vapor, ammonia, and carbon dioxide served as calibrating gases for the spectrometer.

Raman spectra of the solid samples (several milligrams) were obtained with a Cary Model 81 spectrophotometer equipped with a helium–neon CW laser source. Scattering from samples placed in a conical holder was viewed coaxially along the laser beam by the monochromator. Spectral slit widths varied from 2.5 to 3 cm^{-1}. Spectra were calibrated with atomic neon lines and are probably accurate to ± 2 cm^{-1}.

A crucial point in obtaining quality Raman spectra is to eliminate all traces of fluorescing material from the samples. For the systems examined in this study, sublimation of the samples under vacuum appears to be most effective. Under some circumstances, repeated sublimation is necessary.

The dimers were prepared by previously published procedures as indicated in Table VI.

TABLE VI

Dimer	Mp, °C	Lit. mp, °C	Lit. reference
1	126–126.5	125–126.5	4
2	69–70	66–67	4
3	51–52	53–55	5
4	77–78	79–80	5
5	146–147	146–147	6
6	68–69	68–69	6
7	118.5–190	188.5–190	7
9[a]	112–113.5	112–113.5	7
8[a]	211–213	211–213	7
10	286–288	293	9
11	229–235	225–266	10

[a] The structural assignments of **8** and **9** are tentative.

Registry No.—**1**, 2065-43-2; **2**, 21876-87-9; **3**, 712-27-6; **4**, 21876-89-1; **5**, 21876-90-4; **6**, 21927-71-9; **7**, 21899-39-8; **8** and **9**, 21865-12-3; **10**, 21899-40-1; **11**, 17062-18-9.

Acknowledgments.—We wish to thank Miss Glenna Christie for her assistance in obtaining the Raman spectra. Also, we wish to thank Dr. O. Chapman for kindly supplying samples of isophorone dimers.

Studies in Alkylation. II. Reactions of Epoxyalkyl Bromides[1]

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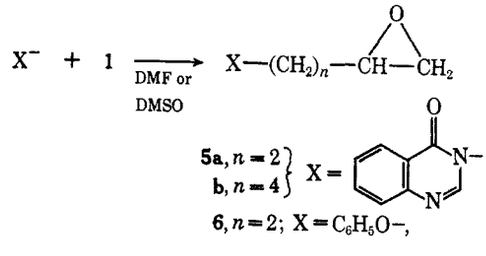
Alkylation reactions of the bifunctional ω-bromo-1,2-epoxyalkanes have been found to be markedly dependent upon the solvent and the nature of the nucleophile. In alcoholic media, compounds which generate an anion with a localized electron pair react by opening the oxirane ring to give β-hydroxy-ω-bromoalkyl derivatives. In aprotic solvents, these same compounds react by displacement of bromide ion to give epoxyalkyl derivatives. Compounds which generate anions with a delocalized electron pair react exclusively by displacement of bromide ion. Subsequent cyclization reactions may occur in alcohol if the initial product can be converted into an anion and if the proper spatial relationship exists between the epoxy group and the nucleophilic carbon.

As part of a program to prepare compounds for screening as antimalarial agents,[2] a series of amino alcohols of general structure **4** was required. Our approach to the synthesis of these compounds involved condensation of appropriate nucleophiles with the homologous ω-bromo-1,2-epoxyalkanes **1**, followed by aminolysis of the bromo alcohol **2** (Scheme I). During the course of this work novel solvent and nucleophile dependent reactions of the epoxyalkyl bromides **1** were encountered.

Results

The anions of 4(3H)-quinazolone and of phenol were found to react with an excess of 4-bromo-1,2-epoxybutane (**1a**) in alcohol to give the expected products, the 4-bromo-2-hydroxybutyl derivatives **2a** and **3** (Table I). A similar reaction with 6-bromo-1,2-epoxyhexane (**1c**) and 4(3H)-quinazolone gave the homologous product 3-(6-bromo-2-hydroxyhexyl)-4-quinazolone (**2b**). These compounds were characterized by infrared spectrometry (hydroxyl absorption at 3350 cm^{-1}), nmr chemical shifts and coupling constants (Table II), and mass spectrometry (Table III).

When the same anions were allowed to react with the ω-bromo-1,2-epoxyalkanes in dimethylformamide or dimethyl sulfoxide, bromine free products were obtained. Elemental and spectrometric analyses identified the products as the epoxyalkyl derivatives **5** and **6**



(Table IV). The infrared spectra were free of hydroxyl absorption. The nmr spectra established that the oxirane ring has been retained; chemical shifts and coupling constants (Table V) were in close agreement with published values for mono substituted epoxides.[3] Prominent molecular ions were observed in the mass spectra as well as daughter ions corresponding to known fragmentation mechanisms for structures of this type (Table VI).[4]

Diethyl sodiomalonate (**7**, R = H) and diethyl sodiomethylmalonate (**7**, R = CH_3) also were found to react with the epoxyalkyl bromides in dimethylformamide to give the corresponding epoxyalkylmalonates **8** (Table IV), as evidenced by the nmr chemical

(1) This paper was presented before the Division of Organic Chemistry, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., September 1968, Abstract ORGN 71.

(2) M. Fishman and P. A. Cruickshank, *J. Heterocycl. Chem.*, **5**, 467 (1968).

(3) E. Lippert and H. Prigge, *Ber. Bunsenges. Phys. Chem.*, **67**, 415 (1963).

(4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, pp 450–458.

TABLE I

ω-BROMO-β-HYDROXYALKYL DERIVATIVES

X-CH_2-CHOH-$(CH_2)_n$-Br

Compound	X	n	Reaction solvent[a]	Reaction time, hr	Yield, %	Mp or bp (mm),[b] °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2a	3-Quinazolonyl[c]	2	M	3	56	142.5–145[d]	$C_{12}H_{13}BrN_2O_2$	48.5	4.38	9.43	48.9	4.38	9.66
2a	3-Quinazolonyl[c]	2	B	3	8[e]	143–145[d]							
2b	3-Quinazolonyl[c]	4	M	240	23	89–90[d]	$C_{14}H_{17}BrN_2O_2$	51.7	5.23	8.62	51.7	5.47	8.37
3	C_6H_5O	2	E	3	46	107(0.06)	$C_{10}H_{13}BrO_2$	49.0	5.31	32.7 (Br)	49.3	5.52	33.0 (Br)

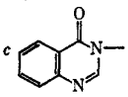
[a] M, methanol; B, *t*-butyl alcohol; E, ethanol. [b] Uncorrected. [c]  [d] Recrystallized from benzene. [e] One equivalent of 4-bromo-1,2-epoxybutane.

TABLE II

NMR DATA ON ω-BROMO-β-HYDROXYALKYL DERIVATIVES[a]

X-CH_2-CHOH-$(CH_2)_n$-Br

Compound	CH_2Br[b]	$(CH_2)_{n-1}$[c]	X-CH_2[c]	CHOH[c]	CHOH[d]	X[c]
2a	3.52[e]	2.10 (2)	4.32 (2)	3.52[e]	4.90 (1)	7.42 (3)
						7.92 (2)
2b	3.42[e]	1.4–2.1 (6)	4.18 (2)	3.42[e]	4.72 (1)	7.43 (3)
						8.00 (2)
3	3.53 (2)	2.03 (2)	3.88 (2)	4.06 (1)	3.08 (1)	6.92 (3)
						7.27 (2)

[a] $CDCl_3$ solution using tetramethylsilane (TMS) as internal standard; chemical shift values are in parts per million downfield from TMS; relative areas are in parenthesis. [b] Triplet; J = 7.0 Hz. [c] Multiplet centered at value given. [d] Singlet. [e] Total integral for three protons.

TABLE III

SIGNIFICANT IONS IN THE MASS SPECTRA OF ω-BROMO-β-HYDROXYALKYL DERIVATIVES[a]

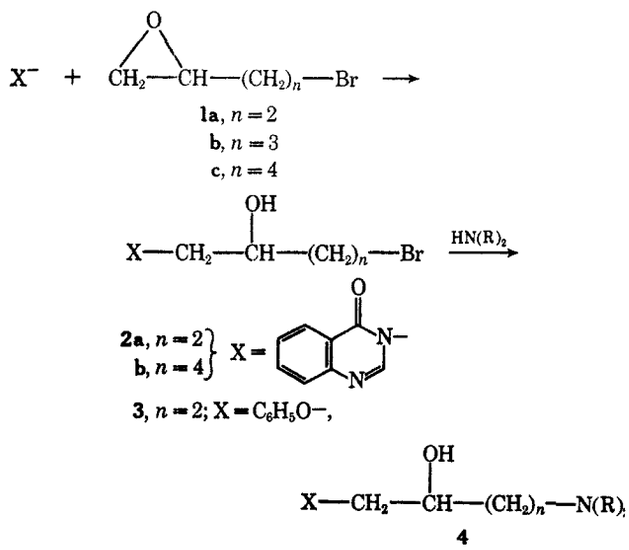
X-CH_2-CHOH-$(CH_2)_n$-Br

A

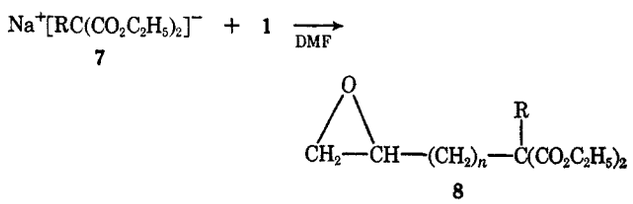
Ion	Compound 2a	Compound 2b	Compound 2c
M^+	298 (1)	326 (0.5)	246 (5)
	296 (1)	324 (0.5)	244 (5)
A^+	139 (1)	167 (25)	139 (3)
	137 (1)	165 (25)	137 (3)
$[XCH_2 + H]^+$	160 (43)	160 (55)	108 (14)
$[X + 2H]^+$	147 (100)	147 (100)	
$[X + H]^+$			94 (100)

[a] Mass spectra were obtained at an ionizing voltage of 70 eV.

SCHEME I



shifts and coupling constants (Table V). Only diethyl 5,6-epoxyhexane-2,2-dicarboxylate gave a molecular ion in the mass spectrometer, but daughter ions con-



a, R = H; n = 2
b, R = H; n = 3
c, R = H; n = 4
d, R = CH_3; n = 2

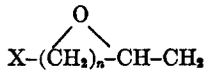
taining the side-chain moiety were observed in all cases (Table VII). These ions, together with all other prominent ions in the mass spectra, were consistent with published fragmentation patterns for malonate esters.[5]

When the epoxyalkyl bromides and the sodiomalonates were allowed to react in ethanol, bromine-free products were obtained rather than bromo alcohols analogous to **2**. With diethyl sodiomalonate and 6-bromo-1,2-epoxyhexane (**1c**), and with diethyl sodiomethylmalonate and 4-bromo-1,2-epoxybutane (**1a**), the products were identified as the epoxyalkyl derivatives **8c** and **8d**. However, the major products obtained from diethyl sodiomalonate and 4-bromo-1,2-epoxybutane (**1a**) and 5-bromo-1,2-epoxypentane (**1b**) did not contain an oxirane ring, although some of the epoxyalkyl derivative **8a** was observed by gas–liquid phase chromatography in the former case.

(5) J. H. Bowie, D. H. Williams, S. D. Lawesson, and G. Schroll, *J. Org. Chem.*, **31**, 1792 (1966).

TABLE IV

EPOXY COMPOUNDS



Compound	X	n	Reaction solvent[a]	Yield, %	Mp or bp (mm)[b] °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
5a	3-Quinazolonyl[c]	2	DMF	40	102–104[d]	$C_{12}H_{12}N_2O_2$	66.7	5.59	13.0	66.9	5.57	12.8
5a	3-Quinazolonyl[c]	2	DMSO	68	101–104[d]							
5b	3-Quinazolonyl[c]	4	DMF	91	72–75[d]	$C_{14}H_{16}N_2O_2$	68.8	6.60	11.5	69.1	6.72	11.3
6	C_6H_5O	2	DMF	70	58 (0.06)	$C_{10}H_{12}O_2$	73.1	7.37		73.0	7.30	
8a	$(C_2H_5O_2C)_2CH$	2	DMF	81	87–94 (0.07)	$C_{11}H_{18}O_5$	57.4	7.88		57.3	8.00	
8b	$(C_2H_5O_2C)_2CH$	3	DMF	59	98 (0.06)	$C_{12}H_{20}O_5$	59.0	8.25		59.3	8.32	
8c	$(C_2H_5O_2C)_2CH$	4	DMF	64	109 (0.06)	$C_{13}H_{22}O_5$	60.4	8.59		60.7	8.73	
8c	$(C_2H_5O_2C)_2CH$	4	M	33	108 (0.06)							
8d	$(C_2H_5O_2C)_2C(CH_3)$	2	DMF	81	80 (0.05)	$C_{12}H_{20}O_5$	59.0	8.25		59.3	8.51	
8d	$(C_2H_5O_2C)_2C(CH_3)$	2	M	42	78 (0.05)							

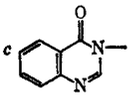
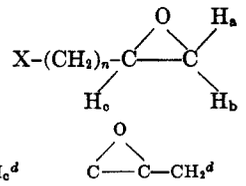
[a] DMF, dimethylformamide; DMSO, dimethyl sulfoxide; M, methanol. [b] Uncorrected. [c]  . [d] Recrystallized from benzene.

TABLE V

NMR DATA ON EPOXY COMPOUNDS[a]

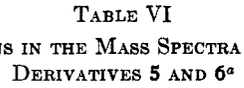


Compound	H_a[b]	H_b[c]	H_c[d]	[d]	CH_3–X	$(CH_2)_{n-2}$[d]	$CH(CO_2C_2H_5)_2$[e]	CH_3[f]
1a	2.58 (1)	2.82 (1)	3.09 (1)	2.10 (2)	3.55 (2)[g]			
1b	2.47 (1)	2.72 (1)	2.87 (1)	[h]	3.49 (2)[g]	[h]		
1c	2.48 (1)	2.76 (1)	2.90 (1)	1.88 (2)	3.44 (2)[g]	1.61 (4)		
5a	2.52 (1)	2.78 (1)	3.01 (1)	2.00 (2)	4.20 (2)[g]			
5b	2.49 (1)	2.75 (1)	2.96 (1)	1.90 (2)	4.06 (2)[g]	1.65 (4)		
6	2.44 (1)	2.69 (1)	3.02 (1)	1.89 (2)	3.99 (2)[g]			
8a	2.49 (1)	2.75 (1)	2.92 (1)	2.00 (2)	1.65 (3)[d]		3.42 (1)	
8b	2.49 (1)	2.75 (1)	2.92 (1)	2.00 (2)	1.60	(4)[d]	3.36 (1)	
8c	2.44 (1)	2.71 (1)	2.88 (1)	1.90 (2)	1.51	(6)[d]	3.32 (1)	
8d	2.49 (1)	2.75 (1)	2.92 (1)	2.00 (2)	1.65 (2)[d]			1.41 (3)

[a] $CDCl_3$ solution using tetramethylsilane (TMS) as internal standard; chemical shift values are in parts per million downfield from TMS; relative areas are in parentheses. [b] Quartet; $J_{gem} = 5.0$, $J_{trans} = 2.2$–2.6 Hz. [c] Quartet; $J_{gem} = 5.0$, $J_{cis} = 4.0$ Hz. [d] Multiplet centered at value given. [e] Triplet; $J = 7.3$ Hz. [f] Singlet. [g] Triplet; $J = 6.5$–7.0 Hz. [h] Broad unresolved multiplet 1.5–2.3 (4).

TABLE VI

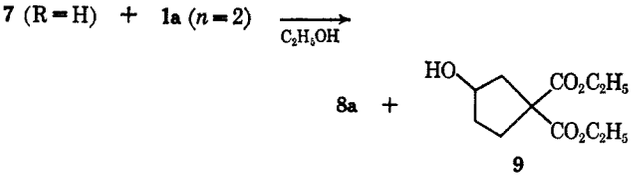
SIGNIFICANT IONS IN THE MASS SPECTRA OF EPOXYALKYL DERIVATIVES 5 AND 6[a]



Ion	Compound 5a	Compound 5b	Compound 5c
M^+	216 (20)	244 (27)	164 (11)
M^+-CH_2OH	185 (12)	213 (3)	133 (5)
$[X(CH_2)_n]^+$	173 (11)	201 (6)	121 (3)
$[XCH_2 + H]^+$	160 (19)	160 (74)	
XCH_2^+	159 (21)		107 (13)
$[X + 2H]^+$	147 (100)	147 (52)	
$[X + H]^+$	146 (82)	146 (100)	94 (100)

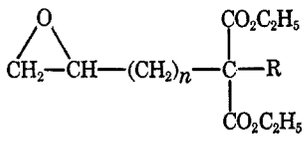
[a] Mass spectra were obtained at an ionizing voltage of 70 eV.

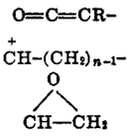
The product from the reaction of diethyl sodiomalonate and 4-bromo-1,2-epoxybutane (**1a**) in ethanol was isomeric with the epoxyalkyl derivative **8a**. Hydroxyl absorption (3450 cm^{-1}) and ester absorption (1725 cm^{-1}) were present in the infrared spectrum. In the nmr spectrum the presence of two chemical shifts for the methylene protons of the ethyl esters (δ 4.20 and 4.22 ppm) indicated different environments for the two ester groups. One rapidly exchangeable proton at δ 3.02 ppm confirmed the presence of a hydroxyl group. Based on this information, the product was identified as diethyl 3-hydroxycyclopentane-1,1-dicarboxylate **9**; the mass spectrum and the balance of the nmr spectrum were consistent with this structure assignment.



The product from the reaction of diethyl sodiomalonate and 5-bromo-1,2-epoxypentane (**1b**) in ethanol was devoid of hydroxyl absorption in the infrared, but did have absorption ascribable to a five-membered lactone (1770 cm^{-1}) and an ester (1735 cm^{-1}). The nmr chemical shifts, coupling constants, and proton integrals confirmed the presence of one ethyl ester group and suggested the presence of a methylene group attached to an oxygen atom and to an asymmetric carbon atom with one hydrogen. This data is consistent with

TABLE VII
SIGNIFICANT IONS IN THE MASS SPECTRA OF THE EPOXYALKYLMALONATES[a]

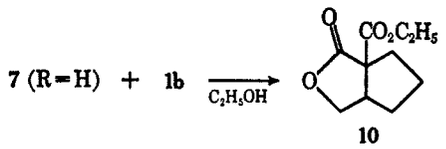




Compound	n	M+	M+-OEt	CH—CH2
8a	2		185 (6)	111 (54)
8b	3		199 (4)	125 (14)
8c	4		213 (4)	139 (11)
8d	2	244 (3)	199 (8)	125 (35)

[a] Mass spectra were obtained at an ionizing voltage of 70 eV.

structure **10**, ethyl 1-oxo-2-oxabicyclo[3.3.0]octane-8-carboxylate. The remainder of the nmr spectrum and the mass spectrum also support this structure.



10

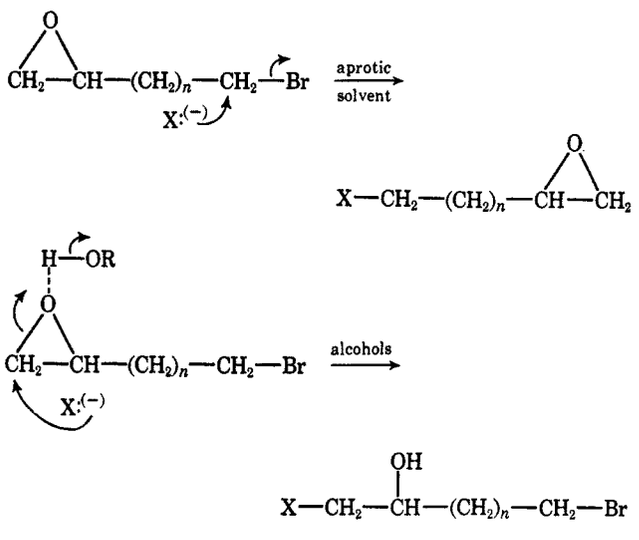
Discussion

Although reactions of α-halo epoxides have been extensively studied, the chemistry of the homologs has received scant attention. Pariselle[6] has reported the synthesis of 4-bromo-1,2-expoxybutane and investigated its reaction with diethyl malonate. Paul[7] has studied the conversion of 5-chloro-1,2-epoxypentane into 3-hydroxypiperidine by reaction with amines. None of these investigations noted any solvent effects in the reactions of the epoxyalkyl halides.

Nucleophilic displacements on 1-halo-2,3-epoxypropanes (epihalohydrins) afford either the 2-hydroxy-3-halopropyl or the 2,3-epoxypropyl derivatives as primary products. The former clearly arises by preferential attack at the primary carbon of the epoxide ring, but the latter could be formed either by direct displacement of the halogen or *via* the halohydrin by reclosure of the oxirane ring. In an effort to determine the mechanism of reactions affording oxirane products from epihalohydrins, Waters and Vander Werf[8] studied the reaction of alcoholic sodium alkoxides with 3-bromo-1,2-epoxybutane and 1-bromo-2,3-epoxybutane. The product in each case was the corresponding 1-alkoxy-2,3-epoxybutane, establishing that the attack occurred at the primary carbon atom regardless of the nature of the substituent on that carbon. With one exception subsequent studies with other nucleophilic agents have corroborated these results.[9] Rowton and Russell,[10] however, found that phenol in aqueous sodium hydroxide reacted with the α-bromoepoxybutanes by initial attack on the epoxide carbon atom remote from the halogen bearing carbon to give isomeric α-phenoxyepoxybutanes. Thus a solvent effect was indicated whereby displacement at the oxirane ring was favored regardless of steric effects.

In our studies with ω-halo-1,2-epoxyalkanes both reactive sites are on primary carbon atoms, thus eliminating the steric problems encountered by Waters and Vander Werf. The results with relatively simple nucleophiles containing an electron pair in a sp^2 hybrid orbital establish a pronounced solvent dependency which can best be explained by hydrogen bonding effects. The localized nucleophilic site in the anions of phenol and 4(3H)-quinazolone readily affords a specific association with the alkylating agent in the transition state. In aprotic solvents the carbon–bromine bond is more susceptible to nucleophilic attack, resulting in formation of epoxyalkyl products. In alcoholic solvents hydrogen bonding at the oxirane group weakens the carbon–oxygen bond such that nucleophilic attack at this site becomes favored (Scheme II). Evidence for this hydrogen bonding is observed in the infrared spectrum of a mixture of 6-bromo-1,2-epoxyhexane (0.2 *M*) and methanol (0.01 *M*) in carbon tetrachloride; the absorbance of the free hydroxyl at 3639 cm^{-1} is reduced 37% from that of methanol alone (0.01 *M*) in carbon tetrachloride; and a broad bonded hydroxyl appears at 3523 cm^{-1}. An infrared spectrum of methanol and 1-bromohexane in carbon tetrachloride did not show evidence of hydrogen bonding effects. Lippert and Prigge[11] have studied the formation of hydrogen bonds between oxiranes and phenol by similar infrared techniques.

SCHEME II



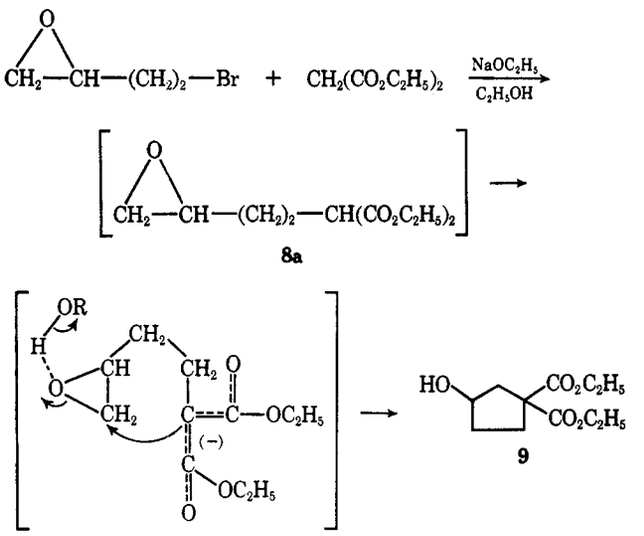
With anions in which the charge is delocalized, *e.g.*, diethyl sodiomalonate, solvent effects do not seem to be important in the initial reaction with ω-bromo-1,2-epoxyalkanes. Exclusive formation of diethyl epoxyalkylmalonates **8** is observed from diethyl sodiomethylmalonate and 4-bromo-1,2-epoxybutane and from diethyl sodiomalonate and 6-bromo-1,2-epoxyhexane in alcoholic or aprotic solvents. The more diffuse as-

(6) H. Pariselle, *Ann. Chim. Phys.*, **24**, 315 (1911).
(7) R. Paul, *Bull. Soc. Chim. Fr.*, 827 (1945); R. Paul and S. Tchelitcheff, *ibid.*, 385 (1946).
(8) R. C. Waters and C. A. Vander Werf, *J. Amer. Chem. Soc.*, **76**, 709 (1954).
(9) T. I. Temnikova and B. A. Ershov, *Zh. Obshch. Khim.*, **32**, 2436 (1962); **33**, 1405 (1963); T. I. Temnikova and S. N. Semenora, *ibid.*, **35**, 27 (1965); T. I. Temnikova, B. A. Ershov, and A. I. Arditi, *ibid.*, **35**, 788 (1965); T. I. Temnikova and S. N. Semenora, *Zh. Org. Khim.*, **2**, 395 (1966).
(10) R. L. Rowton and R. R. Russell, *J. Org. Chem.*, **23**, 1057 (1958).
(11) E. Lippert and H. Prigge, *Ann. Chem.*, **659**, 81 (1962).

sociation between the malonate anion and the alkylating agent apparently allows the steric effects of the solvated reacting species to be the controlling factor. Thus in alcoholic media the halogen-bearing portion of the epoxyalkyl bromides is less solvated and therefore less sterically hindered; in aprotic media the greater reactivity of the carbon–bromine bond as opposed to the nonsolvated epoxide again is the controlling factor.

The reaction of diethyl sodiomalonate and 4-bromo-1,2-epoxybutane in aprotic solvent gave diethyl 4,5-epoxypentane-1,1-dicarboxylate (**8a**) as expected. However, in alcohol these same reactants gave a mixture of two products in which the epoxyalkylmalonate **8a** was the minor component. Formation of the major product, diethyl 3-hydroxycyclopentane-1,1-dicarboxylate (**9**), must involve secondary ionization of the epoxyalkylmalonate, which then can undergo an intramolecular displacement at the primary carbon atom of the solvated oxirane ring (Scheme III). The concept that **8a** can be an intermediate in the formation of **9** was demonstrated by conversion of the former to the latter in ethanolic sodium ethoxide.

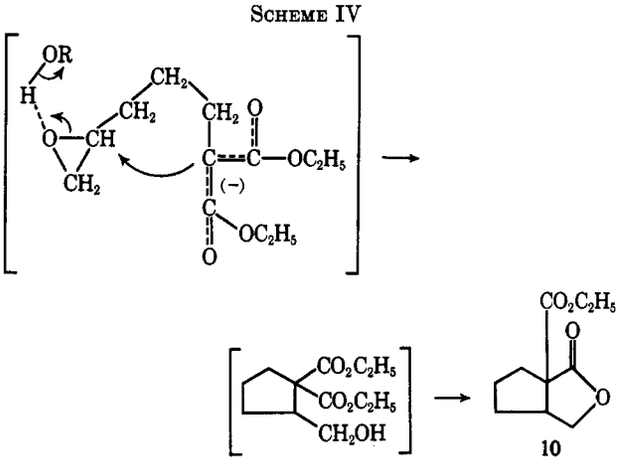
SCHEME III



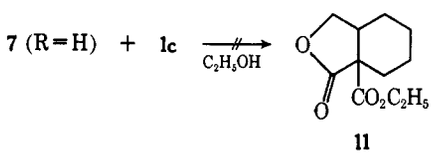
Although Pariselle[6] carried out the condensation of 4-bromo-1,2-epoxybutane and diethyl sodiomalonate, he did not thoroughly characterize the product. Based on a cryoscopic molecular weight and the fact that the material was halogen free, he assigned the epoxyalkyl malonate structure **8a** to his product. Our results indicate the Pariselle's material was primarily the cyclization product **9**.

When 5-bromo-1,2-expoxypentane (**1b**) and diethylsodiomalonate were allowed to react in ethanol, a product characterized as the bicyclic lactone ethyl 1-oxo-2-oxabicyclo[3.3.0]octane-8-carboxylate (**10**) was isolated. A mechanism similar to that described above for formation of diethyl 3-hydroxycyclopentane-1,1-dicarboxylate (**9**) explains formation of this compound: secondary ionization of the epoxypentylmalonate **8b**, intramolecular attack on the *secondary* carbon atom of the solvated oxirane to give a cyclopentane derivative, and attack of the primary hydroxyl on a carbethoxy group to give the lactone **10** (Scheme IV). It is interesting to note that the intramolecular attack on the epoxide occurred at the more hindered secondary carbon

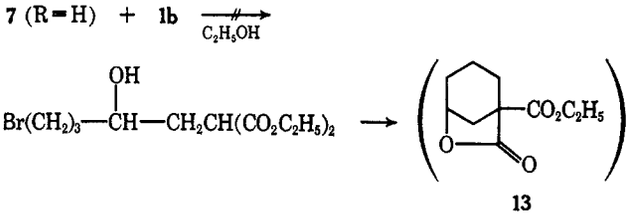
SCHEME IV



to give the five-membered carbocyclic ring. This supports the results of Knipe and Stirling[12] who found that cyclization reactions involving malonates favored formation of five-membered rings over six-membered rings by a factor of *ca.* 10^3. Failure to form ethyl 1-oxo-2-oxabicyclo[3.4.0]nonane-9-carboxylate (**11**) during the condensation of 6-bromo-1,2-epoxyhexane (**1c**) and diethyl sodiomalonate in ethanol also indicates the low tendency for cyclizations involving cyclohexane ring formation.



Formation of the bicyclic lactone **10** during condensation of diethyl sodiomalonate and 5-bromo-1,2-epoxypentane in ethanol rules out formation of cyclic products by initial displacement at the primary carbon of the oxirane to give the bromo alcohol **12**, followed by intramolecular displacement of bromide ion. This mechanism would have given the bicyclic lactone **13** containing a cyclohexane ring, a structure which is not consistent with the nmr spectrum.



Experimental Section

4-Bromo-1,2-epoxybutane (**1a**).—A solution of *m*-chloroperbenzoic acid (112 g, 89% pure, 0.578 mol) in 1.28 l. of methylene chloride was added dropwise with stirring to an ice-cooled solution of 4-bromo-1-butene (72.5 g, 0.537 mol) in 320 ml of methylene chloride. After the addition the mixture was stirred at room temperature for 20 hr, during which time *m*-chlorobenzoic acid precipitated. The reaction mixture was washed with 4 *N* sodium hydroxide until the aqueous phase remained strongly alkaline and with water until neutral. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to give 76 g (94%) of **1a**. Decomposition occurred during distillation attempts; so the product was characterized by nmr spectrometry (Table V)

(12) A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc., B*, 67 (1968).

and used without purification. 5-Bromo-1,2-epoxypentane (**1b**) and 6-bromo-1,2-epoxyhexane (**1c**) were prepared in an identical manner.

3-(ω-Bromo-β-hydroxyalkyl)-4-quinazolones (2) and 4-bromo-2-hydroxy-1-phenoxybutane (3), listed in Table I, were prepared by adding an excess (approximately fivefold) of the appropriate ω-bromo-1,2-epoxyalkane (**1**) to an alcoholic solution of sodio-4(3H)-quinazolone or sodium phenoxide. After stirring at room temperature for the specified time, the reaction mixtures were diluted with water and the the alcohol evaporated *in vacuo*. The resultant aqueous solutions were extracted with chloroform, and the extracts were washed with 10% aqueous sodium hydroxide, dried ($MgSO_4$), and freed of solvent *in vacuo*. The residues were crystallized or distilled to obtain pure products.

Epoxyalkyl derivatives, listed in Table IV, were prepared by adding 3 equiv of the appropriate ω-bromo-1,2-epoxyalkane (**1**) to dimethylformamide or dimethyl sulfoxide solutions of sodio-4(3H)-quinazolone, sodium phenoxide, diethyl sodiomalonate or diethyl sodiomethylmalonate. After 3 hr at room temperature, the reaction mixtures were diluted with water and extracted with chloroform. The extracts were washed with water and dried ($MgSO_4$); the solvent was removed *in vacuo*. The residues were purified by crystallization or by distillation.

Diethyl 3-Hydroxycyclopentane-1,1-dicarboxylate (9). A. From Diethyl Malonate and 4-Bromo-1,2-epoxybutane.—A solution of 5.40 g (0.034 mol) of freshly distilled diethyl malonate in 37.5 ml of 1 *N* ethanolic sodium ethoxide was stirred for 15 min in an ice bath, after which 28.7 g (0.19 mol) of **1a** was added; the mixture immediately turned yellow and cloudy. After stirring at room temperature for 3 hr, the mixture was poured into water and the ethanol evaporated *in vacuo*. The aqueous solution was extracted with chloroform, the extracts dried ($MgSO_4$) and concentrated, and the residue distilled under reduced pressure. Two fractions containing product were collected: 1.0 g (13%), bp 86° (0.05 mm), containing 87% **9** and 13% **8a** by glpc (5% XE-60 on 60–80 mesh Gas-Chrom Q, column 6 ft × 0.0125 in., temperature 120° isothermal); and 2.4 g (31%), bp 90–91° (0.05 mm), containing 93% **9** and 7% **8a**. The latter fraction was subjected to spectrometric analysis: ir (liquid film) 3450 (OH) and 1725 cm^{-1} ($COOC_2H_5$); nmr ($CDCl_3$) δ 4.22 and 4.20 (2q, 4, J = 7.2 Hz, OCH_2CH_3), *ca.* 4.3 (m, 1, CHOH), 3.02 (s, 1, OH), multiplets over the range 1.7–2.7 (6, CH_2), and 1.25 ppm (t, 6, J = 7.2 Hz, (OCH_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 230 (0.2), 212 (0.2), 202 (9), 185 (9), 173 (100), 167 (4), 160 (6), 139 (28), 127 (56), 111 (38), 83 (39), 67 (29).

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.10; H, 7.88.

B. From Diethyl 4,5-Epoxypentane-1,1-dicarboxylate.—A solution of **8a** (2.3 g, 0.01 mol) was dissolved in 10 ml of 1 *N* ethanolic sodium ethoxide and the mixture was stirred at room temperature. Aliquots were removed at intervals, quenched with glacial acetic acid, and analyzed by glpc. After 1 hr 25% **8a** was converted into **9**, after 3 hr 55% was converted, and after 15 hr 85% was converted. The reaction mixture was worked up as described in part A. Careful distillation of the product gave pure **9** with physical and spectrometric properties identical with those described above.

Ethyl 1-Oxo-2-oxabicyclo[3.3.0]octane-8-carboxylate (10).—A solution of 3.40 g (0.021 mol) of diethyl malonate in 25 ml of 1 *N* ethanolic sodium ethoxide was allowed to react with 17.2 g (0.10 mol) of **1b** and the reaction mixture was worked up in the manner described for preparation of **9**. Distillation of the product gave 1.7 g (40%) of **10**: bp 77° (0.05 mm); ir (liquid film) 1770 (5-membered lactone) and 1735 cm^{-1} ($CO_2C_2H_5$); nmr ($CDCl_3$) δ 4.25 (q, 2, J = 7.2 Hz, OCH_2CH_3), 4.59 (q, 1, J_{gem} = 9.4 and J_{vic} = 8.5 Hz) and 4.10 (q, 1, J_{gem} = 9.4 and J_{vic} = 2.8 Hz) both assigned to the CH_2O of the lactone, 3.09 (m, 1, bridgehead CH), 2.30 (m, 2, $CH_2C{=}CO_2C_2H_5$), 1.80 (m, 4, cyclopentane CH_2) and δ 1.27 ppm (t, 3, J = 7.2 Hz, OCH_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 154 (10), 153 (12), 126 (15), 125 (24), 111 (8), 109 (23), 108 (13), 95 (15), 81 (100), 80 (17), 79 (24), 67 (26) (no molecular ion).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.86; H, 7.18.

Registry No.—**1a**, 13287-42-8; **1b**, 21746-87-2; **1c**, 21746-88-3; **2a**, 21746-89-4; **2b**, 21746-90-7; **3**, 27146-91-8; **5a**, 21746-92-9; **5b**, 21779-59-9; **6**, 21746-93-0; **8a**, 21746-94-1; **8b**, 21746-95-2; **8c**, 21746-96-3; **8d**, 21746-97-4; **9**, 21736-07-2; **10**, 21746-98-5.

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Alkylating Agents Containing a Quaternary Nitrogen Group[1]

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A series of 18 new, water-soluble alkylating agents was synthesized. The structures contain an alkylsulfonate group as the alkylating function and a quaternary ammonium salt group attached to a hydrocarbon backbone.

A large body of literature exists on the blocking or inhibition of the enzyme acetylchlolinesterase by various phosphorus poisons.[2] Thus, alkyl methylphosphonofluoridates become attached to the enzyme site, presumably by phosphonylation of an O-serine component of the enzyme protein.[3] The result is that the normal enzyme function of hydrolyzing acetylcholine is prevented. Removal of the phosphonate inhibition has been successfully accomplished by various oxime "reactivators" such as 2-pyridinealdoxime methiodide (2-PAM). Reactivation may be complicated, however, by a phenomenon known as "aging" whereby the alkyl group of the phosphonate inhibitor is cleaved, presumably generating an oxygen anion.[4] The net result is

(1) This work was performed under Edgewood Arsenal Contract DA 18-108-AMC-262(A).

(2) "Handbuch der Experimentallen Pharmakologie," Vol. XV, G. B. Koelle, Subeditor, "Cholinesterases and Anticholinesterase Agents," 1963, and/or R. D. O'Brien, "Toxic Phosphorus Esters," Academic Press, New York, N. Y., 1960.

(3) N. K. Schaffer, S. C. May, Jr., and W. H. Summerson, *J. Biol. Chem.*, **202**, 67 (1953).

(4) F. Berends, C. H. Posthumus, I. V. D. Sluys, and F. A. Deserkauf, *Biochim. Biophys. Acta*, **34**, 576 (1959).