Attempted preparation of 6H-indeno(2,1-b)quinolin 1-oxide. To 1.09 g. (0.005 mole) of I in 15 ml. of glacial acetic acid, was added 0.7 ml. of 20% hydrogen peroxide. The solution was heated at 65–69° for 3 hr., after which an additional 0.3 ml. of 30% hydrogen peroxide (0.0085 mole total) was added, followed by 19 hr. of supplementary heating at 69°. The brown-black mixture was evaporated to dryness under vacuum, triturated with hot saturated sodium carbonate solution until basic and extracted with chloroform. A red-brown solid, weighing 0.74 g. (63.8% yield), was obtained by ethanol treatment of the residue from chloroform evaporation. All attempts at purification by recrystallization techniques were fruitless; however, sublimation of 100 mg. at 150°/0.1 mm. resulted in 50 mg. of a yellow solid, m.p. 185–189°. A mixture melting point experiment and the infrared spectrum indicated the product to be ketone II.

6H-Indeno(2,1-b)quinoline-11-carboxylic acid (XI). A mixture of 4.0 g. (0.0302 mole) of 2-indanone and 7.0 g. (0.0476 mole) of isatin was heated on a steam bath for 30 min. in a basic media of 6 g. of sodium hydroxide in 70 ml. of water and allowed to cool overnight. The sodium salt of XI was collected by vacuum filtration, washed with cold water and heated in the presence of 25% acetic acid. A pale tan solid, weighing 4.85 g. (61.6% yield), was collected after trituration with methanol. Compound XI was quite insoluble in most organic solvents; however, recrystallization of the sodium salt from water, subsequent acidification with dilute acetic acid and washing with a variety of solvents gave a pale tan powder, which melted above 350°, after darkening at 275°; λ_{max} (methanol and potassium hydroxide) 216, 259 (sho.), 265, 289, 314, 328, 343 mμ ($\epsilon \times 10^{-3}$ 35.4, 34.4, 36.3, 9.65, 12.9, 13.2, 15.1).

Anal. Calcd. for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found: C, 77.98; H, 4.55; N, 5.50.

4-Chloro-6H-indeno(2,1-b)quinoline-11-carboxylic acid (XII). A mixture of 0.66 g. (0.005 mole) of 2-indanone and 1.09 g. (0.006 mole) of 7-chloroisatin was heated in a basic solution of 1.5 g. of sodium hydroxide in 20 ml. of water. Heating was continued for 30 min., after which the mixture was cooled to precipitate needles of the sodium salt. Filtration, washing with cold water, and drying was followed by heating the salt in 25% aqueous acetic acid. The acid was collected which, after trituration with hot acetone, weighed 0.91 g. (61.5% yield). Three recrystallizations from pyridine-acetone gave XII as a pale tan powder, decomposing at 308–310° after darkening at 275°; λ_{max} (methanol and potassium hydroxide) 216, 258 (sho.), 272, 317, 329, 344 mμ ($\epsilon \times 10^{-3}$ 33.7, 27.4, 30.1, 13.2, 13.2, 11.7); infrared bands (potassium bromide pellet) γ_{OH} 3440/40, γ_{COOH} 1715/80, 1681/51.

Anal. Calcd. for $C_{17}H_{10}NO_2Cl$: C, 69.04; H, 3.41; Cl, 11.99. Found: C, 68.51; H, 3.64; Cl, 11.52.

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LINCOLN, NEB.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, COMMERCIAL SOLVENTS CORP.]

Periodate Oxidations of Oxazolines

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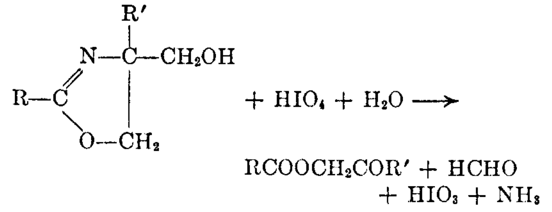
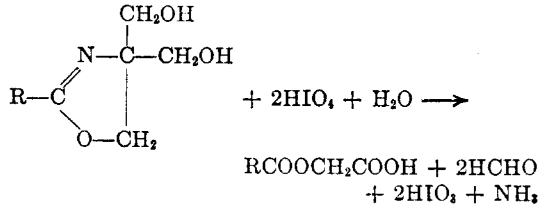
The reaction of 2-oxazolines with periodic acid has been studied. Those 2-oxazolines containing an hydroxymethyl group in position 4 are quantitatively oxidized in aqueous solution at room temperature. The effect of varying the ring substituents and the effect of the addition of alkali and acid to the reaction media have been determined. Oxidation products have been isolated in certain instances. A reaction scheme involving preliminary hydrolysis of the oxazoline is presented to account for the results obtained.

During the course of a study of methods for the analysis of mixtures of amino alcohols and oxazolines, it was discovered that 2-oxazolines containing one or more hydroxymethyl groups in position 4 are quantitatively oxidized by aqueous periodic acid according to Equations 1 and 2.



$+ HIO_4 + H_2O \longrightarrow RCOOCH_2COR' + HCHO + HIO_3 + NH_3$ (1)



$+ 2HIO_4 + H_2O \longrightarrow RCOOCH_2COOH + 2HCHO + 2HIO_3 + NH_3$ (2)

These results were unexpected in view of the information previously published regarding periodate oxidations.

Application of the glycol-splitting agent, periodic acid, to the cleavage of amino alcohols was first reported by Nicolet and Shinn.[1] As in the case of glycols, only those amino alcohols with the functional groups attached to adjacent carbon atoms are oxidized.

As *N*-acylated amino alcohols and tertiary amino alcohols are not oxidized or are only very slowly oxidized by periodic acid at room temperature, it was not expected that 4-hydroxymethyl-2-oxazolines would be readily oxidized. That 4-hydroxymethyl-2-oxazolines are readily oxidized by periodic acid is established by the results given in the Experimental Section of this report.

The quantitative nature of the reaction is indicated by the results shown in Table II. Products

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[1] B. H. Nicolet and L. A. Shinn, *J. Am. Chem. Soc.*, 61, 1615 (1939).

other than oxazolines are included for comparison. One mole of periodic acid is consumed for each hydroxymethyl group present in position 4 of the oxazoline ring. Two moles of periodic acid are consumed in the oxidation of tris(hydroxymethyl)aminomethane. As expected, essentially no oxidation takes place with *N*-[tris(hydroxymethyl)methyl]lauramide, $C_{11}H_{23}CONHC(CH_2OH)_3$, or 2-dimethylamino-2-methyl-1-propanol, $(CH_3)_2NC(CH_3)_2CH_2OH$.[2]

The rate of the periodate oxidation of 4-hydroxymethyl-2-oxazolines under standardized conditions depends in part on the substituent present in position 2. Those oxazolines containing an ethyl group in position 2 are completely oxidized in two hours, while those with a phenyl group require approximately twenty-four hours. Oxazolines containing both methyl and hydroxymethyl groups in position 4 consume, on long standing, greater amounts of periodic acid than required according to Equation 1. This is undoubtedly due to the partial hydrolysis of the primary oxidation product to hydroxyacetone which is oxidizable with periodic acid. This is not observed with 4,4-bis(hydroxymethyl)-2-oxazolines as the primary oxidation product, acyloxyacetic acid, on hydrolysis yields a nonperiodate-oxidizable product.

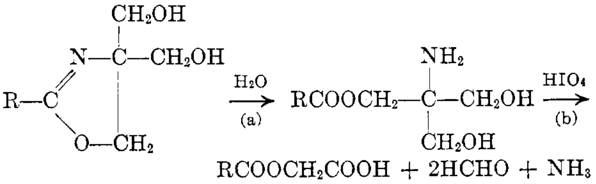
The effect of *p*H on this oxidation of oxazolines is complex and significant in respect to the mechanism of the reaction. The effect of *p*H on the comparable oxidation of tris(hydroxymethyl)aminomethane was also investigated since it is of importance to the understanding of the oxazoline reaction. Results are given in Table III.

Previous work[3] has demonstrated that amino alcohols of suitable structure are oxidized by periodic acid under neutral or alkaline conditions but not under strongly acidic conditions.

The present study shows that, without added alkali, the oxidation of tris(hydroxymethyl)aminomethane is approximately half completed in one hour, three-quarters in four hours and fully completed in twenty-two hours. Two moles of periodic acid are consumed per mole of tris(hydroxymethyl)aminomethane. In the presence of bicarbonate, the reaction is complete in fifteen minutes or less. The reaction is completely inhibited by sulfuric acid.

The effect of *p*H on the periodate oxidation of 2-ethyl-4,4-bis(hydroxymethyl)-2-oxazoline is more complicated than it is on the periodate oxidation of tris(hydroxymethyl)aminomethane. Again, sulfuric acid completely inhibits the reaction. The reaction rate is markedly reduced, however, by bicarbonate. With no added alkali or acids the reaction is slow, requiring twenty-four hours for completion. This rate is comparable to that of the oxidation of the amino polyol. Very significantly, the reaction is complete in less than two hours if it is carried out first in the presence of acid and then in the presence of bicarbonate.

From these results it is concluded that the over-all reaction is accomplished in at least two steps. The first step is an acid-catalyzed, bicarbonate-retarded reaction; the second is an acid-inhibited, bicarbonate-catalyzed reaction. The following sequence of reactions is proposed.



Reaction (a) is hydrolysis of a type known to be acid catalyzed and alkali retarded.[4] Reaction (b) is oxidation of a type known to be alkali catalyzed and acid inhibited.[3] Periodic acid ($K_1 = 2.3 \times 10^{-2}$) probably serves as the catalyst for step (a) in the reactions carried out in the absence of sulfuric acid. This proposed sequence of reactions is consistent with the results of this investigation and with the information available in the literature regarding periodate oxidations.

Benzoxyacetone and benzoxyacetic acid were prepared by the periodate oxidation of 2-phenyl-4-methyl-4-hydroxymethyl-2-oxazoline and 2-phenyl-4,4-bis(hydroxymethyl)-2-oxazoline, respectively, to establish the over-all course of the reaction and to illustrate the possible preparative utility of the oxidation procedure. Formaldehyde was detected by odor in both instances.

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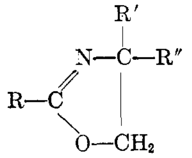
(2) Under the conditions used in this investigation 2-dimethylamino-2-methyl-1-propanol consumed only 0.07 mole of periodic acid per mole of amino alcohol in 24 hr. This is consistent with the report of Nicolet and Shinn (ref. 1) which indicates that diethylaminoethanol shows practically no reaction with periodic acid. A report by P. Fleury, J. Courtois, and M. Grandchamp, *Bull. soc. chim. France*, **88** (1949), indicates that triethanolamine and methyldiethanolamine are only very slowly oxidized by periodic acid, although in a matter of days an appreciable quantity of periodic acid is reduced. A report by E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, and K. Gerzon, *J. Am. Chem. Soc.*, **76**, 3121 (1954) indicates that diethylaminoethanol and even the non-vicinally substituted 3-diethylamino-1-propanol are periodate oxidizable at a slow rate, the former consuming 0.9 mole equivalent of periodate in 51 hr. and the latter 0.99 mole equivalent in 45 hr. Further work in this area would seem warranted.

(3) See for example: D. D. Van Slyke, A. Hiller, and D. A. MacFadyen, *J. Biol. Chem.*, **141**, 681 (1941); A. Wickstrom, *Ann. pharm. franc.*, **8**, 86 (1950); G. E. McCasland and D. A. Smith, *J. Am. Chem. Soc.*, **73**, 5164 (1951).

(4) S. Gabriel and T. Heymann, *Ber.*, **23**, 2495 (1890); A. Salomon, *Ber.*, **26**, 1321 (1893); M. Bergmann and E. Brand, *Ber.*, **56B**, 1280 (1923); F. Bettzieche, *Z. physiol. Chem.*, **146**, 227 (1925); *Chem. Abstr.*, **19**, 3254 (1925); A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1919 (1948); R. H. Wiley and L. L. Bennett, Jr., *Chem. Revs.*, **44**, 458 (1949); J. W. Cornforth, *Heterocyclic Compounds*, Vol. 5, R. C. Elderfield, ed., Wiley, New York, 1957, p. 386.

TABLE I

OXAZOLINES



R	R′	R″	Yield, %	B.P. (Mm.)	M.P.	N, % Calcd.	N, % Found	Neut. Equiv. Calcd.	Neut. Equiv. Found[a]
C_2H_5	CH_3	CH_3	76	129–130; 72–73 (100)		11.01	11.38	127.2	128.0 128.9
C_2H_5	CH_3	$HOCH_2$	89	100–102 (10)		9.78	10.06	143.2	144.7 145.1
C_2H_5	$HOCH_2$	$HOCH_2$	81		83–84	8.80	8.72	159.2	159.1
C_6H_5	CH_3	$HOCH_2$	70		102–103[b]	7.33	7.05	191.2	193.2
C_6H_5	$HOCH_2$	$HOCH_2$	75		138–140[c]	6.76	6.54	207.2	210.0 210.4

[a] By nonaqueous titration. [b] Lit.[8] m.p. 103–104°. [c] Lit.[8] m.p. of crude material, 125–128°.

TABLE II

PERIODATE OXIDATIONS OF OXAZOLINES AND RELATED MATERIALS

Compound	Hr. 0.5	1.0	2.0	3.0	4.0	5.0	8.0	24	30	64
	Moles of Periodic Acid Consumed Per Mole of Compound									
2-Ethyl-4,4-dimethyl-2-oxazoline			0.0							
2-Ethyl-4-methyl-4-hydroxymethyl-2-oxazoline			1.02							
	0.62	0.82	0.99	1.01						
2-Ethyl-4,4-bis(hydroxymethyl)-2-oxazoline	1.63	1.91	1.97		1.97					
2-Phenyl-4-methyl-4-hydroxymethyl-2-oxazoline		0.10	0.18			0.43	0.60	1.06		1.18
2-Phenyl-4,4-bis(hydroxymethyl)-2-oxazoline		0.47	0.89			1.51	1.79	2.01	2.01	
Tris(hydroxymethyl)aminomethane		2.00								
N-[Tris(hydroxymethyl)methyl]lauramide			0.0							
2-Dimethylamino-2-methyl-1-propanol								0.07		

EXPERIMENTAL

All melting points and boiling points are uncorrected. The melting points were determined with the Fisher-Johns apparatus.

Amino alcohols. The amino alcohols used in the synthesis of the various oxazolines were commercial-grade materials. 2-Dimethylamino-2-methyl-1-propanol was prepared by the reductive methylation of 2-amino-2-methyl-1-propanol.[5,6] The tris(hydroxymethyl)aminomethane used for analytical purposes was Standard of Reference Grade material obtained from the G. Frederick Smith Chemical Co. *N*-[Tris(hydroxymethyl)methyl]lauramide was prepared by Mr. J. A. Frump of these laboratories according to the method of Schramm.[7]

Oxazolines. All the oxazolines were prepared by the reaction of either propionic anhydride or benzoic acid with the appropriate amino alcohol by refluxing in toluene with azeotropic removal of water. The liquid products were purified by distillation, and the solid products by recrystallization from either acetone, cyclohexane, or ethanol. The results are summarized in Table I.

Periodate oxidations, standard procedure. The behavior of the various products toward periodic acid was determined by the following standardized procedure[9]:

To an aqueous solution or suspension of a suitably sized sample (50–250 mg.) of the oxazoline or other material in a 500-ml. iodine flask was added 20 ml. of approximately 0.1*M* periodic acid. The solution, *p*H approximately 2, was kept at room temperature for a timed interval, and then 50 ml. of saturated sodium bicarbonate solution and 25 ml. of approximately 0.1*M* sodium arsenite solution were added to yield a solution with a *p*H of about 9. After 15 min. the excess arsenite was determined by titration with standard 0.1*N* iodine solution. Blank determinations were run concurrently. A rough rate study was made with most compounds to establish that the reactions proceeded to a definite final stage. The results are given in Table II.

Effect of pH. The effect of *p*H on the periodate oxidation of tris(hydroxymethyl)aminomethane and of 2-ethyl-4,4-bis(hydroxymethyl)-2-oxazoline was investigated. The following five procedures were used.

A. Standard procedure, already described.

B. The sample was added to 10 ml. of 0.1*M* periodic acid. After the indicated interval at room temperature, 20 ml. of 15% sulfuric acid, 100 ml. of water and 20 ml. of 30% potassium iodide solution were added. After 10 min. the liberated iodine was titrated with standard thiosulfate solution.

C. The sample was added to a mixture of 10 ml. of 0.1*M* periodic acid and 5 or 10 ml. of saturated sodium bicarbonate solution yielding a solution with a *p*H of approximately 8. After the indicated interval at room temperature, 36 or 50 ml. of 15% sulfuric acid, 100 ml. of water, and 20 ml. of

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(5) V. Rosnati, *Gazz. chim. ital.*, **80,** 663 (1950); *Chem. Abstr.*, **46,** 429 (1952).

(6) Available as a developmental chemical from Commercial Solvents Corp.

(7) C. H. Schramm, U. S. Patent **2,927,081** (1960).

(8) J. H. Billman and E. E. Parker, *J. Am. Chem. Soc.*, **67,** 1069 (1945).

(9) The method used here for the determination of periodate in the presence of iodate was first reported by P. F. Fleury and J. Lange, *J. pharm. chim.*, [8] **17,** 107 (1933).

TABLE III

EFFECT OF *p*H ON PERIODATE OXIDATIONS

	Moles of Periodic Acid Consumed				
Procedure	Per mole of tris(hydroxymethyl)aminomethane	Reaction time, hr.	Per mole of 2-ethyl-4,4-bis(hydroxymethyl)-2-oxazoline	Reaction time, hr.	Conditions
A	2.00	2.0	1.96	2.0	No additive for 2 hr., then bicarbonate
			1.96	2.0	
B	0.91	1.0			
	1.23	2.0	1.07	2.0	No additive for reaction time shown, then sulfuric acid
	1.50	4.0	1.66	6.0	
	2.00	22	1.94	24	
C	2.04	0.25	0.17	2.0	Bicarbonate for reaction time shown, then sulfuric acid
			0.22	2.0	
			0.43	6.0	
			0.91	24	
D	—	—	1.70	0.5	Sulfuric acid for reaction time shown, then bicarbonate
			1.92	1.0	
			1.96	1.5	
			1.96	2.0	
			2.00	5.0	
E	0.00	1.0	0.0	2.0	Sulfuric acid present throughout reaction
			0.0	2.0	
			0.0	6.0	
			0.1	24	

30% potassium iodide solution were added. After 10 min. the liberated iodine was titrated with standard thiosulfate solution.

D. The sample was added to a mixture of 20 ml. of 0.1*M* periodic acid and 5 ml. of 15% sulfuric acid yielding a solution with a *p*H of approximately 0.8. After the indicated interval at room temperature, 66 ml. of saturated sodium bicarbonate solution and 25 ml. of 0.1*M* sodium arsenite solution were added. The excess arsenite was titrated with standard iodine solution after 15 min.

E. The sample was added to a mixture of 10 ml. of 0.1*M* periodic acid and 20 ml. of 15% sulfuric acid yielding a solution with a *p*H close to 0. After the indicated interval at room temperature, 100 ml. of water and 20 ml. of 30% potassium iodide solution were added. After 10 min. the liberated iodine was titrated with standard thiosulfate solution.

The results are given in Table III. Each entry under Reaction Time, hr., refers to a separate experiment.

Preparation of benzoxyacetone. 2-Phenyl-4-methyl-4-hydroxymethyl-2-oxazoline (19 g., 0.1 mole) was added to a solution of 25 g. of periodic acid in 100 ml. of water. The clear solution that was obtained was shaken mechanically for 24 hr. at room temperature. Formaldehyde was detected by odor. The mixture was diluted with 200 ml. of water, neutralized with bicarbonate solution, and extracted with four 100-ml. portions of benzene. The dried benzene extract was distilled. Benzoxyacetone (14.1 g., 80% yield) was collected at 100–103°/1 mm. The reported[10] boiling point is 188–190°/60 mm.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66. Found: C, 67.05; H, 5.60; N, 0.70.

Preparation of benzoxyacetic acid. 2-Phenyl-4,4-bis(hydroxymethyl)-2-oxazoline (10.5 g., 0.05 mole) was added to a solution of 25 g. of periodic acid in 250 ml. of water. The mixture was shaken mechanically for 24 hr. at room temperature, then was cooled for 3 hr. in a refrigerator and filtered. The white solid obtained (8.5 g., 94% yield) melted at 104–106°. Recrystallization of this material from water yielded 5 g. of benzoxyacetic acid, m.p. 111–111.5°. The reported melting point is 110–111°[11] or 112°.[12]

Anal. Calcd. for $C_9H_8O_4$: Equiv. wt., 180.2. Found: Equiv. wt. by nonaqueous titration, 182.4.

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[10] A. Brewer and T. Zincke, *Ber.*, **13**, 639 (1880).

[11] J. D. Riedel, German Pat. **555,931** (1930); *Chem. Abstr.*, **26**, 5970 (1932).

[12] P. Brigl and H. Grúner, *Ber.*, **65**, 641 (1932).