanism is indicated in which a positive bromine from *N*-bromosuccinimide first adds at the 3-position of dihydropyran to form a reactive intermediate which can either lose a proton or add a negative group to give the observed products. A small acceleration of rate in the presence of oxygen or peroxide suggests that a free-radical reaction is also involved to some extent. No product of direct alpha methylenic substitution on dihydropyran was obtained. The polarizing effect of the oxygen alpha to the double bond is considered to increase the nucleophilic character and thus favor a polar mechanism.

N-Bromosuccinimide can undergo either a homolytic dissociation to free radicals or a heterolytic dissociation to give a positive halogen. The reaction most often observed with this reagent and simple olefins[1] is an alpha substitution of bromine by a free-radical mechanism. In addition to these allylic brominations, there have been a number of examples of addition to the double bond. In some cases[2] where reactions were accelerated by peroxides, the addition would appear to proceed by a free-radical mechanism. Other examples are reported where addition leading to the corresponding dibromide is promoted by the presence of inorganic salts[3,4] and alkyl ammonium salts.[4] Bailey and Bello[3] report that whereas *N*-bromosuccinimide brominates crotonitrile in the allylic position, allylic bromination is inhibited by an electron-withdrawing group attached directly to the alpha carbon.

The presence of an electron-releasing group adjacent to a double bond should increase the tendency toward reaction by a polar mechanism with an electrophyllic reagent such as a positive halogen. Dihydropyran was selected for study as an example of such a compound which also contains an alpha methylene group. The object of the investigation was thus to see whether *N*-bromosuccinimide would react with this compound to give allylic bromination by a free-radical mechanism or attack on the double bond by a polar mechanism.

Previous studies of the reaction of *N*-bromosuccinimide with dihydropyran (I) have been reported to yield tars[5] and an addition product, 2-succinimidyl-3-bromotetrahydropyran VI.[6]

Discussion. *N*-Bromosuccinimide reacted with I to give a mixture of products which appeared as a very viscous, clear residue when solvent was removed. Attempts to distil the products gave only small amounts of I and a mixture of 3-bromo-5,6-dihydro-4*H*-pyran (II) and 2,3-dibromotetrahy-

---

(1) M. S. Kharasch, R. Malec, and N. C. Yang, *J. Org. Chem.*, **22**, 1443 (1957).

(2) P. L. Southwick, L. A. Pursglove, and P. Numerof, *J. Am. Chem. Soc.*, **72**, 1600, 1604 (1950).

(3) W. J. Bailey and J. Bello, *J. Org. Chem.*, **20**, 525 (1955).

(4) E. A. Braude and E. S. Waight, *J. Chem. Soc.*, 116 (1952).

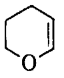
(5) C. D. Hurd, J. Moffat, and L. Rosnati, *J. Am. Chem. Soc.*, **77**, 2793 (1955).

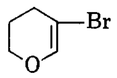
(6) R. Paul and S. Tchelitcheff, *Compt. rend.*, **236**, 1968 (1953).

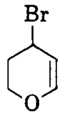
dropyran (IV), before rapid decomposition of the residue set in. Chromatographic separation of the reaction mixture resulted in the isolation of the addition product (VI).

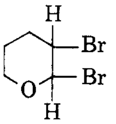
It appeared desirable at this point to devise an analytical scheme for quantitatively measuring some of the products obtained. It was of particular interest to determine whether any allylic bromination leading to the formation of the unknown 4-bromodihydropyran (III) was obtained, and if so in what yield.

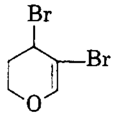
It was found that if solutions of known concentration of I were titrated with bromine and the resulting dibromide treated with silver nitrate, silver bromide formed corresponding to 96–100% replacement of the bromine atom alpha to the oxygen.

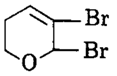

I

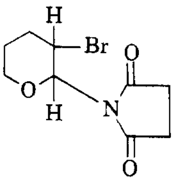

II

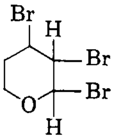

III


IV


Va


Vb


VI


VII

Based on this observation a method of analysis was employed which involved treating reaction mixtures of N-bromosuccinimide and I as follows:

A. Titration with bromine, and then

B. Reaction with silver nitrate

C. Reaction of a second but identical run with silver nitrate, without prior titration with bromine

In order for this scheme to be applicable to any system, any of the products that react must do so quantitatively or at least nearly so. As was previously mentioned, I and IV were tested and found to meet this requirement. When II, prepared independently by dehydrohalogenation of IV, was tested, it was found neither to add bromine nor react with silver nitrate. The behavior of III (as predicted by analogy with I and IV) should include both addition of bromine and, as a vinylogous α-bromoether, reaction with silver nitrate. The analytical procedure thus gives no information about II and involves only compounds I, III, IV, and a dibromodihydropyran (V) which was included on the basis of the report by Paul and Tchelitcheff[6] that N-bromosuccinimide reacts with II to give V. The reaction presumably involves allylic attack on II to give Va, and by rearrangement of the intermediate free radical (or rearrangement of Va) to form Vb. Since II was isolated in this study, some conversion of II to V was considered probable. By analogy with the observed behavior of II and IV, it was expected that V would not add bromine, but would react with silver nitrate and would accordingly be indistinguishable in the analysis from IV. For this reason the results given in Table I and Table II have compounds IV and V grouped together as dibromides.

TABLE I

Effect of Benzoyl Peroxide

Benzoyl peroxide (wt. %)[a]	0	1.0	3.0
Reaction time (min.)[b]	25.8	21.0	17.7
Dihydropyran (I)[c]			
Millimoles[d]	0.97	1.21	1.10
% yield[a]	9.7	12.1	11.0
4-Bromodihydropyran (III)			
Millimoles	0.03	−0.03	0.03
% yield	0.3	−0.3	0.3
Dibromides (IV + V)			
Millimoles	0.83	1.11	1.28
% yield	17	22.2	25.6

Effect of Oxygen

Atmosphere	N_2	Air	O_2
Reaction time (min.)[e]	38.4	33.0	31.5
Dihydropyran (I)			
Millimoles[d]	0.97	1.20	1.23
% yield[a]	9.7	12.0	12.3
4-Bromodihydropyran (III)			
Millimoles	0.13	0.04	0.00
% yield	1.3	0.4	0.0
Dibromides (IV + V)			
Millimoles	0.57	0.76	0.87
% yield	11	15	17

[a] Based on N-bromosuccinimide. [b] Average of 4 runs (±1.5 min.); time required for disappearance of the last particles of NBS. [c] Unreacted I, corrected for excess initially present. [d] Ten millimoles of N-bromosuccinimide was used in all reactions. [e] Average of 2 runs (±1.7 min.); time required for disappearance of last particles of NBS.

The method of calculation follows:

(*a*) The equivalents of bromine (A) which added to the reaction mixture correspond to the equivalents of I and III, *i.e.*,

$$A = \mathrm{I} + \mathrm{III} \qquad (1)$$

(*b*) The equivalents of silver bromide (B) formed by subsequent reaction of the mixture with silver nitrate correspond to the sum of the equivalents of I, III, IV, and V. (I and III are included since addition of bromine converts them to the α-bromoethers IV and VII.)

$$B = \mathrm{I} + \mathrm{III} + \mathrm{IV} + \mathrm{V} \qquad (2)$$

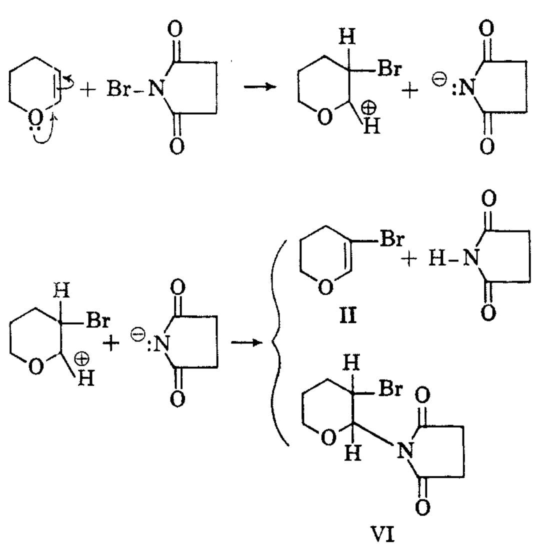
(*c*) The equivalents of silver bromide (C) formed by reaction of a second reaction mixture with silver nitrate correspond to the sum of the equivalents of III, IV, and V.

$$C = \mathrm{III} + \mathrm{IV} + \mathrm{V} \qquad (3)$$

By grouping IV and V together as dibromides, simultaneous solutions of equations (1), (2), and (3) gave the results shown in Table I for a series of reactions intended to investigate the possible effect of peroxide and of oxygen on the reaction. In all these reactions a 25% excess of I was employed; however, this was subtracted from the calculated amount of unreacted I. The results in Table I show that in the absence of peroxide 0.83 mM. of dibromide was obtained and that 0.97 mM. of I was left in excess. Since the formation of a dibromide requires two moles of *N*-bromosuccinimide to react with one mole of I, then for every mole of dibromide formed there should be one mole of unreacted dihydropyran. The close agreement between the yield of dibromide obtained by analysis and amount of unreacted I may be considered as supporting evidence for the validity of the method of analysis. In all cases the calculated yield of III was essentially zero, but there was a small acceleration of the reaction rate in the presence of peroxide. The increased rate of formation of dibromide in the presence of peroxide could have resulted in part from radical attack on II to form Vb.

Similar results were observed with oxygen as shown in Table I. In the absence of oxygen an 11% yield of dibromide was obtained which was increased to 17% in an oxygen atmosphere. There appears to be little tendency toward allylic bromination of I to form III even in the presence of oxygen or peroxides.

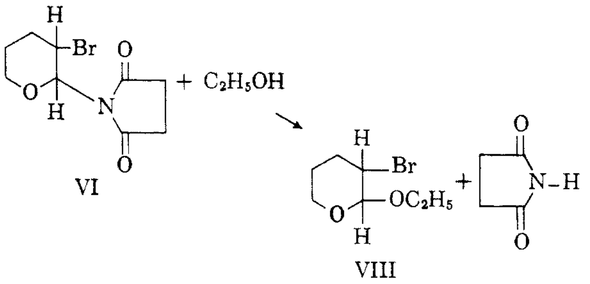
The major products obtained from the reaction of *N*-bromosuccinimide with I, as demonstrated by actual isolation and identification, are the substitution product II (8% based on *N*-bromosuccinimide) and the addition product VI (7%). The dibromide IV was isolated in lesser amount (2.5%) and isolation of succinimide formed in the reaction accounted for 12.5% of the *N*-bromosuccinimide used. The following reaction scheme accounts for the formation of the major products by a polar mechanism:



The formation of dibromide IV by a polar mechanism is more difficult to explain although a mechanism has been proposed by Braude and Waight.[4] The by-product positive and negative succinimide groups are considered to unite, followed by homolytic cleavage and abstraction of hydrogen from solvent or reactants to form succinimide.

The formation of II at least in part by the dehydrohalogenation of IV in the process of isolation must be recognized as a possibility, even though the distillation was carried out at reduced pressure and undecomposed IV was obtained in the same distillate. Even if the formation of II could be accounted for in this way, the formation of VI as a coproduct would still provide strong support for a mechanism in which initial attack involves addition of a positive halogen at the double bond.

Paul and Tchelitcheff[6] presented evidence which indicated that the reaction of *N*-bromosuccinimide with I resulted in addition to give VI. Their evidence was based on the fact that refluxing the reaction mixture with absolute ethanol led to 2-ethoxy-3-bromotetrahydropyran and succinimide, and accordingly they formulated the reaction as:



In the present investigation the product of the initial reaction of I with *N*-bromosuccinimide was filtered to remove succinimide formed in the reaction, stripped of solvent, and then refluxed with ethanol to give a 17% yield of VIII and 13% of succinimide. When pure VI was similarly refluxed with ethanol, it was recovered unchanged with no evidence of any formation of succinimide. The observed difference in behavior between the crude mixture and pure VI has not been explained. It may be that some polar component of the reaction mixture catalyzes the reaction with VI.

The isolation of VI was accomplished by chromatographic separation of the reaction mixture. The first crystals were isolated when one of the fractions, which deposited a gummy residue on removal of eluent, formed crude crystals on standing for several days. Recrystallization from water gave VIa melting at 84.5–86.0°. When the procedure was repeated on a larger sample, a higher melting (m.p.130–130.5°) product (VIb) was obtained (in addition to VIa) which appeared to be the geometrical isomer of the lower melting product. No determination of absolute configuration was attempted. The identification of these products as isomers was based on the similarity of their infrared spectra, elemental analysis, and conversion to the same 2,4-dinitrophenylosazone.

Woods and Temin[7] found that 2-ethoxy-3-bromo-Δ^3-dihydropyran gave a 2,4-dinitrophenylhydrazone derivative of 2-bromo-5-hydroxy-2-pentenal. The formation of this derivative involves ring cleavage of the dihydropyran ring with elimination of the ethoxyl group. It was found in the present work that under similar conditions 2-ethoxy-3-bromotetrahydropyran (VIII) lost both the ethoxyl group and bromine to form the 2,4-dinitrophenylosazone of 2,5-dihydroxypentanal. Hurd and Kelso[8] obtained the same osazone from tetrahydropyran-2,3-diol.

The conversion of both VIa and VIb to this same osazone established the positions of the succinimidyl group and bromine in the 2- and 3-positions, since the formation of this osazone from VI resulted in displacement of both the succinimidyl group and bromine. It was further found that VI did not react with silver nitrate, whereas 2,3-dibromotetrahydropyran (IV) as an α-bromoether forms silver bromide with silver nitrate. The bromine in VI must, therefore, be in the 3-position and the succinimidyl group must be in the 2-position, rather than the reverse.

It was of interest, in connection with this work, to learn that Hurd, Moffat, and Rosnati[5] on treating *N*-bromophthalimide with I isolated an 83.5% yield of 1:1 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. The fact that they obtained no replacement of bromine on shaking the product with silver acetate in acetic acid for one week seems inconsistent with a structure including an α-bromoether, even though the product dissolved slowly in hot dilute alkali with liberation of halide. By analogy to the results of the present study the product they isolated probably was 3-bromo-2-phthalimidotetrahydropyran formed by an ionic mechanism.

Reaction of *N*-bromosuccinimide with I in absolute ethanol proceeded rapidly and smoothly to give a 58% yield of 2-ethoxy-3-bromotetrahydropyran (VIII). Similarly, when the reaction was conducted in glacial acetic acid, a 76% yield of 2-acetoxy-3-bromotetrahydropyran (IX) was obtained. Other examples of this general type have been reported in the literature, *e.g.*, *N*-bromosuccinimide and 1-ethoxybutadiene have been reported[9] as leading to 64% α-bromocrotonaldehyde diethyl acetal. These reactions of *N*-bromosuccinimide apparently proceed by an ionic mechanism involving heterolytic cleavage of *N*-bromosuccinimide to give positive bromine.[9]

It is evident that *N*-bromosuccinimide can react by either a polar or a free-radical mechanism depending upon reaction conditions and the nature of the other reactant. Dihydropyran has an alpha methylene available for allylic bromination, but the polarizing effect of the oxygen alpha to the double bond apparently increases the nucleophilic character so that a polar reaction with the positive bromine available from *N*-bromosuccinimide predominates. The reaction appears to proceed by initial attachment of the positive halogen at the 3-position of dihydropyran with subsequent loss of hydrogen or combination with a negative group.

EXPERIMENTAL

2,3-Dibromotetrahydropyran (IV). To a solution of I (16.8 g., 0.2 mole) in 50 ml. of carbon tetrachloride, immersed in an ice bath, was added dropwise and with stirring 10 ml. of bromine in 50 ml. of carbon tetrachloride. Bromine addition was stopped when the bromine color persisted and then one drop of I was added to react with the excess bromine. A sample of this solution was used to record the infrared spectrum of IV in carbon tetrachloride solution. The remaining solution was used to prepare II.

3-Bromo-5,6-dihydro-4H-pyran (II). To the above solution was added 150 ml. of pyridine (a highly exothermic reaction resulted) and most of the carbon tetrachloride was then removed by distillation. When the temperature of the distillate reached 90°, the distillation was stopped and the residue refluxed overnight (16 hr.). After cooling, the solution was decanted into a separatory funnel with 200 ml. of water. The organic layer was separated and washed with several portions of 0.5*M* hydrochloric acid until all the pyridine was removed, and then with a solution of sodium bicarbonate and finally with water until neutral to litmus. The organic layer was separated, dried over anhydrous magnesium sulfate and distilled through a short packed column to give 2.1 g. (16%) of II b_{60} 83.5–84°, n_D^{25} 1.5068, d_4 1.533. The literature[10] gives b_{22} 63°, n_D^{16} 1.51194, d_{15}^{16} 1.54.

Anal. Calcd. for C_5H_7OBr: C, 36.84; H, 4.33; Br, 49.0. Found: C, 36.73; H, 4.92; Br, 48.3.

To test the reactivity of II with bromine and silver nitrate, a sample (153.5 mg.) of II was accurately weighed out and washed into an iodine flask with 50 ml. of carbon tetrachloride. One drop (0.02 ml.) of 0.493*M* bromine solution added to the solution of I was not decolorized. One drop of I was added to decolorize the solution which was then shaken with silver nitrate solution to give 6.9 mg. of silver bromide. Correcting for the bromine that was added, this corresponded to 0.03 meq. of silver bromide or 3% replacement of the bromine of II.

Standardization of bromine solution. An 0.5*M* solution of bromine was prepared by diluting 13 ml. of bromine to one liter with carbon tetrachloride. This solution was standardized against an exactly 0.2500*M* solution of I in carbon tetrachloride.

For the titration, an aliquot sample (5–20 ml.) of the solution of I was pipetted into a 125-ml. iodine flask and diluted to a total volume of 50–60 ml. with carbon tetrachloride. The end point was taken as the point at which the bromine color persisted for 1 min.

---

(7) G. Woods and S. Temin, *J. Am. Chem. Soc.*, **72**, 139 (1950).

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

(9) W. Flaig, Report No. 52025, Office of the Publication Board, U. S. Dept. of Commerce; *Chem. Abstr.*, **41**, 6189 (1947).

(10) R. Paul, *Compt. rend.*, **198**, 275 (1934).

Reactions with silver nitrate. To the resultant solution from the above reaction was added 25 ml. of an aqueous alcoholic solution of 0.25*M* silver nitrate and the resultant mixture immediately placed on a wrist action shaker for 20 min. The precipitated silver bromide was filtered through a medium grade fritted glass funnel and washed with alternate portions of water and ethanol and dried in an oven at 90–100° to constant weight.

The silver bromide recovered was found to be equivalent in millimoles to 96–100% of the dihydropyran originally reacted with bromine.

Reaction of N-bromosuccinimide with I in carbon tetrachloride. Fifty ml. of an 0.2500*M* solution of I in carbon tetrachloride and 1.780 g. (0.01 mole) of *N*-bromosuccinimide were combined in a 100 ml. round-bottom flask equipped with a reflux condenser and drying tube and refluxed in a bath of boiling water. At the completion of the reaction, the flask was removed from the bath and allowed to cool to room temperature. 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*-bromosuccinimide.

This reaction was also conducted under a nitrogen atmosphere by passing a slow stream of nitrogen into the reaction vessel. The nitrogen was dried by bubbling through concentrated sulfuric acid followed by a drying tube filled with anhydrous calcium sulfate. The reaction was conducted under an oxygen atmosphere in a similar manner.

At the completion of the reaction a completely homogeneous, colorless to pale yellow solution was obtained. Succinimide gradually separated out as the solution was allowed to cool to room temperature.

Succinimide was identified by melting point (123–124°) mixture melting point and infrared spectrum.

Composition of the reaction mixture. Two reactions of *N*-bromosuccinimide and I were conducted simultaneously. After cooling to room temperature one of the mixtures was titrated with bromine (*A*), and then with silver nitrate (*B*). The second cooled mixture was treated directly with silver nitrate (*C*). The amount of bromine consumed (*A*) was taken as equivalent to the sum of unreacted I and of any III formed in the reaction. The silver bromide subsequently formed (*B*) was taken as equivalent to the amount of unreacted I, III, IV, and V. The amount of silver bromide (*C*) was taken as equivalent to the sum of III, IV, and V.

Isolation of reaction products. N-Bromosuccinimide (17.8 g., 0.100 mole) and 500 ml. of a 0.2500*M* solution of I in carbon tetrachloride were allowed to react and the cooled solution was stripped of I and carbon tetrachloride under reduced pressure. The distillate, collected in a flask immersed in an ice bath and followed by a Dry Ice–acetone trap, was titrated with bromine and found to contain 0.033 mole of I (8% unreacted I based on *N*-bromosuccinimide).

The residue taken up in carbon tetrachloride and filtered gave 1.23 g. (12.5%) succinimide. The filtrate was distilled free of solvent and then distilled at *ca.* 5-mm. pressure while gradually increasing the pot temperature (the pot was immersed in a water bath) until the residue started to darken and resinify. The distillate amounted to 1.54 g. of a clear, colorless liquid with n_D^{25} 1.5138. By infrared analysis involving comparison with known samples, the distillate was shown to be a mixture of II and IV. The amount of IV was found to be 0.29 g. (2.4% yield based on *N*-bromosuccinimide) by reaction of the mixture with silver nitrate. The amount of II was calculated, by difference, as 1.25 g. (7.6% yield). The mixture did not add bromine.

Isolation of 2-succinimidyl-3-bromotetrahydropyran (VI). *N*-Bromosuccinimide (1.78 g.) and I (1.05 g.) in 50 ml. of carbon tetrachloride were allowed to react in the usual manner. The cooled mixture was washed with water to remove succinimide, dried over magnesium sulfate, and passed through a column (50 × 2 cm.) of aluminum oxide. The column was eluted with 100 ml. of carbon tetrachloride and 100 ml. of chloroform and then three 200-ml. portions of chloroform. These last three portions extracted with hot water cooled and seeded gave 115 mg. (4.4%) of VIa m.p. 83–84°. The first seed crystals were obtained by chromatographic separation of the mixture and formed when the percolate stripped of solvent was allowed to stand for several days. Seeding was frequently, but not always, necessary to obtain crystallization.

In a subsequent experiment 9.8 g. of *N*-bromosuccinimide and 6.3 g. of I in 125 ml. of carbon tetrachloride were reacted. Succinimide (0.71 g., 13%) was filtered off and the filtrate chromatographed on an aluminum oxide column (10 × 4.5 cm.). The column was eluted with 600 ml. of carbon tetrachloride, 900 ml. of 50/50 chloroform–carbon tetrachloride and finally 150 ml. of chloroform, and collected in 10 fractions as follows: fraction 1, 175 ml.; fractions 2–8, 150 ml. each; fraction 9, 300 ml.; fraction 10, drained the column. Each fraction was stripped of solvent and extracted with hot water to give VI as follows:

Fractions 1 and 2—no crystals
Fraction 3—94 mg., m.p. 84.5–87.5°
Fraction 4—154 mg., m.p. 84.5–87°
Fraction 5—138 mg., m.p. 84–86.5°
Fraction 6—94 mg., m.p. 83–85.5°
Fraction 7—129 mg., m.p. 127.5–130°
Fractions 8 to 10—no crystals

Spectrum analysis and mixture melting points showed fractions 3–6 to be the same. The spectrum of fraction 7 indicated it to be an isomer of the preceding product. This was later confirmed by analysis and conversion to the same 2,4-dinitrophenylosazone.

The crude products from fractions 3–6 were combined and taken up in hot water, and 95% ethanol was added dropwise to the cooled solution until a clear solution was obtained. The solution on seeding deposited VIa, m.p. 84–85°. The crude product from fraction 7, recrystallized from water gave VIb, m.p. 130–130.5°.

Anal. Calcd. for $C_9H_{12}BrNO_3$: C, 41.24; H, 4.62; Br, 30.5; N, 5.35. Found (VIa): C, 41.33; H, 4.41; Br, 30.4; N, 5.30. Found (VIb): C, 41.23; H, 4.37; Br, 30.6; N, 5.35.

The residues from fractions 3–6 were again extracted with hot water to give 415 mg. of additional crude VIa, m.p. 82–83.5°. The total yield of VI amounted to 1.02 g. (7.1%) of which 0.89 g. (6.2%) was VIa and 0.13 g. (0.9%) was VIb.

Synthesis of 2-ethoxy-3-bromotetrahydropyran (VIII). To a mixture of *N*-bromosuccinimide (17.8 g., 0.1 mole) and 58 ml. of absolute ethanol, compound I (10.5 g., 0.125 mole) was added dropwise with stirring. After the *N*-bromosuccinimide was completely consumed, the succinimide was filtered off and most of the excess ethanol removed from the filtrate, under the reduced pressure of a water pump, causing the separation of more succinimide. The residue filtered and distilled gave 13.3 g. (58%) of VIII. On redistillation, the product was collected b_{18} 61–62.5°, n_D^{25} 1.4750, d_4^{25} 1.365. The literature[11] reports b_{18} 94–96°, n_D^{25} 1.4752.

Anal. Calcd. for $C_7H_{13}BrO_2$: C, 40.21; H, 6.27; Br, 38.2. Found: C, 40.54; H, 6.42; Br, 38.7.

Synthesis of 2-acetoxy-3-bromotetrahydropyran (IX). To a mixture of *N*-bromosuccinimide (89.0 g., 0.5 mole) and 290 ml. of acetic acid in an ice bath, compound I (52.5 g., 0.625 mole) was added dropwise and with stirring. When the addition was completed a clear, colorless solution was obtained which was washed with a solution of sodium bicarbonate, extracted with ether, and washed with water until neutral to litmus. The extract, dried over magnesium sulfate and distilled free of ether, gave 84.7 g. (76% theor.) of crude IX. The crude product was twice distilled and the middle fraction, $b_{0.75}$ 82°, collected. Analysis of the product col-

---

(11) G. F. Woods and H. Sanders, *J. Am. Chem. Soc.*, 68, 2483 (1946).

lected indicated it was still somewhat impure. The literature[12] reports b_4 60–75°.

2,4-Dinitrophenylosazone. 2,4-Dinitrophenylhydrazine (0.1 g.), 5 ml. of 95% ethanol, 1 ml. of water and 0.5 ml. of concentrated hydrochloric acid were heated on a steam cone until complete solution was obtained and then *ca.* 0.1 g. of VIII was added. The osazone derivative started precipitating in about 5–10 min., but heating was continued until no more precipitate formed. The precipitate filtered, and recrystallized from ethanol–ethyl acetate and ethanol gave bright orange crystals, m.p. 240–241° (dec.). The literature reports m.p. 235–236° (dec.)[13] and m.p. 242°.[8]

Anal. Calcd.: C, 42.86; H, 3.39; N, 23.52. Found: C, 42.94; H, 3.25; N, 22.76.

The same procedure repeated with IV, VI, and IX gave the same derivative as shown by melting point and mixture melting point.

Reaction of ethanol with products of reaction of N-bromosuccinimide with I. *N*-Bromosuccinimide was treated with I (1.05 g.) in 50 ml. of carbon tetrachloride as previously described. The reaction mixture was cooled and 134 mg. of succinimide (13.5 %) filtered off. The filtrate was stripped of solvent and the residue refluxed overnight with 25 ml. of absolute ethanol. Ethanol was removed by distillation and the residue extracted with carbon tetrachloride and water. The carbon tetrachloride layer dried over magnesium sulfate and distilled gave 0.36 g. (17%) of VIII, $b_{1.2}$ 51–54°, n_D^{25} 1.4710. The product was confirmed as VIII by comparison of its infrared spectrum with the product obtained from the reaction of *N*-bromosuccinimide with I in ethanol.

The water extract, distilled free of water and crystallized from 95% ethanol gave 121 mg. (13%) succinimide.

Reaction of ethanol with VI. Five ml. of absolute ethanol and 6.3 mg. of VIb were combined and refluxed overnight. The mixture was distilled free of most of solvent and then poured into an evaporating dish. The air dried residue taken up in 95% ethanol and chilled gave VIb, m.p. 127–129°. Identification was based on the melting point and comparison of the infrared spectrum with that of the starting material.

The same procedure repeated with VIa gave similar recovery of only starting material when the residue was crystallized from aqueous ethanol.

Acknowledgment. The authors wish to thank the Lubrizol Corp. for the fellowship grant which made this study possible. The work reported here is taken from the Ph.D. thesis of Cataldo Cialdella.

CLEVELAND 6, OHIO

---

[12] J. G. M. Brenner and D. G. Jones, Brit. Patent **605,107** (1948).

[13] S. Swadesh and A. P. Dunlop, *J. Org. Chem.*, **14,** 692 (1949).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Selective Sulfonation of Amino Groups in Amino Alcohols

DONALD T. WARNER AND LESTER L. COLEMAN

Received January 17, 1958

The use of the pyridine–sulfur trioxide complex as a sulfonating reagent for amino alcohols has been investigated in an aqueous alkaline medium. Under these conditions, the reagent selectively sulfonates the amino group. The reaction is applicable to insoluble or soluble amino alcohols, and has also been applied to the hydroxyamino acid, serine.

The discovery of sulfonated amino groups in heparin,[1] a naturally occurring sulfated polysaccharide having alternating glucosamine and glucuronic acid units, has stimulated considerable interest in the preparation of synthetic compounds having similar constituents. For the preparation of such sulfated polysaccharides, one of the starting materials has been chitosan, the polyglucosamine which is readily obtained by alkaline hydrolysis of chitin, a naturally occurring polyacetylglucosamine present in crab shells.

In our earlier work with chitosan[2] we reported the sulfation of this polyglucosamine as a heterogeneous phase with liquid sulfur dioxide–sulfur trioxide. In this system the reaction of the amino groups was not complete, and the yields of product were variable because of the heterogeneous reaction medium. Doczi[3] and coworkers reported the preparation of sulfated chitosans having a high degree of sulfonation on the amino group, although the details of their procedure were not disclosed. Wolfrom[4] also obtained an *N*-sulfated-*O*-sulfated chitosan by the use of chlorosulfonic acid and pyridine in a heterogeneous system.

In attempting to obtain improved yields of sulfated chitosans having a high degree of *N*-sulfonation, we have studied a number of sulfonation systems. From these experiments, a method has been obtained for the selective sulfonation of amino groups in the presence of hydroxyl groups which now appears to be a reaction of general application. The procedure makes use of a well-known reagent, the pyridine–sulfur trioxide complex,[5] which has been previously reacted with both amines and

---

[1] (a) J. E. Jorpes, H. Bostrom, and V. Mutt, *J. Biol. Chem.*, **183,** 607 (1950). (b) K. H. Meyer and D. E. Schwartz, *Helv. Chim. Acta*, **33,** 1651 (1950).

[2] L. L. Coleman, L. P. McCarty, D. T. Warner, R. F. Willy, and J. H. Flokstra, presented before the Division of Medicinal Chemistry of the American Chemical Society, Los Angeles, Calif., March 1953; see Abstracts of Papers, 123rd Meeting, p. 19 L.

[3] J. Doczi, A. Fischman, and J. A. King, *J. Am. Chem. Soc.*, **75,** 1512 (1953).

[4] M. E. Wolfrom, T. M. Shen, and C. G. Summers, *J. Am. Chem. Soc.*, **75,** 1519 (1953).

[5] P. Baumgarten, *Ber.*, **59,** 1976 (1926).