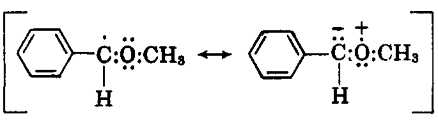
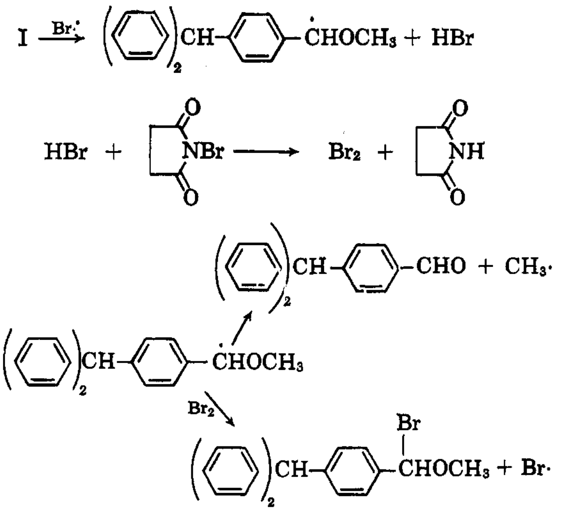
than with bromotrichloromethane as the brominating agent. The greater selectivity of the trichloromethyl radical may result because it is more stable than a bromine atom and, therefore, more discriminating in its attack on alternate reaction centers. With both brominating agents benzyl methyl ether is, however, substantially more reactive than the several alkylbenzenes which have been investigated. Presumably the methoxyl substituent like the phenyl group makes a significant contribution (IV) to stabilization of the radical formed by extraction of one of the benzylic hydrogen atoms of the ether.[17]



IV

It has been inferred that the initial product of radical bromination of benzyl methyl ether is α-bromobenzyl methyl ether, which decomposes rapidly to form benzaldehyde and methyl bromide.[1] It is questionable, however, whether the bromo ether necessarily must be an intermediate in the formation of the aldehyde. In the reaction of *p*-benzhydrylbenzyl methyl ether three high boiling products are formed in significant quantity. These are *p*-benzhydrylbenzaldehyde, tertiary bromide, and the α-bromo ether III. It has been found that the composition of products is not noticeably affected by varying the period of reflux of the reaction mixture from one to four hours; α-bromo ether in this mixture is not decomposing during the course of the reaction to form the aldehyde. This does not preclude the possibility that on distillation of the product the bromo ether may decompose to the aldehyde. It is, therefore, probable that two alternate paths (equations 3–5), in addition to that leading to the formation of tertiary bromide, are available to the ether I, when it reacts with N-bromosuccinimide.



(3)

(4)

(5a)

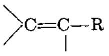
(5b)

It is interesting to note that aldehydes are not the dominant products in the reactions of N-bromosuccinimide with either *p*-nitrobenzyl methyl ether[1] or *p*-bromophenyl benzyl ether.[18] It is improbable from an energetic standpoint that the radical intermediates in these two reactions should decompose by processes of the type depicted in equation 5a.

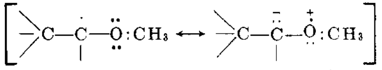
Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

---

[17] As was noted by a referee, the reactivities of substances of the type



$>C{=}C{-}R$ with respect to radical initiated polymerization vary with R in the order H ~ OCH_3 < OAc ~ CH_3 < Cl < COOR, etc. (C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 120). Apparently resonance stabilization of the radical intermediate



$\left[>C{-}\dot{C}{-}\ddot{O}{:}CH_3 \longleftrightarrow >C{-}\overset{-}{C}{-}\overset{+}{O}{:}CH_3 \right]$ is not a dominant rate-influencing factor in the reaction of a vinyl ether. There is other evidence that substituent effects on the rates of hydrogen abstraction processes in benzylic or allylic halogenations cannot be predicted on the basis of the effects of those same substituents on vinyl polymerization. For example, although –COOR is an activating group in the latter process, methyl vinylacetate yields $BrCH_2CHBrCH_2COOCH_3$ rather than $CH_2{=}CHCH(Br)COOCH_3$ as the primary product of reaction with N-bromosuccinimide [E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2251 (1963)].

[18] L. L. Braun and J. H. Looker, *J. Org. Chem.*, **26**, 574 (1961).

Small Charged Rings. IV. Expansion of the Aziridinium Ring by Reaction with Aldehydes[1-3]

NELSON J. LEONARD, E. F. KIEFER, AND LEONARD E. BRADY

Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

Received May 16, 1963

Aromatic aldehydes have been shown to react with an aziridinium salt (III) to produce oxazolidinium compounds (V) by inclusion of the carbonyl group. The ring structure present in the products was established by n.m.r. spectral studies and by chemical degradation. The generality of the new ring-expansion reaction has been demonstrated by varying the aziridinium compound (VIII, X, XII) as well as the aldehyde reactant.

The introduction of a general method for the synthesis of aziridinium salts II (X = ClO_4 or BF_4) by nucleophilic attack of diazomethane on ternary iminium compounds I[1,4,5] has permitted a detailed study of the chemistry of the aziridinium ring system. The reactions of ethylene oxide with carbonyl compounds to form di-

---

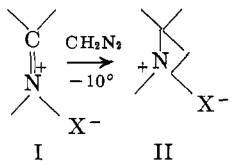
[1] For the preceding article in this series, see N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963).

[2] This investigation was supported by a research grant (USPHS-RG5829, currently GM 05829-05) from the National Institutes of Health, U. S. Public Health Service, to whom we are pleased to acknowledge our thanks.

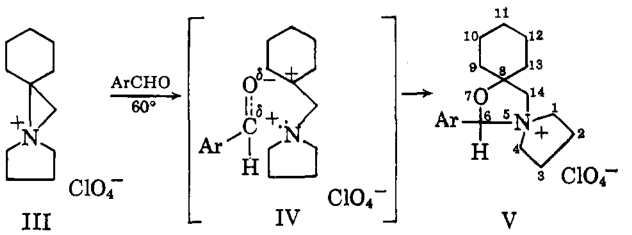
[3] Introduced at the 17th National Organic Chemistry Symposium of the American Chemical Society, June, 1961, Bloomington, Ind. (see Abstracts, pp. 1-10), and presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963 (see Abstracts, p. 30M).

[4] N. J. Leonard and K. Jann, *J. Am. Chem. Soc.*, **84**, 4806 (1962).

[5] N. J. Leonard and K. Jann, *ibid.*, **82**, 6418 (1960).



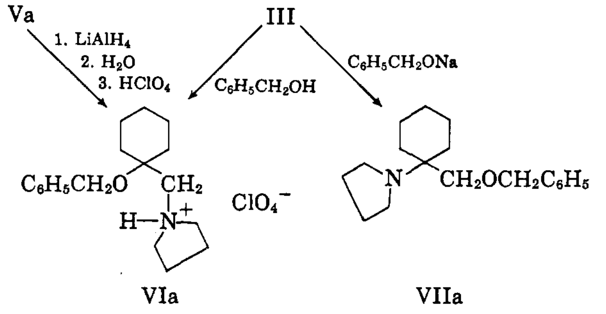
oxolanes[6] and of ethylenimine with carbonyl compounds to give oxazolidines[7] suggested that the structurally analogous aziridinium salts might undergo similar conversion. Further encouragement was found in the reactions, *e.g.*, solvolysis[4,5] and thermal rearrangement,[3] of 5-azoniadispiro[4.0.5.1]dodecane perchlorate (III), which appear to proceed with development of the more stable carbonium ion IV resulting from aziridinium ring opening. Thus a weak nucleophile such as an aldehyde carbonyl could theoretically react to effect ring expansion (V).



	Ar		Ar		Ar
a,	C_6H_5	d,	o-$CH_3OC_6H_4$	g,	2′,6′-$Cl_2C_6H_3$
b,	p-$CH_3C_6H_4$	e,	p-$(CH_3)_2NC_6H_4$	h,	2′,3′-$(CH_3O)_2C_6H_3$
c,	p-$CH_3OC_6H_4$	f,	p-BrC_6H_4	i,	2′-Furyl

When 5-azoniadispiro[4.0.5.1]dodecane perchlorate (III), $C_{11}H_{20}ClNO_4$,[4,5] was heated in excess benzaldehyde a new compound $C_{18}H_{26}ClNO_5$, m.p. 149–150°, was formed. The assigned structure 6-phenyl-7-oxa-5-azoniadispiro[4.2.5.1]tetradecane perchlorate (Va), was supported by the infrared and n.m.r. spectra. No absorption attributable to $^{+}$N—H or C=O appears in the infrared spectrum. The n.m.r. spectrum in deuteriochloroform shows a one-proton singlet at a τ value of 3.75 p.p.m., which is assigned to the methinyl proton adjacent to phenyl, oxygen, and positively charged nitrogen. At the highfield end of the spectrum appears a broad unresolved complex of signals due to the pyrrolidinium ring (τ *ca.* 8.1 p.p.m.) and to the protons of the six-membered saturated ring (τ at band center *ca.* 8.5 p.p.m.). The signals of the α-methylene protons of the pyrrolidinium ring occur in *two* bands centered at 6.11 and 6.57. This separation is presumably the result of long-range shielding of one of the pyrrolidinium α-methylene groups due to the diamagnetic anisotropy of the aromatic nucleus.[8] Coincidental with the band at 6.1 appears a signal due to the methylene protons of the oxazolidinium ring. This assignment was confirmed by synthesis of the corresponding compound in which the oxazolidinium methylene (C-14) was partially deuterated. The synthesis was accomplished by treatment of N-cyclohexylidenepyrrolidinium perchlorate with diazomethane-d_2[9] and subsequent reaction of the aziridinium salt with benzaldehyde. The n.m.r. spectrum of the deuterated oxazolidinium compound showed diminution of the band at τ 6.1 by almost two protons based on the integration values of Va and Va, 14-d_2. Nuclear magnetic resonance double resonance experiments on the C-14 deuterated compound Va located the complex signals for the β-protons on the pyrrolidinium ring at τ value ranges of 8.04–8.15 and 8.27–8.42, respectively, corresponding to the two bands centered at 6.11 and 6.57 for the α-protons.

Chemical evidence for the structure Va was obtained by reductive ring-opening. Treatment with lithium aluminum hydride in refluxing tetrahydrofuran followed by hydrolysis of the reaction mixture gave N-(1-benzyloxycyclohexylmethyl)pyrrolidine, which was isolated as the perchlorate salt VIa. This product was shown to be identical with that resulting from benzyl alcoholysis of 5-azoniadispiro[4.0.5.1]dodecane perchlorate (III). The structure of the solvolysis product was assignable by analogy with the methanolysis product, which was formed by S$_N$1-type fission of the aziridinium ring in III.[1,4,5] Moreover, the S$_N$2-type ring-opening of the three-membered ring (III) with sodium benzylate in dimethyl sulfoxide produced N-(1-benzyloxymethylcyclohexyl)pyrrolidine (VIIa). This *isomeric* product is the one which would have resulted from the lithium aluminum hydride reduction of an oxazolidinium ring obtained by insertion of benzaldehyde between the aziridinium *methylene* carbon and the quaternary nitrogen of III. The assigned structure of the product of aziridinium ring expansion in III with benzaldehyde as Va is thus amply secured.



The same product, 6-phenyl-7-oxa-5-azoniadispiro[4.2.5.1]tetradecane perchlorate (Va), was formed by heating III with benzaldehyde in nitrobenzene solution, but the modification seemed to offer no advantage over that employing excess benzaldehyde as the solvent. The generality of the method was established by heating III with a series of aromatic aldehydes representing a wide variety of ring substitution. The reactions were carried out in excess of the aldehyde at approximately 60°, or at higher temperature if necessary to keep the reaction mixture fluid, for 20–48 hours. Yields of the corresponding oxazolidinium perchlorates (Vb–i) were very high (*ca.* 90%), but sacrifice of yield had to be made in obtaining a pure product. Each new oxazolidinium salt was characterized by analytical and spectral data and by structural analogy with Va.

It was logical to assume that further generality of the ring expansion reaction might be achieved by variation in the aziridinium ring compound. We have provided three examples to satisfy ourselves of an extended scope in this direction. Thus, benzaldehyde was found to react with 6-azoniadispiro[5.0.5.1]tridecane perchlorate

---

(6) M. T. Bogert and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **55**, 3741 (1933).

(7) J. B. Doughty, C. L. Lazzell, and A. R. Collett, *ibid.*, **72**, 2866 (1950).

(8) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959, p. 18.

(9) The n.m.r. spectrum of the deuterated aziridinium salt confirmed earlier signal assignments for III[4,5] by diminution of the band at τ 6.93 p.p.m. ($CDCl_3$–CH_2Cl_2) ascribed to the aziridinium methylene protons.

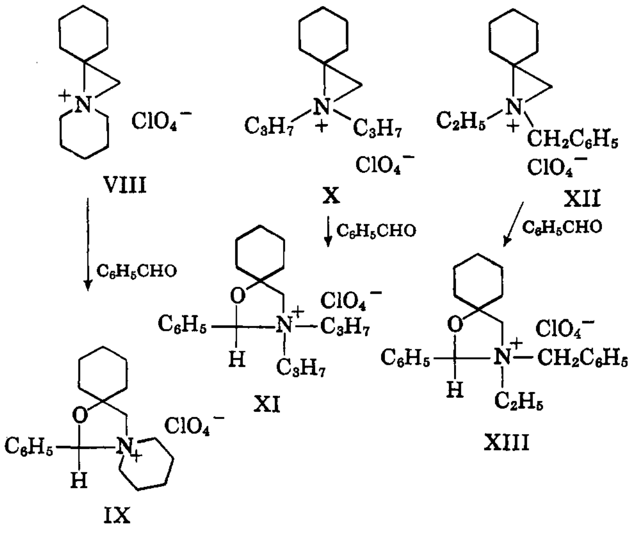
TABLE I

OXAZOLIDINIUM COMPOUNDS PRODUCED

Perchlorate[a]	Yield, %[b]	M.p., °C.	Formula	C, % Calcd.	C, % Found
6-Phenyl-7-oxa-5-azoniadispiro-[4.2.5.1]tetradecane (Va)	55	149–50[c]	$C_{18}H_{26}ClNO_5$	58.14	58.30
6-*p*-Tolyl-7-oxa-5-azoniadispiro-[4.2.5.1]tetradecane (Vb)	67	146–7[c]	$C_{19}H_{28}ClNO_5$	59.13	59.41
6-*p*-Methoxyphenyl-7-oxa-5-azoniadispiro[4.2.5.1]-tetradecane (Vc)	44	127–8[c]	$C_{19}H_{28}ClNO_6$	56.77	56.76
6-*o*-Methoxyphenyl-7-oxa-5-azoniadispiro[4.2.5.1]-tetradecane (Vd)	40	121–2[c]	$C_{19}H_{28}ClNO_6$	56.77	56.92
6-*p*-Dimethylaminophenyl-7-oxa-5-azoniadispiro[4.2.5.1]-tetradecane (Ve)	67	184–5[d]	$C_{20}H_{31}ClN_2O_5$	57.89	57.71
6-*p*-Bromophenyl-7-oxa-5-azoniadispiro[4.2.5.1]tetradecane (Vf)	68	149.5–150.5[c]	$C_{18}H_{25}BrClNO_5$	47.95	47.94
6-(2′,6′-Dichlorophenyl)-7-oxa-5-azoniadispiro[4.2.5.1]-tetradecane (Vg)	(13)	169–70[e]	$C_{18}H_{24}Cl_3NO_5$	49.04	48.87
6-(2′,3′-Dimethoxyphenyl)-7-oxa-5-azoniadispiro[4.2.5.1]-tetradecane (Vh)	55	152[f]	$C_{20}H_{30}ClNO_7$	55.61	55.05
6-(2′-Furyl)-7-oxa-5-azoniadispiro[4.2.5.1]tetradecane (Vi)	59	109–10.5[c]	$C_{16}H_{24}ClNO_6$	53.11	53.41
7-Phenyl-8-oxa-6-azoniadispiro-[5.2.5.1]pentadecane (IX)[k]	54	172.5–3.5[c]	$C_{19}H_{28}ClNO_5$	59.14	59.09
2-Phenyl-3,3-dipropyl-1-oxa-3-azoniaspiro[4.5]decane (XI)[l]	66	136.5–7.5[g]	$C_{20}H_{32}ClNO_5$	59.76	59.96
3-Benzyl-3-ethyl-2-phenyl-1-oxa-3-azoniaspiro[4.5]decane (XIII)[m]	47	161–1.5[h]	$C_{23}H_{30}ClNO_5$	63.37	63.34

[a] IUPAC rules are followed; see "Definitive Rules for Nomenclature of Organic Chemistry," *J. Am. Chem. Soc.*, **82,** 5545 (1960). [b] Crude yields were about 90%. The figures reported represent yields of analytically pure products and may be considered minima. [c] Recrystallization solvent, ethyl acetate–isopropyl alcohol. [d] Recrystallized from ethanol. [e] Recrystallized from methanol–pentane. [f] Recrystallized from ethyl acetate. [g] Recrystallized from ethanol–ether. [h] Recrystallized from ethyl acetate–pentane. [i] G. V. D. Tiers, "Tables of τ Values for a Variety of Organic Compounds," 3-M Co., St. Paul, Minn., 1958; G. V. D. Tiers,

(VIII) to give 7-phenyl-8-oxa-6-azoniadispiro[5.2.5.1]-pentadecane perchlorate (IX), with 1,1-dipropyl-1-azoniaspiro[2.5]octane perchlorate (X) to give 2-phenyl-3,3-dipropyl-1-oxa-3-azoniaspiro[4.5]-decane perchlorate (XI), and with 1-benzyl-1-ethyl-1-azoniaspiro[2.5]octane perchlorate (XII) to give 3-benzyl-3-ethyl-2-phenyl-1-oxa-3-azoniaspiro[4.5]decane perchlorate (XIII). Finally, the aziridinium ring-expansion reaction is not limited to aldehydes, and in sequels to this paper we shall describe the reaction of aziridinium salts with other weak nucleophiles, represented by ketones and nitriles.



Experimental[10]

6-Phenyl-7-oxa-5-azoniadispiro[4.2.5.1]tetradecane Perchlorate (Va). A.—A solution of 2.66 g. (10 mmoles) of 5-azoniadispiro[4.0.5.1]dodecane perchlorate (III) in 10 ml. of benzaldehyde was heated at 60° for 48 hr., then poured slowly with vigorous stirring into 150 ml. of anhydrous ether. The oil solidified upon standing to give 3.45 g. of sticky crystals smelling of benzaldehyde. Recrystallization from acetone–ether gave 2.05 g. (55%) of colorless prisms, m.p. 149–150° (see Table I). This is the general method which was applicable to the synthesis of a variety of oxazolidinium salts (Va–i).

B.—A solution of 0.133 g. (0.50 mmole) of 5-azoniadispiro-[4.0.5.1]dodecane perchlorate (III) and 0.116 g. (1.09 mmoles)

---

(10) All melting points are corrected, boiling points are uncorrected. We are indebted to Mr. Josef Nemeth, Mrs. Mary Rose Kung, Mrs. Mary-Ann Weatherford, and Mr. G. D. Callahan for the microanalyses and to Mr. Dick H. Johnson, Miss Gail Gregory, and Miss Dorothy Wood for the n.m.r. spectra, obtained with a Varian Associates Model A-60 n.m.r. spectrometer. We also wish to thank Mr. Johnson for the infrared spectra, obtained with a Perkin-Elmer Model 21 spectrophotometer, and Mr. O. W. Norton for the n.m.r. double resonance experiments using a modified Varian Associates Model HR-60 n.m.r. spectrometer.

BY AZIRIDINIUM RING EXPANSION

H, %		N, %		
Calcd.	Found	Calcd.	Found	Selected n.m.r. signals in $CDCl_3$ (τ values in p.p.m.)[i,j]
7.05	7.23	3.77	3.65	2.1 to 2.5 um, 3.75 s, 5.8 to 6.3 um, 6.11 s, 6.4 to 6.8 um, 7.5 to 8.8 um
7.31	7.33	3.63	3.76	2.2 to 2.8 um, 3.85 s, 5.7 to 6.9 um, 6.10 s, 7.57 s, 7.7 to 8.9 um
7.02	7.20	3.48	3.48	2.33 d, 3.00 d, 3.85 s, 5.8 to 6.3 um, 6.14 s, 6.4 to 6.7 um, 7.6 to 8.8 um
7.02	7.05	3.48	3.50	2.2 to 3.1 um, 3.55 s, 6.03 s, 6.10 s, 6.3 to 6.8 um, 7.7 to 8.8 um
7.53	7.55	6.75	6.85	2.49 d, 3.30 d, 3.94 s, 6.0 to 6.4 um, 6.4 to 6.8 um, 7.00 s, 7.6 to 8.9 um
5.59	5.60	3.11	3.31	2.32, 2.78 s, 5.5 to 7.0 um, 6.08 s, 7.7 to 8.9 um
5.49	5.59	3.18	3.08	2.47, 3.20 s, 5.7 to 7.0 um, 7.4 to 8.7 um
7.00	7.22	3.24	3.27	2.75, 3.72 s, 6.0 to 7.2 um, 6.02 s, 6.11 s, 7.6 to 9.0 um
6.68	6.75	3.87	3.69	2.37 dd, 2.96 dd, 3.46 dd, 3.86 s, 5.7 to 6.8 um, 6.08 s, 7.3 to 9.0 um
7.31	7.29	3.63	3.57	2.41, 4.03 s, 5.8 to 7.3 um, 7.4 to 9.0 um
8.02	7.93	3.48	3.38	2.42, 3.97 s, 6.23 s, 6.5 to 7.2 um, 7.8 to 8.8 um, 8.8 to 9.2 um
6.94	7.08	3.21	3.15	2.32, 3,73 s, 5.37 s, 5.8 to 7.5 um, 7.8 to 8.7 um, 8.89 t[n]

J. Phys. Chem., **62**, 1151 (1958). [j] s = singlet, d = doublet, t = triplet, dd = doublet of doublets, um = unresolved multiplets. [k] Prepared from 6-azoniadispiro[5.0.5.1]tridecane perchlorate (VIII) (ref. 4). [l] Prepared from 1,1-dipropyl-1-azoniaspiro[2.5]octane perchlorate (X); N. U. Leonard and P. C. Kelley, unpublished results. [m] Prepared from 1-benzyl-1-ethyl-1-azoniaspiro[4.5]decane perchlorate (XII) with benzaldehyde for 4 hr. at 60° or 74 hr. at 25° (footnote *l*). [n] In trifluoroacetic acid.

of benzaldehyde in 0.40 ml. of nitrobenzene was heated in a rubber-sealed glass ampoule immersed in an oil bath at 77° for 7.5 hr., then poured into 20 ml. of anhydrous ether. The orange oil solidified almost immediately, and filtration gave 0.131 g. of crude product which was recrystallized from ethanol by addition of ether, yielding 78 mg. (42%) of crystalline product identical with that described previously. No infrared bands corresponding to $\geqslant N^+{-}H$ or $>C{=}O$ were observed for any of the compounds, Va–i.

N-(1-Benzyloxycyclohexylmethyl)pyrrolidine perchlorate (VIa) was prepared by routes A, lithium aluminum hydride reduction of 6-phenyl-7-oxa-5-azoniadispiro[4.2.5.1]tetradecane perchlorate (Va), and B, benzyl alcoholysis of 5-azoniadispiro-[4.0.5.1]dodecane perchlorate (III).

A.—A mixture of 137 mg. (3.61 mmoles) of lithium aluminum hydride in 50 ml. of tetrahydrofuran was chilled in an ice bath and to the stirred mixture was added in one portion 1.34 g. (3.61 mmoles) of 5-azoniadispiro[4.0.5.1]dodecane perchlorate. After 20 min. at room temperature the mixture was heated under reflux for 2 hr., allowed to cool and treated with 0.14 ml. of water, 0.14 ml. of 15% sodium hydroxide solution, and 0.42 ml. of water. The resulting white suspension was heated under reflux for 1 hr., cooled, and filtered. The residue was washed with 25 ml. of ether and then with 75 ml. of boiling anhydrous acetone. The acetone solution was concentrated, and the oily residue was treated with 50 ml. of ether, yielding 72 mg. of starting material identified by melting point, mixture melting point, and comparison of infrared spectra. The combined tetrahydrofuran and ether-wash solutions were dried (Drierite) and treated dropwise with aqueous ethanolic perchloric acid to the congo red end point, then with ether until turbid. Refrigeration overnight caused the separation of crystalline product identified as N-(1-benzyloxycyclohexylmethyl)pyrrolidine perchlorate, m.p. 106–107°; yield, 0.92 g. (72% based on unrecovered Va). A sample was recrystallized twice from ethanol–ether for analysis; m.p. 121.5–122°; ν_{max}^{KBr} 3130 cm.$^{-1}$; n.m.r. τ values (deuteriochloroform, 2.65, 5.49 (singlet, $C_6H_5C\underline{H}_2O$), 5.8 to 6.5 (unresolved multiplet), 6.60 (doublet, $\rangle C{-}C\underline{H}_2\overset{+}{N}HR_2$, *J* = 6 c.p.s.), 6.7 to 7.3 (unresolved multiplet), 7.7 to 8.7 (unresolved multiplet).

Anal. Calcd. for $C_{18}H_{28}ClNO_5$: C, 57.82; H, 7.55; N, 3.75. Found: C, 57.86; H, 7.57; N, 3.91.

B.—A solution of 1.00 g. (3.76 mmoles) of 5-azoniadispiro[4.0.-5.1]dodecane perchlorate (III) in 5 ml. of benzyl alcohol was heated for 20 hr. at 80°. The mixture was cooled and added dropwise to a stirred solution of 4 drops of (approximately) 3.5 molar aqueous ethanolic perchloric acid in 150 ml. of ether. The precipitate was collected by filtration, washed with ether, and recrystallized from ethanol–ether; yield, 1.14 g. (81.0%); m.p. 121.5–122°. Mixture melting point, infrared and n.m.r. spectra showed this product to be identical with that prepared by route A.

N-(1-Benzyloxymethylcyclohexyl)pyrrolidine Perchlorate (VIIa).—To 20 ml. of benzyl alcohol was added 0.23 g. (10 mg.-atom) of sodium metal, and the mixture was stirred until reaction was complete. The excess benzyl alcohol was removed on a rotary evaporator, and the crystalline residue was dissolved in 20 ml. of dimethyl sulfoxide. To this solution was added 1.33 g. (5.0 mmoles) of 5-azoniadispiro[4.0.5.1]dodecane perchlorate (III). After standing overnight, the solution was treated with 25 ml. of water and 50 ml. of ether. The layers were separated and the aqueous phase further extracted with two 25-ml. portions of ether. The combined ether solution was dried over Drierite and then acidified to the congo red end point with aqueous ethanolic perchloric acid. The crystalline material (platelets) which separated represented a quantitative yield of N-(1-benzyloxymethylcyclohexyl)pyrrolidine perchlorate, recrystallized from ethanol–ether, m.p. 114–115°; $\nu_{\max}^{\mathrm{KB}}$ 3100 cm.$^{-1}$; n.m.r. τ values (deuterichloroform), 1.8 to 2.5 (unresolved), 2.56, 5.39 (singlet, $\mathrm{C_6H_5C_2\underline{H}O}$), 6.27 (singlet, $\mathrm{O\underline{C}H_2C}\leqslant$), 6.35 to 6.90 (unresolved multiplet), 7.65 to 9.05 (unresolved multiplet).

Anal. Calcd. for $\mathrm{C_{18}H_{28}ClNO_5}$: C, 57.82; H, 7.55; N, 3.75. Found: C, 57.81; H, 7.43; N, 3.62.

Oxidation Products of Vitamin E and Its Model, 6-Hydroxy-2,2,5,7,8-pentamethylchroman. V. Studies of the Products of Alkaline Ferricyanide Oxidation

W. A. SKINNER AND P. ALAUPOVIC

Department of Pharmaceutical Chemistry, Stanford Research Institute, Menlo Park, California, and the Cardiovascular Section, Oklahoma Medical Research Institute, and Department of Biochemistry, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma

Received May 23, 1963

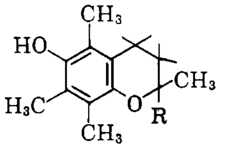
In addition to the previously reported dimeric, keto ether III or IV, other products of the alkaline ferricyanide oxidation of *dl*-α-tocopherol and its model, 6-hydroxy-2,2,5,7,8-pentamethylchroman, were isolated and one of them, compound A, a trimer, was proposed to be XIV or XV. From the spectral and chromatographic characteristics of compound A it appears to be the same as one of the liver metabolites (compound "O") previously obtained from *dl*-α-tocopherol. The free radical initiated oxidation of 6-hydroxy-2,2,5,7,8-pentamethylchroman was also studied and the products compared with those from the alkaline ferricyanide oxidation.

With increasing interest in the biological role of vitamin E, chemical and metabolic studies of the tocopherols are assuming major importance. The chemical oxidation of *dl*-α-tocopherol (I) and comparison of the oxidation products with the metabolites formed in the body would appear to be a promising approach to the identification of these metabolites and for obtaining sufficient quantities of them for their biological evaluation. With this approach in mind, studies on the oxidation of *dl*-α-tocopherol (I) and its model, 6-hydroxy-2,2,5,7,8-pentamethylchroman (II), with alkaline ferricyanide were undertaken.

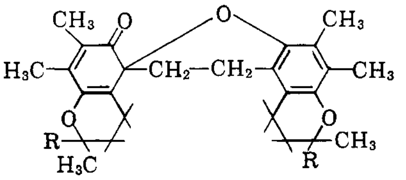
Martius and Eilingsfeld,[1] Draper, *et al.*,[2] Nelan and Robeson,[3,4] and Schudel, *et al.*,[5] have reported on the alkaline ferricyanide oxidation of *d*- or *dl*-α-tocopherol and in some cases the model chroman II. Some confusion arose due to the difficulty of purifying the oxidation products from one another. Martius reported an absorption maximum of the yellow oily product from *dl*-α-tocopherol oxidation to be at 235–236 mμ with a weaker band at 300 mμ. Draper, *et al.*, reported a maximum at 295 mμ, $E^{1\%}_{1\mathrm{cm}}$ 36, while Nelan and Robeson reported the maximum to be at 300 mμ, $E^{1\%}_{1\mathrm{cm}}$ 53.8. Our spectral data on this product gave a maximum at 300 mμ, $E^{1\%}_{1\mathrm{cm}}$ 56. Chemical studies on this yellow oil from the alkaline ferricyanide oxidation of *dl*-α-tocopherol led Nelan and Robeson to postulate structure III for it. However, three other isomers also would fit the chemical data. They are V, VII, and IX and differ only by positions of methyl groups. Nelan and Robeson[3,4] also reported that the oxidation of II yielded a yellow crystalline compound, m.p. 126–127°, that was analyzed for the dimer IV.

In our laboratories[6] we have found the yellow, crystalline dimer from the oxidation of II and the oils from the oxidation of I to be extremely difficult to purify from other isomeric materials, especially trimer XV. After repeated chromatography on a silica gel (Schlesinger) column and fractional crystallization from methanol–water, an analytical sample of the dimer [($\mathrm{C_{28}H_{36}O_4}$), m.p. 77–79°, mol. wt. (in benzene), 433 (calcd. 436)] was obtained from the oxidation of II with alkaline ferricyanide. This compound no longer showed even trace spots due to isomeric impurities on silica gel thin-layer chromatography. The infrared and ultraviolet absorption maxima agreed with those reported by Nelan and Robeson, *i.e.*, ultraviolet maximum at 300 mμ, and in the infrared the absence of OH (2.90–3.00 μ) and presence of α,β-unsaturated C=O (5.98), aryl (6.05), C=C (6.28), and chroman C—O—C (9.15 μ).

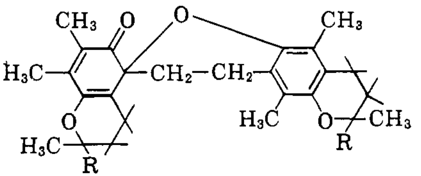
Since the nuclear magnetic resonance spectra of the yellow oil from the oxidation of I and the crystalline solid from the oxidation of II do not enable one to distinguish between the four possible structures of the di-



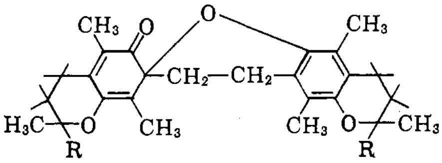
I, R = $\mathrm{C_{16}H_{33}}$,
II, R = $\mathrm{CH_3}$



III, R = $\mathrm{C_{16}H_{33}}$
IV, R = $\mathrm{CH_3}$



V, R = $\mathrm{C_{16}H_{33}}$
VI, R = $\mathrm{CH_3}$



VII, R = $\mathrm{C_{16}H_{33}}$
VIII, R = $\mathrm{CH_3}$

---

[1] C. Martius and H. Eilingsfeld, *Ann.*, **607**, 159 (1959).

[2] H. H. Draper, A. S. Csallany, and S. N. Shah, *Biochim. Biophys. Acta*, **59**, 527 (1962).

[3] D. R. Nelan and C. D. Robeson, *Nature*, **193**, 477 (1962).

[4] D. R. Nelan and C. D. Robeson, *J. Am. Chem. Soc.*, **84**, 2963 (1962).

[5] P. Schudel, H. Mayer, R. Rüegg, and O. Isler, *Chimia* (Aarau), **16**, 368 (1962).

[6] W. A. Skinner and P. Alaupovic, *Science*, **140**, 803 (1963).