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PARTICIPATION IN THE FORMATION OF IODO UREAS FROM 3-BUTEN-1-OL DERIVATIVES

A REINVESTIGATION[1]

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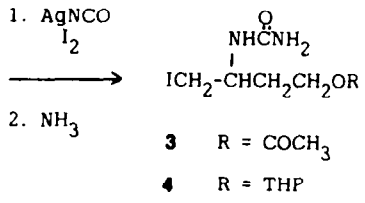
Abstract—Treatment of O-substituted derivatives of 3-buten-1-ol with silver cyanate and iodine, followed by ammonia, gave cyclic derivatives **5** and **6**. These compounds were previously assigned the linear structures **3** and **4**, respectively. Evidence in support of the proposed structural reassignment was obtained from high-field ^1H and ^{13}C NMR studies. Both **5** and **6** undergo loss of the ureido group upon treatment with water to give **9** and **10**, and **12**, respectively. Potential mechanisms for the observed reactions are discussed.

Alkenes are readily converted to β-iodo isocyanates upon treatment with silver cyanate and iodine.[3] Subsequent treatment of these adducts with ammonia gives the corresponding ureas.[4] This two-step procedure generally yields regioisomers despite the electrophilic nature of the initially generated iodine isocyanate reagent.[4,5] Recently, two of us reported on the selective formation of β-iodo ureas **3** and **4** from the corresponding acetyl-(**1**) and tetrahydropyranyl-(**2**) derivatives of 3-buten-1-ol.[6] The unusually high regiospecificity observed for these two reactions was attributed to the O atom of the alcohol protecting group. This atom should preferentially stabilize the incipient carbonium ion generated at C-3 in the first step, thereby leading to the formation of the Markovnikov products **3** and **4**.

CH_2=$CHCH_2CH_2OR$

1 R = $COCH_3$

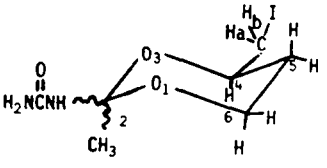
2 R = THP



3 R = $COCH_3$

4 R = THP

The structure of the two reported ureas (**3** and **4**) were based primarily on their ^1H NMR spectra along with combustion analyses.[6] However, the anomalous position of the Me proton absorption for **3** has prompted reexamination of the ^{13}C and ^1H NMR spectral properties of these compounds at high field. Our findings now require revision of structures **3** and **4** to **5** and **6**, respectively. This reassignment suggests an even greater participatory role by the O atom of the protecting group in these reactions than originally envisaged. In this paper, we wish to report the evidence in support of **5** and **6**, as well as some of the chemical properties for these compounds.



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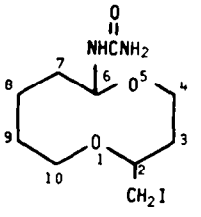

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RESULTS

Syntheses. Compounds **5** and **6** were prepared starting from commercially available 3-buten-1-ol[7] (**7**). Initial protection of the alcohol function of **7** according to established procedures[8] gave the corresponding O-substituted derivatives **1** and **2**, respectively. Subsequent treatment of an ether suspension of the alkene (**1** and **2**) and freshly prepared silver cyanate with iodine afforded the corresponding β-iodo isocyanates. These adducts were not isolated but were directly converted to **5** and **6** in 95 and 80% yield, respectively, by passing ammonia through a prefiltered solution containing the isocyanate. Neither compound could be purified by recrystallization or by chromatography.

CH_2=$CHCH_2CH_2OH$

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Spectral studies of compounds **5** *and* **6**. The 400.1 MHz ^{1}H NMR spectrum for compound **5** shown in Fig. 1a, is summarized in Table 1. Noteworthy, each of the ring protons as well as the exocyclic methylene protons are resolved into distinct multiplets. This simplification of the proton spectrum along with a complete proton–proton decoupling analysis (Experimental) permitted both the chemical shift assignments given in Table 1 and the determination of the approximate proton–proton coupling constants for **5**. These latter values were further refined by computer simulation studies using the SIMEQ (Varian Instruments) program on a Varian FT80A NMR instrument and are listed in Table 2. The simulated spectrum is depicted in Fig. 1b. The insulated C-2 Me group and the N–H protons were not included.

The double irradiation studies provide substantial evidence against the previously proposed structure **3**. Irradiation of the N–H proton of the β-iodo urea **3** should have simplified the signal for the adjacent C–H proton. No alteration of the spectrum was observed upon decoupling of either N–H proton. These results are in agreement with structure **5**, an interpretation further supported by the appearance of the acetal-type Me group at δ 1.50.[9]

Additional evidence for the proposed cyclic structure **5** stemmed from the high-field ^{13}C NMR spectrum (Table 3). Two downfield signals (101.76 and 159.69 ppm) were detected in the decoupled spectrum. Each resonance line remained a singlet of considerably greater half-width in

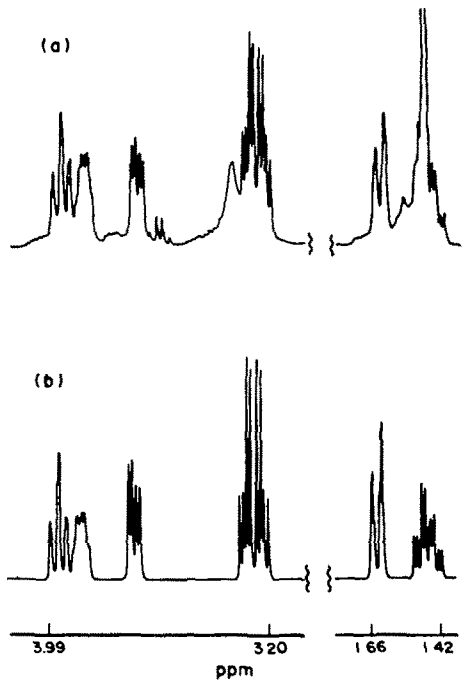


Fig. 1.(a). 400 MHz ^{1}H NMR spectrum for compound **5** in DMSO-d_6. (b) Simulated spectrum of compound **5** with the acetal-type methyl (C_2–CH_3) group not included.

Table 1. 400.1-MHz ^{1}H NMR Data for compound **5** in DMSO-d_6.

Chemical Shift	Multiplicity	Integral	Assignment
δ 1.48	m	1H	C_5-Ha
1.50	s	3H	C_2-CH_3
1.65	br d	1H	C_5-He
3.23	q	1H	C_4-CHaHbI
3.28	q	1H	C_4-CHaHbI
3.68	dd	1H	C_6-He
3.87	m	1H	C_4-H
3.95	td	1H	C_6-Ha
5.70	s	2H	C_2-NHCNH$_2$
6.46	s	1H	C_2-NHCNH$_2$

Table 2. ^{1}H-^{1}H Coupling constants for compound **5**[a]

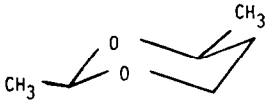
C_4H-C_6Ha	1.19 Hz	C_4H-C_5He	2.43 Hz
C_6Ha-C_6He	11.13	C_4H-C_5Ha	10.98
C_6Ha-C_5He	2.43	C_6He-C_5He	1.00
C_6Ha-C_5Ha	11.13	C_6He-C_5Ha	5.02
C_4H-C_6He	1.09	C_4CHaHbI-C_4CHaHbI	10.37
C_4H-C_4CHaHbI	5.18	C_5Ha-C_5He	12.81
C_4H-C_4CHaHbI	5.79		

[a] Values obtained from computer simulation.

Table 3. 100.6 MHz ^{13}C NMR Data for compound **5** in DMSO-d_6

Chemical Shift	Multiplicity	($J^{13}C$-^1H)	Assignment
δ 10.86	t	(J=151 Hz)	C_4-$\underline{C}H_2I$
26.55	q	(J=128 Hz)	C_2-$\underline{C}H_3$
29.53	t	(J=128 Hz)	C_5
58.49	t	(J=144 Hz)	C_6
67.64	d	(J=145 Hz)	C_4
101.76	s		C_2
156.69	s		C_2-NH$\underset{\underset{O}{\|}}{\underline{C}}NH_2$

the corresponding coupled spectrum. These chemical shift values are in good agreement with the anticipated values for C_2[10] and the urea carbonyl C[11] in **5**, respectively and are incompatible with β-iodo urea **3**. In the close model **8**[10], which lacks only the ureido substituent at C_2 and the iodine, the C_2 absorption occurred at 98.8 ppm. Since the addition of a ureido group to C_2, which already bears two O atoms, would be expected to have little effect, the 101.76 ppm signal is appropriate for C_2. Moreover, the chemical shift value for the acetyl C in **3** would be expected to be approximately 171 ppm.[11]



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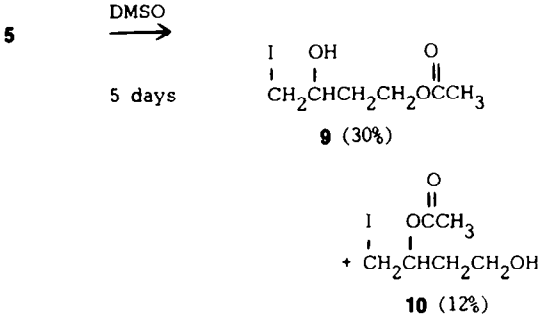
A similar set of studies were conducted on compound **6**. The high-field ^1H and ^{13}C NMR data are listed in Tables 4 and 5, respectively. The complexity of both spectra did not permit a definitive assignment for each nucleus. Still, irradiation of the doublet pattern at δ6.37–6.39 (C_6-NHC(=O)NH_2) in the proton spectrum altered the multiplet at δ5.00–5.04 (C_6-H). This latter resonance was previously attributed to the C-2′ tetrahydropyranyl ring proton in **4**, and should have remained unaffected in this double irradiation experiment. The tentative ^{13}C assignments are listed in Table 5. The proton decoupled ^{13}C NMR spectrum exhibited low-field peaks located at 64.19, 67.76, 77.35, and 80.65 ppm. In the corresponding proton coupled ^{13}C NMR spectrum, a triplet, triplet, doublet, and doublet pattern, respectively, were centered at these signals. The tentative assignments of the doublet resonances at 77.35 and 80.65 ppm to carbons 2 and 6 in compound **6** are in agreement with values reported for similar carbons.[11]

Chemical properties of compounds **5** and **6**. Prolonged dissolution of compound **5** in dimethyl sulfoxide (r.t., 5 days) led to the complete disappearance of starting material (tlc analysis). Purification of the reaction mixture (≥3 compounds) by extraction, followed by preparative thick-layer chromatography gave **9** and a small amount of material tentatively identified as **10**.[12] A comparable result was observed in the treatment of **5** with water (100°, 2 hr).



The IR, ^1H and ^{13}C NMR, and mass spectral (low and high resolution) properties supported the proposed structures for compounds **9** and **10** (Experimental). Fur-

Table 4. 400.1 MHz ^1H NMR Data for compound **6** in DMSO-d_6

Chemical Shift	Multiplicity	Integral	Assignment
δ 1.33-1.75	m	8H	C_3-H_2, C_7-H_2 C_8-H_2, C_9-H_2
3.27-3.54	m	5H	C_2-CH_2I, C_2-H
3.64-3.70	m	2H	C_4-H_2, C_{10}-H_2
5.00-5.04	m[a]	1H	C_6-H
5.50-5.52	s	2H	C_6-NHC(=O)NH_2
6.37-6.39	d	1H	C_6-NHC(=O)NH_2

[a] Irradiation of the doublet at δ 6.37-6.39 (C_6-NHC(=O)NH_2) altered the multiplet at δ 5.00-5.04 (C_6-H).

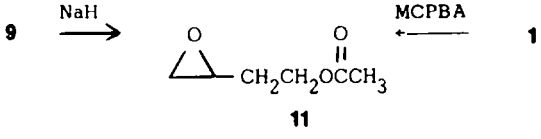
Table 5. ^{13}C NMR Data for compound 6 in DMSO-d_6

Chemical Shift[a]	Multiplicity	$(J^{13}C\text{-}^{1}H)$[b]	Assignment
12.4	t	(J=151 Hz)	C_2-$\underline{C}H_2I$
21.4	t	(J=129 Hz)	
27.1	t	(J=125 Hz)	C_3, C_7
33.6	t	(J=122 Hz)	C_8, C_9
34.4	t	(J=125 Hz)	
64.2	t	(J=100 Hz)	C_4, C_{10}
67.8	t	(J=138 Hz)	
77.4	d	(J=147 Hz)	C_2, C_6
80.7	d	(J=154 Hz)	
157.8	s		C_6-NH$\underset{\underline{\underline{O}}}{\underline{C}}NH_2$

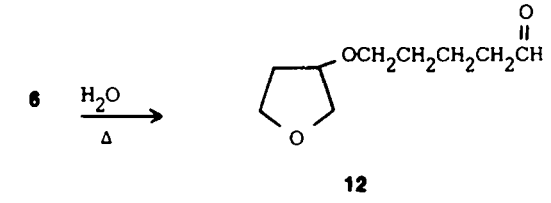
[a] Values obtained from Varian XL-100 NMR.

[b] Values obtained from Bruker WH-400 NMR.

thermore, **9** was converted to epoxide **11** by treatment with sodium hydride in ether (66% yield). This epoxide proved to be identical in all respects with an authentic sample prepared by the addition of 1.4 equivalents of *m*-chloroperbenzoic acid to a methylene chloride solution of **1** (79% yield).

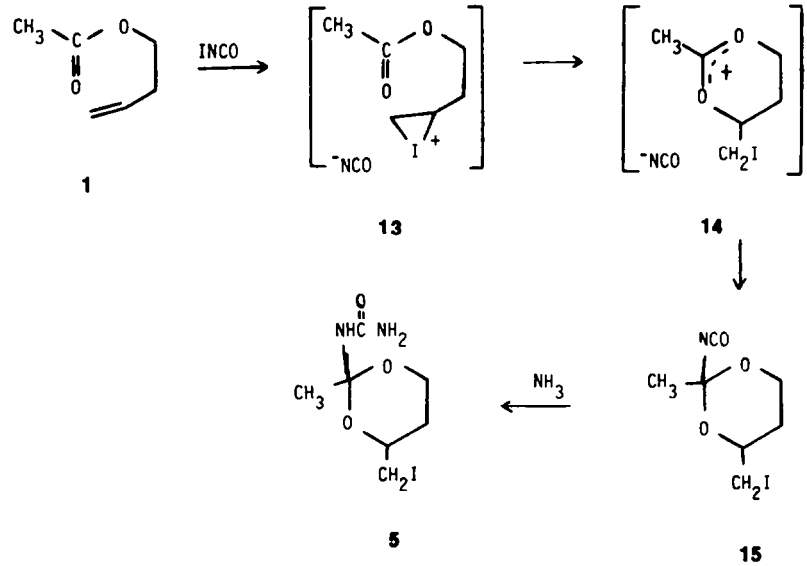


Correspondingly, treatment of **6** with water (100°, 2 hr) led to the disappearance of starting material. The product obtained after work-up and distillation was tentatively identified as **12** on the basis of the observed spectral properties. Noteworthily, the IR spectrum exhibited a prominent band at 1730 cm^{-1}, while the ^1H NMR spectrum showed a finely split triplet (J = 1Hz) at δ9.76. Both signals can be assigned to the aldehyde moiety in **12**[13,14]. The product (**12**) was further characterized as its 2,4-dinitrophenylhydrazone derivative.

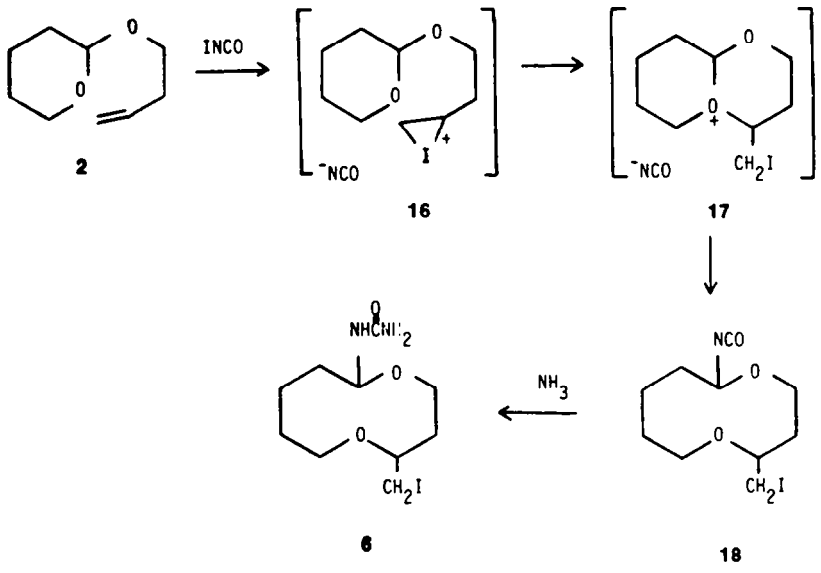


DISCUSSION

The reassignment of the structures for the initially generated adducts in these reactions as **5** and **6** suggests that the O atom of the alcohol protecting group in **1** and **2** plays a direct role in product formation. A mechanism for the formation of **5** and **6** appears in Schemes 1 and 2,



Scheme 1.

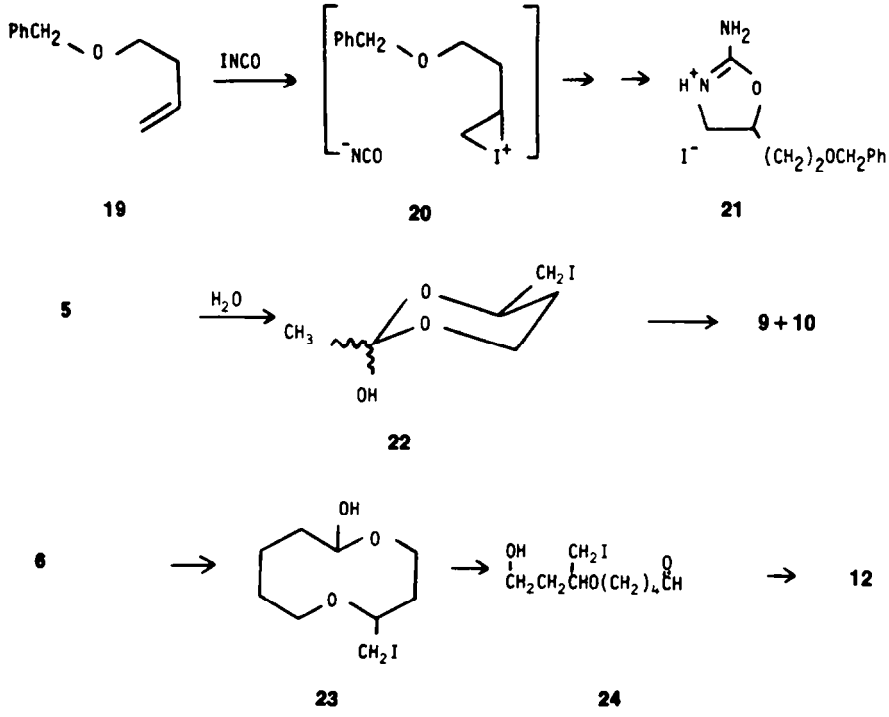


Scheme 2.

respectively. In both cases the O atom is envisaged to attack the incipient carbonium ion generated at C_3 through a 6-membered transition state (**13**→**14**, **16**→**17**). Subsequent attack by the cyanate anion would generate the observed products after treatment with ammonia. There is ample precedent for trapping of dioxolenium ions such as **14** by nitrogen nucleophiles at C_2.[15]

Further support for the participatory role of the O atom in these reactions was obtained from the reactivity of compound **19**. This alkene should yield a mixture of iodo ureas or the corresponding oxazolinium salts. Interestingly, when an ether suspension of **19** and silver cyanate was treated with iodine, a very rapid uptake of iodine was noted. However, when ammonia was bubbled through the pre-filtered solution, no iodo urea precipitated. Upon cooling overnight a crystalline material formed whose spectral and analytical data[16] were consistent with structure **21** (12% yield). No more solid material was obtained upon further cooling. The formation of this oxazolinium salt can easily be rationalized if neighboring group participation by the benzyl ether oxygen preferentially occurred at C_4 through a 5-membered transition state. Subsequent attack by cyanate ion at this site would then lead to the anti-Markovnikov adduct. Conversion of this material to the corresponding iodo urea followed by cyclization would yield **21**.

In the hydrolytic studies, ionization of the ureido group in **5** and **6** by a S_N1 process followed by attack by water should generate **22** and **23**, respectively. These compounds can then ring open to give **9**, **10**, and **12**.



EXPERIMENTAL

General. M.ps were determined with a Thomas–Hoover m.p. apparatus and are uncorrected. IR spectra were run on Perkin–Elmer Models 700 and 237B spectrometers and calibrated against the 1601 cm^{-1} band of polystyrene. ^1H NMR spectra were recorded on a Varian Associates Model T-60 instrument. ^{13}C NMR spectra were determined at 25.1 MHz on a Varian Associates Model XL–100–15 spectrometer, equipped with a Nicolet Technology Corp. TT–100 data system. High-field NMR studies (^2H at 400.1 MHz and ^{13}C at 100.6 MHz) were performed by Dr. Ruth Inners at the NSF sponsored NMR facility at the University of South Carolina on a Bruker WH–400 NMR spectrometer. Chemical shifts are expressed in ppm relative to Me_4Si, and coupling constants (J values) in hertz. Computer simulation studies were conducted using the SIMEQ (Varian Instruments) program on a Varian FT80A NMR instrument. Mass spectral (MS) data were obtained at an ionizing voltage of 70 eV on a Hewlett–Packard 5930 Gas Chromatograph-Mass Spectrometer. High resolution mass spectra were performed by Dr. Ronald Grigsby at the Department of Biochemistry and Biophysics, Texas A&M University on a CEC21-110B double focusing magnetic sector spectrometer at 70 eV. Exact masses were determined by peak matching. Elemental analyses were obtained at Spang Microanalytical Laboratories, Eagle Harbor, Michigan.

The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. When dry solvents were required, methylene chloride was distilled from P_2O_5, and anhydrous ether was distilled and stored over Na metal.

All reactions were run under N_2 and all glassware dried before use unless otherwise noted. Thick-layer preparative chromatography was run on premade plates using Merck silica gel 60 PF–254 + 366 (Cat. No. 7748).

Preparation of 3-butenyl acetate (**1**). To an ice-cooled ether (250 mL) solution containing **7** (10.00 g, 0.14 mol) and Et_3N (20.0 mL, 0.15 mol), AcCl (20.0 mL, 0.28 mol) was slowly added. The reaction was maintained at this temp. for 2 hr, and then raised to room temp. for 18 hr. The mixture was filtered, the filtrate concentrated *in vacuo*, and the remaining oil distilled to give 12.00 g of **1** (75%): b.p. 120–122°; IR (neat, NaCl) 1750, 1650, 1240, 1040 cm^{-1}; NMR ($CDCl_3$) δ 2.05 (s, 3H), 2.20–2.60 (m, 2H), 4.12 (t, J = 7 Hz, 2H), 4.86–5.33 (m, 2H), 5.50–6.20 (m, 1H). (Found: C, 63.10; H, 8.74. Calc. for $C_6H_{10}O_2$: C, 63.13; H, 8.83%).

Preparation of tetrahydropyranyl ether of 3-buten-1-ol (**2**). To a soln containing **7** (10.00 g, 0.14 mol) and dihydropyran (12.00 g, 0.14 mol), conc. HCl aq (0.05 mL) was added. The reaction was stirred at room temp. (3 hr) and then distilled under reduced vacuum to give 20.0 g of **2** (90%): b.p. 183–184°; IR (neat, NaCl) 2950, 2880, 1650, 1210, 1140, 1130 cm^{-1}; NMR ($CDCl_3$) δ 1.35–1.96 (m, 6H), 2.15–2.60 (m, 2H), 3.22–4.16 (m, 4H), 4.52–4.70 (m, 1H), 4.88–5.32 (m, 2H), 5.55–6.30 (m, 1H). (Found: C, 69.19; H, 10.20. Calc. for $C_9H_{16}O_2$: C, 69.19; H, 10.32%).

Preparation of compound **5**. To an ether soln (100 mL) of **1** (2.00 g, 0.0175 mol), 3.00 g (0.020 mol) of *freshly prepared* and dried (P_2O_5) AgNCO was added. I_2 (4.40 g, 0.017 mol) was then added in 4 portions to the vigorously stirred mixture. After each addition, decolorization of the reddish-brown mixture slowly occurred. The first two increments of I_2 were added at 0°, while the last two portions were added at room temp. The mixture was filtered through a Celite bed, yielding a pale yellow soln. Dry ammonia gas was then bubbled (1 hr) through the soln resulting in the formation of a fine white powder. The desired compound was filtered, washed with ether (2 × 50 mL), and dried (P_2O_5) to yield 5.00 g of **5** (95%): m.p. 105° (dec); IR (KBr) 3460, 3180, 1690, 1600, 1140, 1100 cm^{-1}; NMR (WH-400 Bruker) (DMSO-d_6) δ1.48 (m, 1H, C_5–H_a), 1.50 (s, 3H, C_7–CH_3), 1.65 (br d, 1H, C_5–He), 3.23 (q, 1H, C_4–CHaHbI), 3.28 (q, 1H, C_4–CHaHbI), 3.68 (dd, 1H, C_6–He), 3.87 (m, 1H, C_4–H), 3.95 (td, 1H, C_6–Ha), 5.70 (s, 2H, C_7–$NHC(O)NH_2$), 6.46 (s, 1H, C_7–$NHC(O)NH_2$).

Summary of double irradiation experiments. Irradiation of the signals at δ6.46 ($NHC(O)NH_2$) and δ5.70 ($NHC(O)NH_2$) did not simplify the spectrum. Irradiation of the signal at δ3.95 (C_6–Ha) altered the doublet of doublets at δ3.68 (C_6–He), sharpened the broad doublet at δ1.65 (C_5–He) to a doublet of doublets, and altered the multiplet at δ1.48 (C_5–Ha). Irradiation of the signal at δ3.87 (C_4–H) simplified each of the quartets at δ3.28 (C_4–CHaHbI) and δ3.23 (C_4–HaHb) to a pair of doublets, and simplified the multiplet at δ1.48 (C_5–Ha). Partial irradiation of the signal at δ3.68 (C_6–He) simplified the doublet of triplets at δ3.95 (C_6–Ha) to a broad doublet, slightly sharpened the broad doublet at δ1.65 (C_5–He), and simplified the multiplet at δ1.48 (C_5–Ha). Irradiation of the signals at δ3.28 (C_4–CHaHbI) and δ3.23 (C_4–CHaHbI), respectively simplified the multiplet at δ3.87 (C_4–H). Irradiation of the signal at δ1.65 (C_5–He) simplified the triplet of doublets at δ3.95 (C_6–Ha) to a triplet, simplified the complex multiplet at δ3.87 (C_4–H) to a 5-line pattern, sharpened the doublet of doublets at δ3.68, and simplified the multiplet at δ1.48 (C_5–Ha). Irradiation of the signal at δ1.48 (C_5–Ha) altered the triplet of doublets at δ3.95 (C_6–Ha), simplified the complex multiplet at δ3.87 (C_4–H), simplified the doublet of doublets at δ3.68 (C_6–He) to a doublet and altered the broad doublet at δ1.65 (C_5–He).

MS *m/e* (rel%) 241(26), 181(24), 60(100), 44(61), 43(31). (Found: C, 27.88; H, 4.30; N, 9.34. Calc. for $C_7H_{13}IN_2O_3$: C, 28.01; H, 4.37; N, 9.36%).

Preparation of compound **6**. The preceding experiment was repeated using 2.00 g (0.013 mol) of **2**, 2.00 g (0.013 mol) of AgNCO, and 3.10 g (0.012 mol) of iodine. After filtration, and addition of ammonia, 3.50 g (80% yield) of the desired compound was collected: m.p. 102–110° (dec); IR (KBr) 3360, 3205, 2920, 1660, 1540, 1100 cm^{-1}. (Found: C, 34.90; H, 5.73; N, 9.00. Calc. for $C_{10}H_{19}IN_2O_3$: C, 35.10; H, 5.60; N, 8.19%).

Decomposition study of compound **5**. Compound **5** (2.08 g, 6.93 mmol) was dissolved in dimethyl sulfoxide (50 ml), and the colorless soln was allowed to remain at room temp. for 5 days. During this time the color of the soln turned to dark orange. The solution was then dissolved in CH_2Cl_2 (125 mL), and successively washed with basic 10% $Na_2S_2O_3$aq (2 × 75 mL), and water (50 mL). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. Thin-layer analysis of the residue indicated the presence of at least three compounds. The mixture was chromatographed on thick-layer silica gel plates using EtOAc-benzene (1:1) as the eluent. The first zone (R_f 0.50) collected was identified as **9**: yield 0.54 g (30%); IR (neat, NaCl) 3420, 2960, 1735, 1370, 1245, 1040 cm^{-1}; NMR (WH-400 Bruker) (DMSO-d_6) δ1.56–1.64 (m, 1H, C_3–Ha), 1.78–1.86 (m, 1H, C_3–Hb), 1.98 (s, 3H, C_4–$OC(O)CH_3$, 2.53 (s, 1H, C_7–OH), 3.23 (q, J = 5 Hz, 1H, C_1–Ha), 3.29 (q, J = 5 Hz, 1H, C_1–Hb), 3.44–3.49 (m, 1H, C_7–H), 3.98–4.11 (m, 2H, C_4–H_2); ^{13}C NMR (WH-400 Bruker) (DMSO-d_6) 15.79 (t, J = 150 Hz, C_1), 20.16 (q, J = 130 Hz, C_4–$OC(O)CH_3$), 34.69 (t, J = 127 Hz, C_3), 60.36 (t, J = 148 Hz, C_4), 65.91 (d, J = 143 Hz, C_2), 169.80 (s, C_4–$OC(O)CH_3$) ppm. MS *m/e* (rel intensity) 258 (0.6), 240 (10), 180 (65), 171 (13), 170 (6), 142 (6), 141 (8), 117 (47), 99 (7), 71 (100). Mol wt 257.9748 (Calc. for $C_6H_{11}IO_3$, 257.9755).

The second fraction (R_f 0.40) isolated was tentatively identified as **10**: yield 0.22 g (12%); IR (neat, NaCl) 3420, 2960, 1735, 1240, 1055, 1020 cm^{-1}; NMR ($CDCl_3$) δ1.68–2.08 (m, 2H), 2.18 (s, 3H), 3.29–3.49 (m, 2H), 3.58–3.85 (m, 2H), 4.65–5.10 (m, 1H); MS *m/e* (rel intensity) 180 (68), 117 (40), 88 (37), 71 (100), 57 (41); mol wt of fragments: 239.9640 (Calc. for $C_6H_9IO_2$, 239.9649), 179.9434 (Calc. for C_4H_5I, 179.9438).

Reaction of **5** *with water.* Compound **5** (1.00 g, 0.033 mol) was suspended in water (25 mL) and gently heated to reflux (2 hr). The mixture was extracted with CH_2Cl_2 (3 × 25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Distillation of the remaining oil at 70–71° (0.1 torr) gave 0.50 g (58%) of a 78:22 mixture of **9** and **10** (NMR analysis).

Reaction of **6** *with water.* Treatment of **6** (3.00 g, 0.009 mmol) with water (50 mL) according to the previous procedure gave 1.0 g of crude **12**. Distillation of the oil gave 0.30 g (20%) of **12**: b.p. 105–110° (5.0 torr); IR (neat, NaCl) 2960, 2880, 2730, 1730, 1350, 1140–1080, 910 cm^{-1}; NMR ($CDCl_3$) δ 1.42–2.16 (m, 6H), 2.22–2.64 (m, 2H), 3.40 (t, J=6Hz, 2H), 3.64–4.24 (m, 5H), 9.76 (t, J=1Hz, 1H); MS *m/e* (rel intensity) 101 (10), 85 (100), 71 (48), 70 (73), 57 (70).

Aldehyde **12** was further characterized as its 2,4-dinitrophenylhydrazone: m.p. 80–81°; IR (KBr) 3440, 3300, 1625, 1600, 1525, 1430, 1340 cm^{-1}; NMR ($CDCl_3$) δ 1.55–2.22 (m, 6H), 2.30–

2.68 (m, 2H), 3.35–3.64 (m, 2H), 3.64–4.28 (m, 5H), 7.64 (t, J=6Hz, 1H), 7.92 (d, J=10Hz, 1H), 8.28 (dd, J=10Hz, 3Hz, 1H), 9.04 (d, J = 3 Hz, 1H), 11.06 (s, 1H). (Found: C, 50.96; H, 5.75; N, 15.78. Calc. for $C_{15}H_{20}N_4O_6$: C, 51.13; H, 5.72; N, 15.90%).

Treatment of 1-Iodo-4-acetoxy-2-butanol (**9**) *with sodium hydride.* Sodium hydride (50% mineral oil dispersion, 0.10 g, 0.042 mol) was washed successively 3 times with 5 mL of ether and then an additional 5 mL of ether was added to the reaction vessel. Compound **9** (0.45 g; 0.0175 mol) in ether (50 mL) was then slowly added to the sodium hydride soln. The mixture was stirred at room temp. (2 hr), filtered and then concentrated *in vacuo* to yield **11** as a colorless oil: yield 0.15 g (66%): IR (neat, NaCl) 1745, 1240 cm^{-1}; NMR ($CDCl_3$) δ 1.59–1.99 (m, 2H), 2.05 (s, 3H), 2.39–3.18 (m, 3H), 4.19 (t, J=6Hz, 2H).

Preparation of 3,4-epoxybutyl acetate (**11**). To a CH_2Cl_2 (50 mL) solution containing **1**, 2.00 g (0.010 mol) of m-chloroperbenzoic acid (85%) was added. The mixture was stirred at room temp. overnight, filtered, and then the filtrate washed with 5% $NaHCO_3$ aq, dried (Na_2SO_4), and concentrated *in vacuo*. Distillation of the colorless oil at 90–91° (25 torr) gave 0.90 g (79%) of **11**: IR (neat, NaCl) 1745, 1240 cm^{-1}; NMR ($CDCl_3$) δ 1.59–1.99 (m, 2H), 2.05 (s, 3H), 2.39–3.18 (m, 3H), 4.19 (t, J=6Hz, 2H). (Found: C, 55.46; H, 7.71. Calc. for $C_6H_{10}O_3$: C, 55.37; H, 7.75%).

Preparation of benzyl ether of 3-buten-1-ol (**19**). Benzyl chloride (10 mL, 0.087 mol), **7** (2.00 g, 0.028 mol), and KOH (2.00 g, 0.036 mol) were mixed together, transferred to a heavy wall glass tube (250 × 40 mm), sealed with a torch, and heated in an oil bath (3 days) at 80°. The tube was opened, and the contents evaporated *in vacuo*, and then triturated with ether. The filtrate was concentrated and then distilled to give 2.70 g (60%) of **19**: b.p. 60–70° (5 torr); IR (neat, NaCl) 2860, 1645, 1500, 1460, 1365, 1105 cm^{-1}; NMR ($CDCl_3$) δ 2.10–2.66 (m, 2H), 3.32–3.56 (t, J = 6Hz, 2H), 4.43 (s, 2H), 4.82–5.36 (m, 2H), 5.48–6.18 (m, 1H), 7.26 (s, 1H). (Found (162.1038): C, 81.45; H, 8.66. Calc. for $C_{11}H_{14}O$ (162. 1045): C, 81.44; H, 8.70%).

Preparation of **21**. The procedure described for the synthesis of **5** was utilized using 2.00 g (0.012 mol) of **19**, 3.00 g (0.02 mol) of AgNCO, and 3.10 g (0.012 mol) of I_2. Decolorization of the reddish-brown mixture occurred rapidly with each addition of I_2. After filtration and addition of ammonia, no ppt formed. The soln was then placed in the freezer (1 day) which resulted in the precipitation of a pale yellow solid. The ppt was collected and recrystallized from benzene to give 0.50 g (12%) of **21**: m.p. 92–93°; IR (KBr) 3400, 1680, 1620, 1550, 1450, 1360, 1130, 1120, 920 cm^{-1}; NMR (DMSO-d_6) δ 1.99–2.18 (m, 2H), 3.42–3.63 (m, 3H), 3.80–3.98 (m, 1H), 4.48 (s, 2H), 5.03–5.34 (m, 1H), 7.34 (s, 5H), 8.73–9.36 (broad s, 3H). (Found: C, 41.38; H, 4.88; N, 8.17. Calc. for $C_{12}H_{17}N_2O_2I$: C, 41.39; H, 4.92; N, 8.05%).

The free base corresponding to **21** was obtained by neutralization of the salt **21** with 1N KOH (25 mL). The aqueous soln was then extracted with CH_2Cl_2 (3 × 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Recrystallization of the remaining clear oil with pentane gave 0.24 g (76%) of the free base: m.p. 51°; IR (KBr) 3360, 1685, 1660, 1615, 1500, 1460, 1425, 1380 cm^{-1}; NMR ($CDCl_3$) δ 1.70–2.10 (m, 2H), 3.16–4.16 (m, 4H), 4.50 (s, 2H), 4.90 (broad s, 2H), 4.40–5.00 (m, 1H), 7.26 (s, 5H). (Addition of D_2O to the sample resulted in rapid exchange of the peak at δ 4.90). MS (CI mode) P + 1 peak at *m/e* 221). (Found: C, 65.25; H, 7.35; N, 12.71. Calc. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.23; N, 12.72%).

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