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3-BROMO-4,4-DIMETHYL-2-OXAZOLIDINONE

PREPARATION AND INVESTIGATION OF A NEW BROMINATING AGENT[1]

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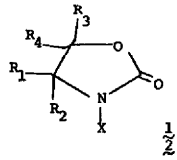
Abstract—A new brominating agent, 3-bromo-4,4-dimethyl-2-oxazolidinone (NBDMO) was prepared and its reactions compared to that of N-bromosuccinimide (NBS). NBDMO was found to have a lower "bromine potential" relative to NBS and, consequently possesses a less polar N-bromine bond. NBDMO was found to be equivalent or better than NBS as a brominating and oxidizing agent in the reactions investigated.

N-Bromosuccinimide is an extremely useful and versatile reagent.[2,3] It is by far the most widely used N-bromo compound among the numerous N-bromamides and N-bromimides available. Its unique brominating ability has been attributed to its almost non-polar N-bromine bond, as well as the favorable geometric arrangement which exists between the N-bromine and carbonyl function. The low polar character of the N-bromine bond in N-bromosuccinimide was explained by the weak acidic character[2] of its corresponding acid, succinic acid. The apparent parallel between the acidity of the parent acid and the polarity of the N-bromine bond in its corresponding N-bromamide and/or N-bromimide lead us to investigate a series of N-bromo compounds based on an even weaker acid than succinic acid. For this purpose, the 2-oxazolidinone derivatives (**1a–g**) were prepared. This class of compounds has the advantage of being based upon the weaker parent acid, carbonic acid, while still maintaining the apparent necessary structural characteristic of a 5-membered ring.

The 2-oxazolidinones (**1a–g**) were prepared by reaction of the appropriate amino alcohol with diethyl carbonate. Halogenation of the 2-oxazolidinones with either chlorine or bromine gave the N-chloro[4] and N-bromo-2-oxazolidinone derivatives respectively. The N-bromo compounds were evaluated on the basis of their stability and the polarity of the N-bromine bond. The 4,4-dialkyl derivative, 3-bromo-4,4-dimethyl-2-oxazolidinone (**2e**) proved to be the most interesting compound in this series since it is by far the most stable and also possesses the least polar N-bromine bond. Previously, we have found that one important mechanism responsible for the degradation of N-halo compounds involves a dehydrohalogenation across the carbon-nitrogen bond.[5] Therefore, it is essential from a stability standpoint to eliminate the hydrogen atoms adjacent to the nitrogen atom by substitution with alkyl or other functional groups. Thus, **2e** is a stable, crystalline solid while the N-bromo derivatives, **2a**, **2f**, and **2g** decompose over a few days in the neat state. Compound **2e** also possesses the least polar N-bromine bond, primarily as a result of the electron-donating inductive effect of the adjacent alkyl groups. In order to compare the polarity of the N-bromine bond in **2e** to that in N-bromosuccinimide, we have introduced the term "bromine potential" in analogy to the "chlorine potential" which has been developed previously.[6,7] The



1 (X=H)
2 (X=Br)

	R_1=	R_2=	R_3=	R_4=
a	H	H	H	H
b	CH_3	H	H	H
c	H	H	CH_3	H
d	H	H	CH_2CH_3	H
e	CH_3	CH_3	H	H
f	CH_3	H	CH_3	H
g	H	H	CH_3	CH_3

"bromine potential" in this case has been defined in terms of the equilibrium constant for the reversible reaction between 3-bromo-4,4-dimethyl-2-oxazolidinone (**2e**) and succinimide (S) to form 4,4-dimethyl-2-oxazolidinone (**1e**) and N-bromosuccinimide (NBS).

The equilibrium constant K was determined spectrophotometrically at 300 nm where 4,4-dimethyl-2-oxazolidinone (**1e**) and N-bromosuccinimide have no appreciable absorbance. The equilibrium constant was calculated using Eqn (1):

$$K = \frac{\left[\frac{A_e - A_0}{A_\infty - A_0}[NBDMO]_0\right]^2}{\left[\left(1 - \frac{A_e - A_0}{A_\infty - A}\right)[NBDMO]_0\right]\left[[S]_0 - \frac{A_e - A_0}{A_\infty - A_0}[NBDMO]_0\right]} \quad (1)$$

where A_e has been defined as the equilibrium absorbance at 300 nm, A_0 is the absorbance at 300 nm for the initial concentration of **2e** and A_∞ is the absorbance at 300 nm assuming a total transformation of **2e** into N-bromosuccinimide. Since the initial concentration of **2e** used in the experiment did not exceed 10^{-3} M, A_∞ is essentially zero. The average equilibrium constant determined for the process using the procedure was $\bar{K} = 0.34$, which indicates that N-bromosuccinimide is a stronger positive bromine releasing agent relative to 3-bromo-4,4-

dimethyl-2-oxazolidinone (**2e**). Consequently, **2e** has a less polar N-bromine bond compared to N-bromosuccinimide which results in the greater stability of **2e** relative to N-bromosuccinimide. A somewhat related brominating agent which has been used in several synthetic procedures with varying degrees of success is 1,3-dibromo-5,5-dimethylhydantoin,[8] which, however, suffers the major disadvantage of containing two N-bromine bonds of different and relatively high polarity.

The next objective of the present work was to investigate the behavior of 3-bromo-4,4-dimethyl-2-oxazolidinone (**2e**) in several reactions characteristic for N-bromosuccinimide, such as selective oxidation of secondary alcohols and allylic bromination. In each instance, the reaction was conducted as described in the literature using N-bromosuccinimide. Concurrently, the identical procedure was also performed replacing N-bromosuccinimide with an equimolar amount of NBDMO (**2e**). The two reactions were compared using thin layer chromatography as well as comparing the yield and purity of the product obtained for each process. The yield of product obtained using NBDMO (**2e**) in the process was not optimized.

The first reaction investigated was the selective oxidation of the 7α-hydroxyl group in cholic acid (**3**) to obtain 3α,12α-dihydroxy-7-ketocholanic acid (**4**).[9] The yield and purity of the keto acid obtained using N-bromosuccinimide or NBDMO (**2e**) were identical.

As a model for the allylic bromination process, the classical transformation[10] of cholesterylbenzoate (**5**) to 7-dehydrocholesterylbenzoate (**6**) was investigated. In this instance, the 7-bromocholesterylbenzoate intermediate was dehydrobrominated *in situ* to give **6**. As was observed in the previous case, the N-bromosuccinimide and NBDMO procedures gave comparable results. However, based on a spectrophotometric analysis of the products obtained, the purity and yield of the product obtained using NDBMO (75%) was better than that obtained using N-bromosuccinimide (65%).

As a further test for the selective oxidation process, the classical oxidation[11] of the 6β-OH group in cholestane-3β,5α,6β-triol (**7**) was investigated (Scheme 1). As observed in the other examples, both reactions using aqueous dioxane gave cholestane-3β,5α-diol-6-one (**8**) almost quantitatively.

However, one controversial point has developed in connection with this investigation. The original work of Fieser[11] describes the direct synthesis of **8** from cholesterol in 47% yield using 1.25 equivalents of N-bromosuccinimide in aqueous acetone. We have repeated this reaction using N-bromosuccinimide as described, as well as using 3-bromo-4,4-dimethyl-2-oxazolidinone (**2e**). In each case, the main product isolated was cholestane-3β,5α,6β-triol (**7**) and not the cholestane-3β,5α-diol-5-one (**8**). The identity of the product as **7** was confirmed by IR and mass spectrometric analysis. In addition, subsequent oxidation of the product with N-bromosuccinimide and NBDMO (**2e**) gave the desired diol-one (**8**) in essentially quantitative yield. Therefore, we have concluded that both N-bromosuccinimide and NBDMO can effectively hydroxylate the C=C double bond of cholesterol to give the *trans*-diol (**7**), which can subsequently be oxidized by these reagents under somewhat different conditions. It should also be pointed out that the purity of **7** and **8** obtained using NBDMO was better than that obtained using N-bromosuccinimide.

In conclusion, we have prepared and investigated a new brominating and oxidizing agent which appears to have some advantages over the widely used N-bromosuccinimide in terms of its stability and selective reactivity. A number of other N-bromo derivatives based on NBDMO can be prepared by variations of R_1, R_2, R_3 and/or R_4. Depending upon the nature of the substituent(s) chosen, it would be possible to predictably control, if necessary, the polarity of the N-bromine bond.

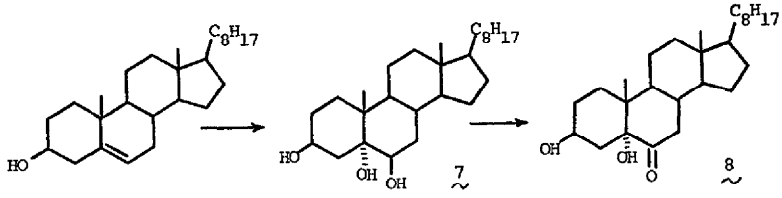
EXPERIMENTAL

3-bromo-2-oxazolidinone (**2a**). 2-Oxazolidinone (**1a**), 4.35 g (0.05 mol) was dissolved in 90 ml of 1 M NaOH and the resulting soln was cooled to 0°. 8.8 g(0.055 mol) bromine was added dropwise with stirring over 10 min and the mixture was stirred at 0° for an additional 20 min. The yellow solution was extracted with dichloromethane. The extracts were combined and dried over Na_2SO_4. Following filtration, the dichloromethane was removed under reduced pressure to afford an orangecolored solid. Trituration of this material in petroleum ether (30–60°) followed by sublimation at 70°/0.1 mm gave 2.0 g (0.012 mol), 24%, **1**, m.p. 109–111°; UV (H_2O) λ_{max} 276 nm, $\epsilon = 218\ M^{-1}\ cm^{-1}$; IR (KBr): 2980, 1720, 1460, 1380, 1200, 1110, 1010 and 710 cm^{-1}, PMR ($CDCl_3$) δ 3.4–4.8 (AA'BB',4H) ppm; mass spectrum (70 eV) *m/e* (rel. intensity) 167(3), 165(3), 108(3), 106(3), 42(100) and 28(52).

3-Bromo-4,4-dimethyl-2-oxazolidinone (**2e**). Compound **1e** 12.3 g (0.11 mol) was dissolved in 180 ml of 1 M NaOH and the resulting soln was cooled to 0°. Br_2 19.2 g; 0.012 mol) was added dropwise with stirring over 0.25 hr and the mixture was stirred at 0° for an additional 0.75 hr. The N-bromamine separated from the mixture as an orange-colored solid. The solid was isolated by filtration and thoroughly washed with cold water. Trituration of this material in petroleum ether (30–60°) gave 16.2 g (0.084 mol), 76%, **3**, m.p. 118–120°; UV (H_2O) λ_{max} 274 nm, $\epsilon = 201\ M^{-1}\ cm^{-1}$; IR (KBr): 2985, 1725, 1370, 1290, 1200, 1165, 1040 and 740 cm^{-1}; PMR ($CDCl_3$) δ 4.27 (s, 2H) and 1.22 (s, 6H) ppm. (Found: C, 31.10; H, 4.20; N, 7.27. Calcd. for $C_5H_8BrNO_2$: C, 30.95; H, 4.15; N, 7.22%).

3-Bromo-5,5-dimethyl-2-oxazolidinone (**2g**). Compound **1g**, (1.15 g; 0.01 mol)was dissolved in 12 ml of 1 M NaOH and the resulting soln was cooled to 0°. Br_2 (1.8 g; 0.011 mol) was added dropwise with stirring over 5 min and the mixture was stirred at 0° for an additional 25 min. The N-bromamine separated from the mixture as a white solid. The solid was isolated by filtration, washed thoroughly with cold water and dried *in vacuo* over $CaSO_4$ to give 0.5 g (0.003 mol), 30%, **2**, m.p. 74–76°; UV (H_2O) λ_{max} 275 nm, $\epsilon = 222\ M^{-1}\ cm^{-1}$; IR (KBr): 2990, 1735, 1480, 1380, 1285, 1195, 1120, 1010 and 715 cm^{-1}; PMR ($CDCl_3$) δ 3.53 (s, 2H) and 1.53 (s, 6H) ppm. (Found: C, 31.05; H, 4.10; N, 7.16. Calcd. for $C_5H_8BrNO_2$: C, 30.95; H, 4.15; N, 7.22%).

3α,12α-Dihydroxy-7-ketocholanic acid (**4**). Compound **3**, (4.30 g; 0.01 mol) was dissolved in a soln of $NaHCO_3$ (2.52 g;



Scheme 1.

0.03 mol) in 80 ml water. The soln at room temp. was treated with 2.43 g (0.013 mol) 3-bromo-4,4-dimethyl-2-oxazolidinone in an analogous manner as described using NBS.[9] (3.1 g; 0.0076 mol), 76%, 3α,12α-Dihydroxy-7-ketocholanic acid was obtained as a pale yellow solid, m.p. 111–114° (EtOAc); IR (KBr): 3420, 2965, 2650, 1700, 1450, 1370, 1240, 1050, and 1000 cm^{-1}; TLC (silica gel: acetone/1% acetic acid): $R_f = 0.86$; mass spectrum (70 eV) *m/e* (rel. intensity) 406(11) and 268(100). The m.p., IR and TLC of this material were identical to those of an authentic sample of 3-α,12α-dihydroxy-7-ketocholanic acid which had been prepared by the oxidation of cholic acid using N-bromosuccinimide.[9]

7-Dehydrocholesteryl benzoate (**6**). A mixture of **5** (2.00 g; 0.004 mol) and 3-bromo-4,4-dimethyl-2-oxazolidinone (0.93 g; 0.0048 mol) in 20 ml hexane was refluxed for 4 min by the light and heat of two 75-watt reflector spot lamps placed 2 in. from the reaction vessel. 0.8 ml of *sym*-collidine was added to the boiling soln, cooled in ice, and filtered to remove 4,4-dimethyl-2-oxazolidinone. The mixture worked up as described in the case using NBS,[10] and thus in 1.3 g (0.003 mol); 75%, 7-dehydrocholesteryl benzoate was obtained, m.p. 120–122°; UV ($CHCl_3$) λ 275, 285 and 297 nm; IR (KBr): 3015, 2975, 1725, 1610, 1470, 1455, 1320, 1270, 1115, 1020, 920 and 700 cm^{-1}; TLC (silica gel: hexane/chloroform): $R_f = 0.90$; mass spectrum (70 eV) *m/e* (rel. intensity) 488(14), 366(62) and 105(100). The m.p., IR and TLC of this material were identical to those of the product obtained from the reaction of cholesteryl benzoate with N-bromosuccinimide.[10]

Cholestane-3β,5α,6β-triol (**7**). A suspension of 4.5 g (0.012 mol) cholesterol in 200 ml acetone and 25 ml water was treated with 2.91 g (0.015 mol) 3-bromo-4,4-dimethyl-2-oxazolidinone and 2.5 ml acetic acid, analogously as described in the literature using NBS.[11] Recrystallization of the crude product from chloroform gave 1.1 g (0.003 mol), 25%, cholestane-3-β-5-α,6-β-triol, m.p. 232–234°, IR (KBr): 3420, 2970, 1470, 1380, 1295, 1160, 1040, 950 and 860 cm^{-1}; TLC (silica gel: acetone/1% acetic acid): $R_f = 0.82$; mass spectrum (70 eV) *m/e* (rel. intensity) 420(3), 402(100), 384(100) and 366(18). The m.p., IR and TLC of this material were identical to those of the product obtained from the reaction of cholesterol with N-bromosuccinimide.[11] However, this product was identified as cholestane-3β,5α-diol-6-one.

Cholestane-3β,5α-diol-6-one (**8**). Compound **7**, (0.5 g; 0.0012 mol) was dissolved in 4.5 ml dioxane, 0.5 ml water and treated with 0.245 g (0.0013 mol) 3-bromo-4,4-dimethyl-2-oxazolidinone which promptly dissolved. In the course of several minutes, the color changed from yellow to orange and the product began to separate. The temp. was kept at 25° by cooling and after 10 min the mixture was cooled in ice. The solid was isolated by filtration and washed thoroughly with 50% MeOH. After extraction with ether, a second crop was obtained. Drying *in vacuo* over $CaSO_4$ gave 0.43 g (0.0010 mol), 83%, cholestane-3β,5α-diol-6-one, m.p. 230–231°; IR (KBr):3410, 2970, 1710, 1465, 1375, 1240, 1160, 1070, 1000 and 970 cm^{-1}; TLC (silica gel: acetone/1% acetic acid): $R_f = 0.92$; mass spectrum (70 eV) *m/e* (rel. intensity) 418(100), 400(27) and 382(17). The yield, m.p., IR and TLC were identical to those obtained from the product of the reaction of cholestane-3β,5α,6β-triol with N-bromosuccinimide using the procedure described by Fieser.[11]

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