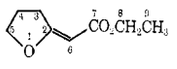
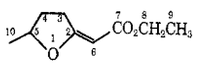
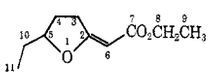
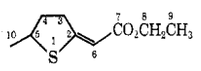
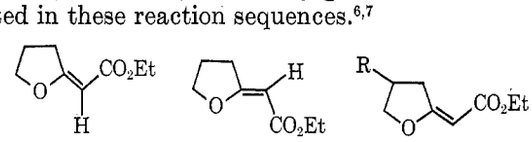
TABLE I

Product	Epoxide (sulfide) used	Bp, °C (0.5 mm)	Yield from ethyl acetoacetate, %
 1		55	54
 6		80	62
 7		100	60
 8		120	57

to the shift reagent increases and that this reagent coordinates on the ester carbonyl oxygen, it follows that isomer **1**, and not **9**, is the only geometrical isomer isolated in these reaction sequences.[6,7]



1 **9** **10**, R = Me or Et

Unsymmetrical epoxides (sulfides) were employed in this study to ascertain the direction of ring opening. In the reactions attempted, the least hindered attack lead to the products (**6**, **7**, and **8**) isolated and shown in Table I. The isomeric enol ether **10** (above) has not been detected by glc, lc, nmr-shift reagent, or ^{13}C studies. However, the yields of **6**, **7**, and **8** do not preclude the formation of such isomeric compounds.

Shift reagents were again employed to clearly show the methine proton resonance (C_5, see Table I for numbering) in compounds **6** and **7** and the absence of any methylene proton resonances that would be observed if isomeric compound **10** (R = Me or Et) were present.[6] In addition, the ^{13}C-proton decoupled nmr of furylidene **6** exhibited single resonances for C_5 and C_8 at the chemical shift expected confirming the homogeneity of this sample.[8] Studies related to the reactivity of these systems are now underway.

Experimental Section

General Method.—The dianion of ethyl acetoacetate was prepared in THF using Weiler's procedure.[2] To this was added the epoxide or sulfide (1.1 equiv) at 0° and the reaction mixture was immediately brought to room temperature. After 3 hr, water (10 ml/10 mmol of dianion) was added, then dilute HCl (aqueous 5%) until the mixture was neutral to weakly basic. This was extracted with ether (three times), and the combined organic phases were washed with saturated, aqueous sodium bicarbonate and brine and dried over sodium sulfate. The volatiles were removed *in vacuo* and the residue was combined with an equal weight of oxalic acid in methylene chloride (50 ml/g of residue) and heated under reflux for 2 hr in an inert atmosphere. After cooling, this mixture was washed with water, sodium bicarbonate (saturated, aqueous), and brine (saturated, aqueous) and dried over sodium sulfate. The volatiles were removed *in vacuo;* the residue was distilled at reduced pressure. (Glc, 5-ft 10% SE-30, 155–175°, and lc, Lichrosorb, cyclohexane–THF elution, analyses were conducted on all carbethoxymethylene compounds.)

Ethyl α-(Tetrahydro-2-furylidene)acetate (1).—Ethylene oxide (~2.2 g, 0.05 mol) was added to the dianion of ethyl acetoacetate (0.05 mol) in the manner described above. This afforded 4.6 g of **1**: 54%; λ_{max}^{film} 1701, 1642 cm^{-1}; λ_{max}^{EtOH} 245 nm (ε 13,400); pmr in $\delta_{TMS}^{CCl_4}$ 5.06 (t, J = 0.4 Hz, 1, C-6 H), 4.08 (t, J = 7.0 Hz, 2, C-5 H's), 3.95 (q, J = 7.0 Hz, 2, $-O-CH_2-CH_3$), 3.00 (m, 2, C-3 H's), 2.01 (m, 2, C-4 H's), 1.18 (t, J = 7.0 Hz, 3, $-OCH_2CH_3$); 156 (*m/e*); bp 50° (0.05 mm); cmr in ppm_{TMS}^{neat} 176.6 (C_2, see Table I for numbering), 167.5 (C_7), 89.0 (C_6), 71.8 (C_5), 58.8 (C_8), 30.2 (C_3), 23.6 (C_4), 14.5 (C_9).

Anal. Calcd for $C_8H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.31; H, 7.11.

Ethyl α-(Tetrahydro-5-methyl-2-furylidene)acetate (6).—The dianion of ethyl acetoacetate (0.05 mol) and propylene oxide (2.91 g, 0.05 mol) afforded 5.27 g of **6**: 62%; λ_{max}^{film} 1701, 1645 cm^{-1}; λ_{max}^{EtOH} 245 nm (ε 13,400); pmr in $\delta_{TMS}^{CCl_4}$ 5.04 (t, J = 0.4 Hz, 1, C-6 H), 4.26 (m, 1, CH_3CHO-), 3.82 (q, J = 7.2 Hz, 2, $-OCH_2-CH_3$), 2.87 (m, 2, C-3 H's), 1.97 (m, 2, $-CHCH_2CH_2-$), 1.17 (d, J = 7.0 Hz, 3, C-5 H), 1.04 (t, J = 7.2 Hz, 3, $-OCH_2CH_3$); 170 (*m/e*); bp 80° (0.05 mm); cmr in ppm_{TMS}^{neat} 176.1 (C_2), 167.5 (C_7), 89.0 (C_6), 80.3 (C_5), 58.3 (C_9), 31.1 (C_3), 30.6 (C_4), 20.1 (C_8), 14.3 (C_{10}).

Anal. Calcd for $C_9H_{14}O_3$: C, 60.74; H, 8.92. Found. C, 60.79; H, 8.99.

Ethyl α-(Tetrahydro-5-ethyl-2-furylidene)acetate (7).—The dianion of ethyl acetoacetate (0.05 mol) with 1,2 butylene oxide (3.60 g, 0.05 mol) afforded 5.52 g of **7**: 60%; λ_{mxx}^{film} 1709, 1645 cm^{-1}; λ_{max}^{EtOH} 245 nm (ε 13,500); pmr $\delta_{TMS}^{CCl_4}$ 5.04 (t, J = 0.4 Hz, 1, C-6 H), 4.14 (m, 1, C-5 H), 3.97 (q, J = 7.4, 2, $-OCH_2CH_3$); 2.95 (m, 2, C-3 H's), 2.00–1.62 (m, 4, C-4 H's and C-10 H's), 1.21 (t, J = 7.0, 3, CH_3CH_2-), 1.10 (t, J = 7.4, 3, $-OCH_2CH_3$); 184 (*m/e*); bp 100° (0.05 mm).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.38; H, 8.72.

Ethyl α-(Tetrahydro-5-methyl-2-thiophenylidene)acetate (8).—The dianion of ethyl acetoacetate (0.048 mol) with propylene sulfide (3.56 g, 0.048 mol) afforded 5.20 g of **8**: 57%; λ_{max}^{film} 1709, 1645 cm^{-1}; λ_{max}^{EtOH} 288 (ε 13,500); pmr δ_{TMS}^{CCl} 5.70 (t, J = 0.4 Hz, 1, C-6 H), 4.06 (q, J = 7.0 Hz, 2, $-OCH_2CH_3$), 3.58 (m, 1, C-5 H), 2.81 (m, 2, C-3 H's), 2.18 (m, 2, $-CHCH_2CH_2-$), 1.37 (d, J = 6.5 Hz, 3, CCH_3), 7.23 (t, J = 7.0 Hz, 3, $-OCH_2CH_3$); 1.86 (*m/e*); bp 120° (0.05 mm).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.05; H, 7.58. Found: C, 58.17; H, 7.47.

Acknowledgments.—This work was supported by the American Cancer Society Grant No. IC-83.

Registry No.—**1**, 40954-14-1; **6**, 40954-15-2; **7**, 40954-16-3; **8**, 40954-17-4;e thylene oxide, 75-21-8; litho sodio ethyl acetoacetate dianion, 40902-62-3; propylene oxide, 75-56-9; 1,2-butylene oxide, 106-88-7; propylene sulfide, 1072-43-1.

(6) The shift reagent used was trisdipivalomethanatoeuropium(III) or Eu(DPM)$_3$.

(7) H. M. McConnell, R. E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958), and references cited therein.

(8) The predicted and observed ^{13}C chemical shift of compound **6** are within experimental error based on model acrylate and tetrahydrofuran systems, as well as the parent unsubstituted furylidene **1**.

The Orientation in Alkaline Halogenation of 2-Butanone

ANTHONY C. KNIPE*

School of Physical Sciences, The New University of Ulster, Northern Ireland

BRIAN G. COX

Department of Chemistry, The University of Stirling, Scotland

Received May 22, 1973

In a recent communication[1] the products of reactions of 2-butanone (I) and its 1-bromo (II) and 3-bromo

(1) C. G. Swain and R. P. Dunlap, *J. Amer. Chem. Soc.*, **94**, 7204 (1972).

TABLE I

REACTIONS[a] OF 1- AND 3-SUBSTITUTED 2-BUTANONES IN AQUEOUS ALKALI AT 25°

Substituent	[Ketone]	[OH⁻]	[Bromine]	$k_{exp} \times 10^3$ sec^{-1}	$k \times 10^2$ M^{-1} sec^{-1}
1-Bromo (II)	<0.001	0.005[b]	0.0019	590	11,800
1-Hydroxy (IV)	0.0025	0.08	0.01	7.70	9.6
3-Bromo (III)	0.0025	0.08	0.01	13.6	17.9
3-Hydroxy (V)	0.0025	0.08	0.01	14.9	
1-Bromo (II)	0.0025	5.0×10^{-4}		76.5	3,060[c]
	0.005[d]	9.2×10^{-5}		3.00	3,260[e]
	0.005[f]	6.9×10^{-5}		2.17	3,150[e]
					Av 3,160[g]
3-Bromo (III)	0.005[h]	1.81×10^{-5}		2.39	13,200[e]
	0.005[i]	1.03×10^{-5}		1.25	12,200[e]
					Av 12,700[g]
H[j]	0.0025	0.1	0.0105	9.43	9.43

[a] Reactions with bromine were followed colorimetrically at 350 nm. Those with hydroxide ion alone were followed conductimetrically or by pH-Stat. All concentrations are in mol dm^{-3}. In each case the hydroxide concentration has been estimated with allowance for hydrolysis of bromine according to the equation $Br_2 + 2OH^- \rightleftharpoons Br^- + OBr^- + H_2O$. [b] An average value. [c] Hydroxide consumption was monitored conductimetrically; thus $k = k_{exp}/[\text{ketone}]$. [d] pH = 9.95, $\mu \simeq 1.5 \times 10^{-3}$, $\gamma = 0.97$. [e] Bromo ketone hydrolysis was monitored by pH-Stat titration; thus $k = k_{exp}/[OH^-]$. [f] pH = 9.82, $\mu \simeq 2.5 \times 10^{-3}$, $\gamma = 0.95$. [g] Second-order rate constant for hydroxide-promoted bromo ketone hydrolysis. [h] pH = 9.25, $\mu \simeq 8 \times 10^{-3}$, $\gamma = 0.92$. [i] pH = 9.00, $\mu \simeq 1.5 \times 10^{-3}$, $\gamma = 0.97$. [j] Reference 6.

(III) derivatives with aqueous NaOBr were reported. The results indicated clearly that, in the NaOH-induced bromination of I, in aqueous solution at 25°, each hydrogen on C-1 and C-3 is attacked equally fast to form the sodium enolate precursors of intermediates II and III which rapidly give mainly sodium propionate and sodium lactate, respectively, along with bromoform. These results are consistent with the traditional ketone halogenation mechanism and obviate the need for different rate-determining steps for alkaline halogenation and deuterium exchange.[2-4]

During a reexamination of the evidence for "Hal B I" and "Hal B II" ketone halogenation mechanisms,[2-4] we reached the following conclusions regarding the fate of II and III (under comparable halogenation conditions) by a study which is complementary to the product study outlined above.

The claim[5,6] that I halogenates much more rapidly at the 1 than at the 3 position is based entirely upon the low yields of α-halogenated propionic acids obtained among the products of reaction of I with NaOBr. We suspected, however, that hydroxide-induced nucleophilic displacement of Br^- from either II or III might compete with their multihalogenation and subsequent fragmentation by the haloform reaction.

For each bromo ketone we therefore determined the product of reaction with hydroxide ion and compared the rate of this reaction with that which occurs in the presence of bromine also.

Reaction of II and III with aqueous NaOH gave only the corresponding 1- and 3-hydroxy ketones (IV and V), respectively. The reactions were monitored by continuous conductivity measurement. Rates of bromine uptake by solutions of II and III in aqueous NaOBr were determined from the decrease with time of the intensity of absorption at 350 nm. Reactions were initiated by both stop-flow and conventional techniques where appropriate. The results are in Table I.

The rate of hydrolysis ($k_{OH^-} = 31.6\ M^{-1}$ sec^{-1}) of II is of the same order of magnitude as that determined for its bromination ($k = 118\ M^{-1}$ sec^{-1}) in aqueous hydroxide; thus it can be shown that the latter rate constant must actually represent the sum of the rate constants for the competing reactions ($k = k_{OH^-} + k_{Br_2}$) and therefore $k_{Br_2} = 86.4\ M^{-1}$ sec^{-1}. The much slower subsequent bromination of the minor product has been monitored and both the bromination rate constant and amount of bromine consumed (relative to the initial fast bromination) are consistent with the competitive formation of IV (27%) during the initial fast step.

The rate of bromination of IV was measured independently for comparison. The rate constants for bromination of II and IV, respectively, are 916 and 1.02 times as fast as that for the bromination of I. The former ratio is comparable with an 800-fold increase in the catalytic rate constant for hydroxide-induced deprotonation brought about by monochlorination of acetone[7] and accounts for the exclusive formation[1] of bromoform and propionic acid upon bromination of II in aqueous NaOBr.

It was, however, found that the *apparent* uptake of bromine by III in aqueous NaOBr is very slow in comparison with the rate of displacement of bromide ion and it is clear that the observed halogenation is that of V which is formed in an initial fast step. It was noted that 13.3% of the overall halogen consumption also occurred rapidly during this initial period and, by analogy with the discussion above, it can be argued that 3-bromo-2-butanone initially undergoes competitive hydrolysis (86.7%) and bromination (13.3%) under these conditions. Thus the bromination rate constant must equal *ca.* $(k_{OH^-} \times 13.3)/86.7 = 19.5\ M^{-1}$ sec^{-1}. An approximate estimate of the rate of the fast step gave $t_{1/2} = 1.3 \pm 0.2$ sec, $k_{exp} = 5.3 \pm 0.8$ sec^{-1} and $k = k_{OH^-} + k_{Br_2} = 133 \pm 20\ M^{-1}$ sec^{-1} which is consistent with this interpretation.

Since the rate of bromination is much slower than the rate of displacement of bromide ion, α-halogenated propionic acids are not the expected products of halogenative degradation of III in aqueous hydroxide. The ultimate products of reaction under these condi-

(2) C. Rappe, *Acta Chem. Scand.*, **20**, 1721 (1966).
(3) C. Rappe, *Acta Chem. Scand.*, **21**, 857, 1823 (1967).
(4) C. Rappe, *Acta Chem. Scand.*, **22**, 219 (1968).
(5) C. F. Cullis and M. H. Hashmi, *J. Chem. Soc.*, 2512 (1956); 1548 (1957).
(6) C. F. Cullis and M. H. Hashni, *J. Chem. Soc.*, 3080 (1957).
(7) R. P. Bell and A. Lidwell, *Proc. Roy. Soc., Ser. A*, **176**, 88 (1940).

tions will be those derived from V which we have found to brominate at a rate comparable with that of I.

The kinetic results support the failure of Swain and Dunlap[1] to detect appreciable deuterium incorporation in unreacted III under conditions where it had undergone 57% conversion to V in alkaline D_2O.

Experimental Section

Materials.—3-Bromo-2-butanone [n^{20}D 1.4575, bp 85° (118 mm)] and 1-bromo-2-butanone [n^{20}D 1.4676, bp 104° (118 mm)] were prepared by the procedure of Catch, *et al.*[8] Upon hydrolysis of the corresponding bromobutanones (5 g, 0.033 mol) in aqueous sodium hydroxide (100 ml, 2 *M*) at room temperature there was obtained 1-hydroxy-2-butanone (n^{20}D 1.4271, bp 158°) and 3-hydroxy-2-butanone (n^{20}D 1.4168, bp 144°), respectively, in high yield.

Kinetics.—Reactions of the bromobutanones with sodium hydroxide were initiated using a Durrum Gibson stop-flow apparatus fitted with a T-jump cell. The syringes contained bromo ketone (0.005 *M*) and sodium hydroxide (0.001 *M*), respectively. Reactions were followed by monitoring change in conductivity between the plates of the T-jump compartment.[9] A Radiometer automatic titration assembly was also used for an alternative pH-Stat procedure.

Reactions of 1- and 3-bromo- and of 1- and 3-hydroxy-2-butanone (0.005 *M*) with bromine (0.024 *M*) in aqueous hydroxide (0.1 *M*) were initiated by stop-flow techniques and followed by colorimetric observation of the change in absorbance at 398 nm. Stop-flow results were consistent with those obtained using a Gilford 2400 spectrometer to monitor (at 350 nm) consumption of BrO^- in a solution which initially contained hydroxide (0.01 *M*), bromine (0.003 *M*), and bromo ketone (<0.001 *M*).

Registry No.—I, 78-93-3; II, 816-40-0; III, 814-75-5; IV, 5077-67-8; V, 513-86-0.

(8) J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

(9) Unpublished procedure: A. C. Knipe and R. L. Tranter.

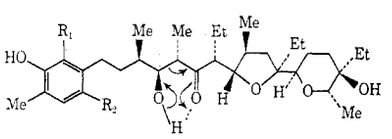
Pyrolytic Cleavage of Antibiotic X-537A and Related Reactions

JOHN W. WESTLEY,* RALPH H. EVANS, JR., THOMAS WILLIAMS, AND ARTHUR STEMPEL

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received April 23, 1973

Investigations into the structure,[1] biosynthesis,[2] nitration,[3] and antibacterial activity[4] of antibiotic X-537A (**1a**) have resulted in the transformation of the



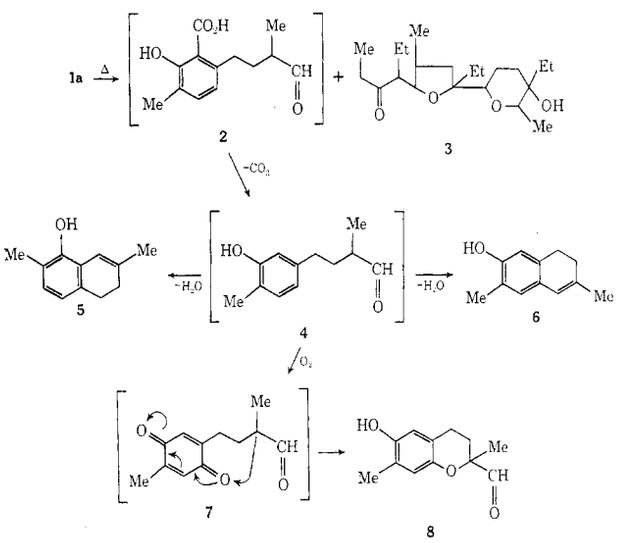
1a, $R_1 = CO_2H$; $R_2 = H$
b, $R_1 = CO_2H$; $R_2 = Br$
c, $R_1 = R_2 = NO_2$

antibiotic into a number of novel compounds. The isolation and characterization of several additional degradation products from **1a** is the subject of this report.

The most useful degradation reaction in the structural and biosynthetic studies on **1a** was the base-catalyzed retroaldol cleavage[1,2] reaction. A competing dehydration reaction[3,4] restricted the yield of the retroaldol ketone **3** to approximately 70%. However, pyrolysis of **1a** has now been shown to give a quantitative yield of **3**, indicating that under pyrolytic conditions, **1a** is degraded *solely via* the retroaldol cleavage route. This reaction is presently under investigation as the basis of a possible pyrolysis–glc method for the assay of **1a**.

The other cleavage product **2** from the pyrolysis of **1a** (Scheme I) spontaneously decarboxylates to the

SCHEME I



phenol **4**, which in turn cyclizes with dehydration to a mixture of 5,6-dihydro-2,7-dimethyl-1-naphthol (**5**) and a 7,8-dihydro-3,6-dimethyl-2-naphthol (**6**). When the antibiotic was heated at 220° for 1 hr in an open tube, 3,4-dihydro-2,7-dimethyl-6-hydroxy-2*H*-1-benzopyran-2-carboxaldehyde (**8**) was isolated in addition to **3**, **5**, and **6**. Production of **8** suggests that, in the presence of air, partial oxidation of the intermediate phenol **4** to a quinone **7** occurred prior to cyclization.

Conversion of **1a** to the 5-bromo derivative **1b** was described in an earlier report.[4] Pyrolysis of **1b** also gave a quantitative yield of the retroaldol ketone **3** together with 3,6-dimethyl-2-naphthol (**9**)[5] and 4-bromo-5,6-dihydro-2,7-dimethyl-1-naphthol (**10**) (Scheme II). The conversion of **1b** into the naphthol **9** in contrast to the 7,8-dihydronaphthol **6** produced on pyrolysis of **1a** was the result of an additional elimination step (loss of HBr) in the case of the bromo derivative. In an analogous reaction, base-catalyzed retroaldol cleavage of **1b** gave 3,6-dimethyl-2-hydroxy-1-naphthoic acid (**11**) whereas base cleavage of **1a** is known[1] to produce the 7,8-dihydro derivative of **11**. Another interesting example of this base cleavage–cyclization reaction was the facile conversion of the dinitrodecarboxy derivative of antibiotic X-537A (**1c**) to 6-hydroxy-2,7-dimethyl-5-nitroquinoline.[3]

(1) J. W. Westley, R. H. Evans, Jr., T. Williams, and A. Stempel, *Chem. Commun.*, 71 (1970).

(2) J. W. Westley, R. H. Evans, Jr., D. L. Pruess, and A. Stempel, *Chem. Commun.*, 1467 (1970).

(3) J. W. Westley, J. Schneider, R. H. Evans, Jr., T. Williams, A. D. Batcho, and A. Stempel, *J. Org. Chem.*, **36**, 3621 (1971).

(4) J. W. Westley, E. P. Oliveto, J. Berger, R. H. Evans, Jr., R. Glass, A. Stempel, V. Toome, and T. Williams, *J. Med. Chem.*, **16**, 397 (1973).

(5) R. Weisgeiner and O. Kruber, *Chem. Ber.*, **52**, 367 (1919).