α,β-Unsaturated Carboxylic Acid Derivatives. XII. A Convenient Synthesis of Oxazole-4-carboxylic and 3,3-Dibromo-2,2-diamino Acids[1)]

Chung-gi SHIN,* Yoshiaki SATO, Hidetoshi SUGIYAMA, Katsumi NANJO, and Juji YOSHIMURA**

Laboratory of Organic Chemistry, Faculty of Technology, Kanagawa University, Rokkakubashi, Kanagawa-ku, Yokohama 221

***Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Ōkayama, Meguro-ku, Tokyo 152*

(Received November 16, 1976)

Treatment of *t*-butyl 2-acetylamino-3-bromo-2-alkenoate with triethylamine gave *t*-butyl 5-alkyl-2-methyloxazole-4-carboxylate by dehydrobromination, but no reaction occurred with primary amines. While treatment of *t*-butyl 2-acetylimino-3,3-dibromoalkanoate with hydroxylamine or several aliphatic and aromatic primary amines gave addition products, *t*-butyl 2-acetylamino-3,3-dibromo-2-(hydroxyamino)- and 2-(substituted amino)-alkanoate, respectively, in fairly good yields.

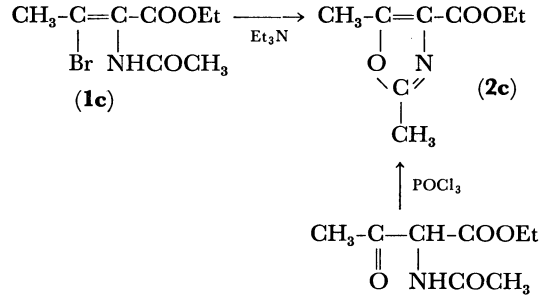
Previously, Shin *et al.* have reported on the facile synthesis of *t*-butyl 2-(*N*-bromoacetylamino)-2-alkenoate by the reaction of *t*-butyl 2-acetylamino-2-alkenoate with *N*-bromosuccinimide (NBS), and its bromine migration into *t*-butyl 2-acetylamino-3-bromo-2-alkenoate (**1**).[2)] Repeated bromination of **1** and its migration gave *t*-butyl 2-acetylimino-3,3-dibromoalkanoate (**4**), to which water or several kinds of alcohol were added readily to give the corresponding 2-hydroxy- and alkoxy derivatives.[1)]

Recently, it has been described that the same addition reaction of aliphatic primary and some secondary amines to methyl 2-acylamino-3,3-dichloroacrylate gave a mixture of methyl 2-acylamino-2-(substituted amino)-3,3-dichloropropanoate and oxazole derivatives.[3,4)] However, not only has the suppositional imino-form intermediate, methyl 2-acylimino-3,3-dichloropropanoate, not been isolated, but also there was no evidence for the presence of the intermediate.

In order to ascertain and extend the above addition reaction, the reaction of **4** with several aliphatic and aromatic primary amines and that of **1** with triethylamine was carried out and these resulted in the convenient synthesis of 3,3-dibromo-2,2-diamino acid derivatives and oxazole-4-carboxylic acids, respectively.[5)]

Results and Discussion

*Reaction of **1** with Triethylamine.* When a solution of **1a,b** (**a**; R=CH_3, **b**; R=C_2H_5) and triethylamine in benzene was refluxed for 2.5 h, a colorless syrup, which gradually crystallized during distillation under reduced pressure, was obtained in a *ca.* 40% yield. The colorless crystals isolated were determined to be *t*-butyl 5-alkyl-2-methyloxazole-4-carboxylate (**2a**, **b**) from elemental analysis and spectroscopic data. A similar treatment of ethyl 2-acetylamino-3-bromo-2-butenoate (**1c**), derived from the reaction of ethyl 2-acetylamino-2-butenoate with NBS, also gave ethyl 2,5-dimethyloxazole-4-carboxylate (**2c**). An independent preparation of **2c**, by the reaction of ethyl 2-acetylamino-3-oxobutanoate with phosphoryl chloride,[6)] demonstrated the structure unambiguously.



Although the assignment of the proper configuration (*E*-, *Z*-) was not successful in this work, the geometric isomer of **1** was subjected to the cyclization reaction (Table 1). Moreover, **2a** was converted into colorless, crystalline, 2,5-dimethyloxazole-4-carboxylic acid (**3a**) in a 57% yield, by treatment with hydrogen chloride in chloroform at room temperature. On the other hand, it was found that conversion of **1** into **2** by ammonia or benzylamine did not occur.

The yields, physical properties, and spectral data of **2** and **3** are summarized in Table 1.

*Reaction of **4** with Several Amines.* The compound **4a,b** (**a**; R=CH_3, **b**; R=C_2H_5) used was prepared according to the method previously reported.[1)] Treatment of **4** with excess gaseous ammonia in ether with stirring below 10 °C gave only *t*-butyl 2-acetylamino-2-amino-3,3-dibromoalkanoate (**5**) as colorless crystals in a *ca.* 70% yield. The subsequent acylation of **5** with acetic anhydride and benzoyl chloride in pyridine at room temperature or below, respectively, gave *t*-butyl 2,2-diacetylamino- and 2-acetylamino-2-benzoylamino-3,3-dibromoalkanoates (**12** and **13**), which could not be obtained independently from the direct addition of the acid amide to **4**. Furthermore, a similar addition reaction of almost equimolar **4** and alkylamines (benzylamine and phenylhydrazine) or arylamines (aniline, ethyl *p*-aminobenzoate, 2-aminopyridine and 2-aminothiazole) in ethanol below 10 °C or at room temperature also gave *t*-butyl 2-acetylamino-2-(substituted amino)-3,3-dibromoalkanoates (**6**—**11**) as colorless crystals in *ca.* 85% yields, without the accompaniment of the expected oxazoline derivatives (**19** and **20**).

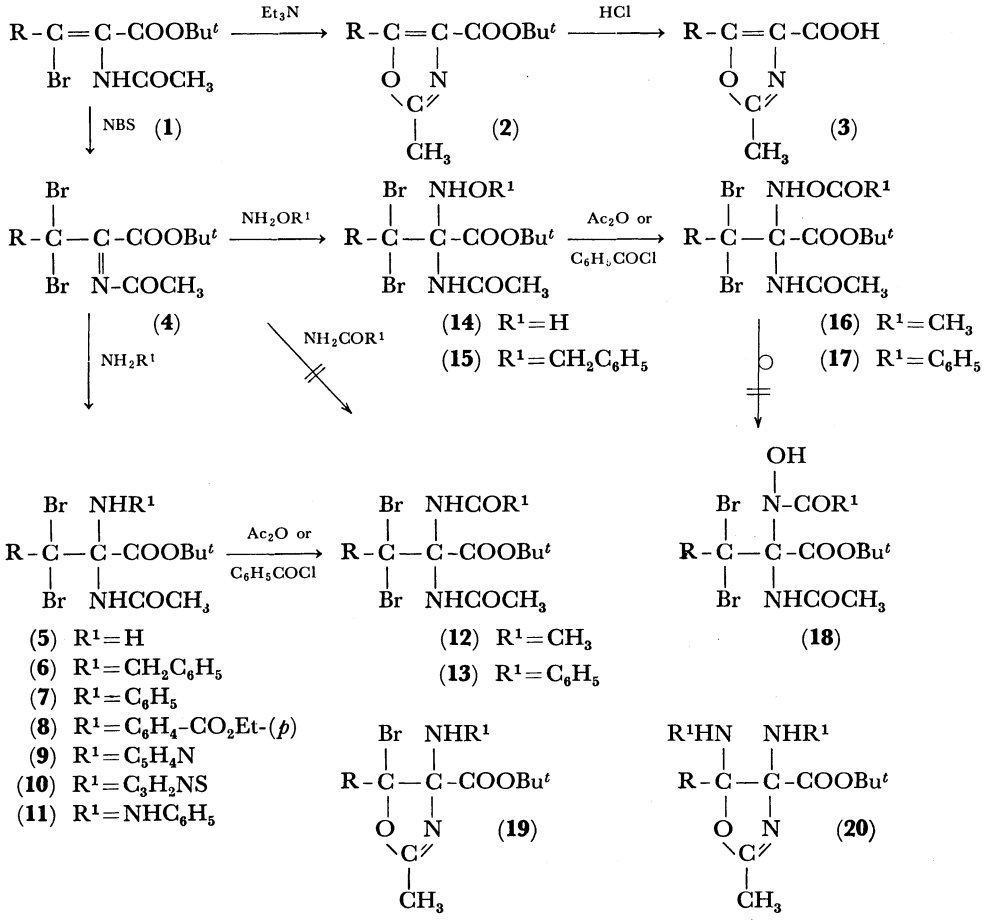
From the above results, it was found that the amino group added readily and dominatly to the carbon-nitrogen double bond in **4**, even in the presence of ethanol.

* To whom all correspondence should be addressed.

TABLE 1. 5-ALKYL-2-METHYLOXAZOLE-4-CARBOXYLIC ACIDS (**2** AND **3**)

Compd No.	Yield (%)	Bp °C/Torr (mp °C)	Formula	Found (Calcd), % C	H	N	IR spectrum, cm^{-1} in KBr	NMR spectrum, δ 5-RCH_2	2-CH_3	COOH
2a	58[a] 25[b]	70—73/1.5 (33—35)	$C_{10}H_{15}NO_3$	60.91 (60.89	7.61 7.69	7.11 7.10)	1735, 1710, 1625	2.57 s (R=H)	2.44[h]	
2b	23[c] 37[d]	85—86.5/2 (28.5—30)	$C_{11}H_{17}NO_3$	62.44 (62.54	8.34 8.11	6.74 6.63)	1727, 1705, 1616	2.75 t J=8.0 Hz	2.45[h]	
2c[e]	41[f]	82—83/2[g]	$C_8H_{11}NO_3$	56.77 (56.79	6.28 6.55	8.32 8.28)	1715, 1623	2.56 s (R=H)	2.45[h]	
3a	57	(182.5—184.5)	$C_6H_7NO_3$	50.96 (51.06	4.94 5.00	9.85 9.93)	1716, 1640	2.60 s (R=H)	2.46	8.87[i]

a) From **1a** (mp 138—139 °C).[e] b) From **1a** (mp 101—102.5 °C).[e] c) From **1b** (mp 84—87 °C).[e] d) From **1b** (syrup).[e] e) Ref. 2. f) From a 1 : 1 mixture of *E*- and *Z*-isomer. g) Ref. 4 (bp 110—115 °C/10 Torr). h) Measured in $CDCl_3$. i) Measured in DMSO-d_6.



Scheme 1.

Moreover, the reaction of **4** with hydroxylamine in ethanol below 10 °C gave the expected *t*-butyl 2-acetylamino-3,3-dibromo-2-(hydroxyamino)alkanoate (**14**) in an unstable crystalline state. The structure of **14** was assigned, on the basis of the appearance of the hydroxyl group absorption band at 3360—3370 cm^{-1} in the IR spectrum and the subsequent acylation of **14**. The acylation of **14** with acetic anhydride and benzoyl chloride in pyridine gave *t*-butyl 2-acetylamino-2-acetoxyamino- and 2-benzoyloxyamino-3,3-dibromoalkanoates (**16** and **17**) as colorless crystals in *ca.* 87% yields. Compounds **16** and **17** showed no coloration with methanolic ferric chloride, indicating the absence of hydroxamic acid structures. However, migration of the acyl group on an oxygen in **16** or **17** to a nitrogen atom, as reported an earlier paper,[7] was not observed. Moreover, a similar treatment of **4** with *O*-benzylhydroxylamine gave *t*-butyl 2-acetylamino-2-benzyloxyamino-3,3-dibromoalkanoate (**15**). In this work, however, the conversion of **15** into **14** was unsuccessful. Although reactions of **4** with other primary amines, for example, butylamine, cyclohexylamine and 2-aminoethanol, occurred, the un-

Table 2. *t*-Butyl 3,3-dibromo-2-(substituted amino)-2-acetamido-2-alkanoates $\left(\begin{array}{l} \mathrm{Br\ \ NH\text{-}R^1} \\ \mathrm{R\text{-}C\text{-}C\text{-}COOBu}^t \\ \mathrm{Br\ \ NHCOCH_3} \end{array}\right)$

Compd No.	R^1	Yield (%)	Mp °C	Formula	Found (Calcd), % C	H	N	IR, cm^{-1}, in KBr NH, (OH), COO, NCO	NMR[b] NH, (OH)
5a	-H	76.6	137—138.5[a,c]	$C_{10}H_{18}N_2O_3Br_2$	32.14 (32.11)	4.80 (4.84)	7.49 (7.51)	3380, 3340, 1730, 1670	2.79, 6.62
5b	-H	67.7	133—134[a,c]	$C_{11}H_{20}N_2O_3Br_2$	34.11 (34.04)	5.13 (5.19)	7.12 (7.22)	3380, 3340, 1730, 1670	
6a	$-CH_2C_6H_5$	94.0	91.5—92.5[d]	$C_{17}H_{24}N_2O_3Br_2$	43.92 (43.99)	5.30 (5.21)	5.91 (6.03)	3380, 3310, 1730, 1680	4.02, 6.76
7a	$-C_6H_5$	97.0	121—122[a,d]	$C_{16}H_{22}N_2O_3Br_2$	42.45 (42.69)	4.97 (4.93)	6.12 (6.22)	3350, 1720, 1690	5.60
7b	$-C_6H_5$	92.5	123.5—124[a,d]	$C_{17}H_{24}N_2O_3Br_2$	44.12 (43.99)	5.24 (5.21)	6.16 (6.03)	3330, 1710, 1680	5.62
8a	$-C_6H_4CO_2Et(p)$	97.6	126—127[a,d]	$C_{19}H_{26}N_2O_5Br_2$	43.63 (43.70)	5.01 (5.02)	5.30 (5.36)	3350, 1710, 1690	
8b	$-C_6H_4CO_2Et(p)$	75.0	111—116[a,d]	$C_{20}H_{28}N_2O_5Br_2$	45.16 (44.80)	5.26 (5.26)	5.29 (5.22)	3350, 1710, 1690	
9a		87.6	138—139[a,e]	$C_{15}H_{21}N_3O_3Br_2$	39.86 (39.93)	4.70 (4.69)	9.05 (9.31)	3350, 1730, 1690	5.99, 8.00
9b		76.0	130—130.5[a,f]	$C_{16}H_{23}N_3O_3Br_2$	41.28 (41.30)	5.08 (4.98)	8.88 (9.03)	3350, 1730, 1690	
10a		73.1	145—146[a,g]	$C_{13}H_{19}N_3O_3SBr_2$	34.38 (34.15)	4.23 (4.19)	9.16 (9.19)	3320, 1730, 1690	
10b		42.9	138—139[a,g]	$C_{14}H_{21}N_3O_3SBr_2$	35.87 (35.69)	4.58 (4.49)	8.89 (8.92)	3300, 1730, 1690	
11a	$-NHC_6H_5$	96.7	127—127.5[a,d]	$C_{16}H_{23}N_3O_3Br_2$	41.08 (41.31)	4.96 (4.98)	8.96 (9.03)	3370, 3260, 1730, 1680	5.74
11b	$-NHC_6H_5$	85.1	124—125[a,d]	$C_{17}H_{25}N_3O_3Br_2$	42.73 (42.61)	5.28 (5.26)	8.94 (8.77)	3320, 3250, 1720, 1660	5.74
12a	$-COCH_3$	60.3	135—136[a,h]	$C_{12}H_{20}N_2O_4Br_2$	34.70 (34.64)	4.88 (4.84)	6.82 (6.73)	3330, 3320, 1740, 1700 1670	
12b	$-COCH_3$	67.5	131—132[c]	$C_{13}H_{22}N_2O_4Br_2$	36.29 (36.30)	5.23 (5.16)	6.49 (6.51)	3310, 3280, 1730, 1670	
13a	$-COC_6H_5$	57.0	133—133.5[a,e]	$C_{16}H_{22}N_2O_4Br_2$	41.31 (41.22)	4.77 (4.76)	5.99 (6.01)	3320, 3300, 1730, 1690 1650	7.02
14a	-OH	87.9	crystals[j]		—	—	—	(3360), 3330, 1740, 1650 3230	
14b	-OH	83.0	crystals[j]		—	—	—	(3370), 3330, 1730, 1650 3220	(7.95) 5.36
15a	$-OCH_2C_6H_5$	82.1	99.5—100.5[i]	$C_{17}H_{24}N_2O_4Br_2$	42.77 (42.52)	5.01 (5.04)	5.85 (5.83)	3360, 3160, 1730, 1680	
15b	$-OCH_2C_6H_5$	78.9	124—125[c]	$C_{18}H_{26}N_2O_4Br_2$	43.88 (43.75)	5.31 (5.30)	5.70 (5.67)	3370, 3200, 1730, 1680	
16a	$-OCOCH_3$	85.6	139—141[a,h]	$C_{12}H_{20}N_2O_5Br_2$	33.62 (33.36)	4.70 (4.67)	6.57 (6.48)	3280, 3220, 1750, 1650	
16b	$-OCOCH_3$	87.4	124—125[c]	$C_{13}H_{22}N_2O_5Br_2$	34.66 (35.00)	4.88 (4.97)	6.21 (6.28)	3380, 3220, 1750, 1690 1730	
17a	$-OCOC_6H_5$	84.3	132.5—133[c]	$C_{17}H_{22}N_2O_5Br_2$	41.51 (41.32)	4.55 (4.49)	5.61 (5.67)	3340, 3200, 1730, 1680 1720	
17b	$-OCOC_6H_5$	91.1	121—122[c]	$C_{18}H_{24}N_2O_5Br_2$	42.97 (42.54)	4.74 (4.76)	5.58 (5.51)	3360, 3190, 1720, 1680	

a) Decomposition. b) δ, in $CDCl_3$. c) Colorless needles from dibutyl ether. d) Colorless needles from ethanol-H_2O. e) Colorless prisms from dibutyl ether. f) Colorless needles from hexane. g) Colorless needles from ethanol. h) Colorless prisms from benzene-petroleum ether. i) Colorless prisms from hexane. j) Unstable.

stable crystalline products obtained could not be confirmed.

The yields, physical properties, and spectral data of **5**—**17** are summarized in Table 2.

Experimental

All boiling and melting points are uncorrected. The IR spectra were recorded with a Hitachi EPI-G3 Spectrometer.

The NMR spectra were measured using a JNM-PS-100 Spectrometer (Japan Electron Optics Laboratory Co., Ltd.) with tetramethylsilane as the internal standard.

Materials. The *E*- and *Z*-isomers of **1a,b** were prepared by the method recently reported.[2] Similarly, **1c** was also obtained by the reaction of ethyl 2-acetylamino-2-butenoate (0.0304 mol) and NBS (0.0335 mol) in carbon tetrachloride (30 ml). Colorless needles from dibutyl ether, yield 55%, mp 108—109 °C. IR (KBr): 3245 (NH), 1720 (COO), 1660 and 1520 (NHCO) cm^{-1}. NMR (δ): 2.34, 2.55 (two s, $COCH_3$), 2.04, 2.07 (two s, CH_3–C=), 7.47, 8.20 (two broad s, NH), contributing to the mixture of the *E*- and *Z*-isomers of **1c**. From the intensity of the amide proton, **1c** was found to be composed of the *E*- and *Z*-isomers in a ratio of 1 : 1. Found: C, 38.52; H, 4.81; N, 5.60%. Calcd for $C_8H_{12}NO_3Br$: C, 38.40; H, 4.80; N, 5.60%.

*Preparation of **2a,b,c**.* A solution of **1a,b,c** (0.0036 mol) and triethylamine (0.0072 mol) in dry benzene (20 ml) was refluxed for 2.5 h. The triethylamine hydrobromide separated out was filtered off, and then the benzene solution was washed three times with water (30 ml). The benzene layer was dried over anhydrous magnesium sulfate and then evaporated under reduced pressure to give a colorless syrup. The residual syrup was distilled under reduced pressure to give crystals of *t*-butyl 2,5-dimethyloxazole-4-carboxylate (**2a**) and *t*-butyl 5-ethyl-2-methyloxazole-4-carboxylate (**2b**) or a syrup (**2c**).

*Preparation of **3a**.* A solution of **2a** (0.0177 mol) in dry chloroform (10 ml) was saturated with dry hydrogen chloride with cooling. After standing overnight at room temperature, colorless crystals gradually separated out from the resulting brown solution. The crystalline product was collected and washed with chloroform and then recrystallized from ethanol to give colorless needles (**3a**).

*Preparation of **5a**.* When a solution of **4a** (1.54 g, 0.0043 mol) in ether (10 ml) was saturated with gaseous ammonia with stirring below 10 °C, a colorless crystalline product precipitated immediately. The crystals were identified to be *t*-butyl 2-acetylamino-2-amino-3,3-dibromobutanoate.

In an analogous manner, *t*-butyl 2-acetylamino-2-amino-3,3-dibromopentanoate (**5b**) was obtained from the reaction of **4b** with ammonia.

*Preparation of **6a**.* A solution of **4a** (0.0043 mol) and benzylamine (0.48 g, 0.0045 mol) in ethanol (10 ml) was stirred below 10 °C. A small quantity of water added to the resulting solution and a similar work up gave *t*-butyl 2-acetylamino-2-benzylamino-3,3-dibromobutanoate.

*Preparation of **7a**.* A solution of **4a** (0.0043 mol) and aniline (0.42 g, 0.0045 mol) in ethanol (10 ml) was stirred below 10 °C and worked up similarly to give *t*-butyl 2-acetylamino-2-anilino-3,3-dibromobutanoate.

In an analogous manner, *t*-butyl 2-acetylamino-2-anilino-3,3-dibromopentanoate (**7b**) was obtained from **4b** and aniline.

*Preparation of **8a**.* *t*-Butyl 2-acetylamino-2-(4-ethoxycarbonylanilino)-3,3-dibromobutanoate was prepared from **4a** (0.0043 mol) and ethyl *p*-aminobenzoate (0.75 g, 0.0045 mol) in a manner similar to the preparation of **6a**.

*Preparation of **9a**.* In a similar manner, *t*-butyl 2-acetylamino-2-(2-pyridylamino)-3,3-dibromobutanoate was synthesized from **4a** and 2-aminopyridine (0.0045 mol).

*Preparation of **8b**.* Into a solution of ethyl *p*-aminobenzoate (0.71 g, 0.0043 mol) in benzene (30 ml), **4b** (1.51 g, 0.0041 mol) was added with stirring at room temperature. After stirring for 5 h, the resulting solution was washed successively once with 3M-hydrochloric acid and once with water. The benzene layer was dried over anhydrous magnesium sulfate and then evaporated under reduced pressure to give crystals of *t*-butyl 2-acetylamino-2-(4-ethoxycarbonylanilino)-3,3-dibromopentanoate.

*Preparation of **9b**.* *t*-Butyl 2-acetylamino-2-(2-pyridylamino)-3,3-dibromopentanoate was obtained from **4b** and 2-aminopyridine in the manner described above.

*Preparation of **10a**.* Into a solution of 2-aminothiazole (0.45 g, 0.0045 mol) in benzene (30 ml), **4a** (0.0043 mol) was added with stirring at room temperature. After stirring for 24 h, the crystalline product separated out was collected and washed with ethanol. The crystals were identified to be *t*-butyl 2-acetylamino-2-(2-thiazolylamino)-3,3-dibromobutanoate.

In an analogous manner, *t*-butyl 2-acetylamino-2-(2-thiazolylamino)-3,3-dibromopentanoate (**10b**) was obtained from **4b** and 2-aminothiazole, after stirring for 4 days.

*Preaparation of **11a**.* A solution of **4a** (0.0043 mol) and phenylhydrazine (0.49 g, 0.0045 mol) in ethanol (10 ml) was stirred below 10 °C, and a similar work up gave *t*-butyl 2-acetylamino-2-phenylhydrazino-3,3-dibromobutanoate.

In an analogous manner, *t*-butyl 2-acetylamino-2-phenylhydrazino-3,3-dibromopentanoate (**11b**) was obtained from **4b** and phenylhydrazine.

*Preparation of **14a**.* Into a solution of **4a** (0.0043 mol) in ethanol (10 ml), a solution of hydroxylamine (made from hydroxylamine hydrochloride (0.33 g, 0.0047 mol) and sodium hydrogencarbonate (0.4 g, 0.0047 mol) in water (3 ml)) was added dropwise with stirring below 10 °C. The reaction was immediately completed and a colorless crystalline product was separated out by adding water (10 ml) to the resulting solution. The crystals were collected and washed with a small quantity of petroleum ether, and identified as *t*-butyl 2-acetylamino-3,3-dibromo-2-hydroxyaminobutanoate.

In an analogous manner, *t*-butyl 2-acetylamino-3,3-dibromo-2-hydroxyaminopentanoate (**14b**) was obtained from **4b** and hydroxylamine.

*Preparation of **15a**.* A solution of **4a** (0.0043 mol) and *O*-benzylhydroxylamine (made from *O*-benzylhydroxylamine hydrochloride (0.72 g, 0.0045 mol) and sodium ethoxide (made from sodium (0.1 g, 0.0045 mol) and ethanol (5 ml)) in ethanol (50 ml) was similarly worked up to give a residual yellowish syrup. After adding benzene (50 ml) to the residue, the benzene solution was washed once with water and dried over anhydrous magnesium sulfate, and then evaporated under reduced pressure to give *t*-butyl 2-acetylamino-2-benzyloxyamino-3,3-dibromobutanoate.

In an analogous manner, *t*-butyl 2-acetylamino-2-benzyloxyamino-3,3-dibromopentanoate (**15b**) was obtained from **4b** and *O*-benzylhydroxylamine.

*Preparation of **12a**, **12b**, **16a**, and **16b**.* The acetylation of **5a**, **5b**, **14a**, and **14b** was carried out by the usual procedure using acetic anhydride and pyridine at room temperature, giving the acetoxyamino compounds, **12a**, **12b**, **16a**, and **16b**, respectively.

*Preparation of **13b**.* A solution of **5a** (3 g, 0.008 mol) and benzoyl chloride (1.24 g, 0.0088 mol) in pyridine (20 ml) was stirred below 10 °C for 3 h, and a similar work up gave *t*-butyl 2-acetylamino-2-benzoylamino-3,3-dibromobutanoate.

*Preparation of **17a** and **17b**.* Similarly, **14a** and **14b** were treated with benzoyl chloride below 10 °C in pyridine, giving the benzoyloxyamino compounds, **17a** and **17b**, respectively.

References

1) Part XI: C. Shin, Y. Sato, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **49**, 1909 (1976). This work was presented

at the 35th National Meeting of the Chemical Society of Japan, Sapporo, August 1976. Preprint Vol 2, pp. 606.

2) C. Shin, K. Nanjo, T. Nishino, Y. Sato, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **48**, 2492 (1975).

3) B. S. Drach and G. N. Mis'kevich, *Zh. Org. Khim.*, **10**, 2315 (1974); *J. Org. Chem., USSR*, **10**, 2329 (1974).

4) K. Matsumura, H. Shimadzu, O. Miyashita, and N. Hashimoto, *Chem. Pharm. Bull.*, **24**, 941 (1976).

5) This work was presented at 30th and 31st National Meetings of the Chemical Society of Japan, Osaka, April, 1974 and Sendai, October 1974.

6) N. Saito and C. Tanabe, *Yakugaku Zasshi*, **76**, 305 (1956).

7) C. Shin, K. Nanjo, E. Ando, and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, **47**, 3109 (1974).