2,4-OXAZOLIDINEDIONES

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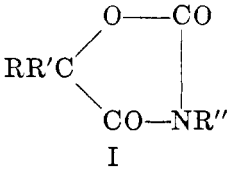
CONTENTS

I. Introduction

A. Structure and nomenclature of 2,4-oxazolidinediones

2,4-Oxazolidinediones are compounds having the structure shown in formula I. About one hundred seventy derivatives are known in which R, R′, and R″ represent hydrogen, alkyl, aralkyl, aryl, or heterocyclic substituents.



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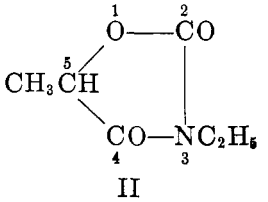


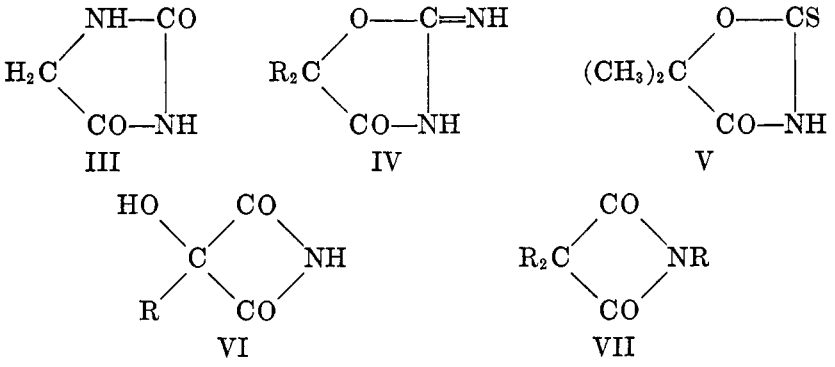
II

Current *Chemical Abstracts* nomenclature and numbering are used throughout this review, e.g., compound II is 3-ethyl-5-methyl-2,4-oxazolidinedione; alternative names are 3-ethyl-5-methyl-2,4-dioxoöxazolidine or -tetrahydroöxazole, and 3-ethyl-5-methyloxazolid-2,4-dione, the latter name being representative of the nomenclature used in the *Journal of the Chemical Society*. Trivial names have been introduced for compounds used in treating petit mal epilepsy, e.g., trimethadione, U.S.P.[1] (tridione, N.N.R.; troxidone, B.P.) for trimethyl-2,4-oxazolidinedione (I: R = R′ = R″ = CH_3) and paramethadione (paradione, N.N.R.) for 5-ethyl-3,5-dimethyl-2,4-oxazolidinedione (I: R = C_2H_5, R′ = R″ = CH_3).

This review deals mainly with the preparation and properties of the 2,4-oxazolidinediones, but a brief account of the medicinal and other uses of 2,4-oxazolidinediones is given in the final section.

B. RELATED RING SYSTEMS

2,4-Oxazolidinediones are stable substances. They are similar in general properties to the hydantoins (III, and derivatives) (180) and are prepared by analogous methods. Indeed, 2-imino-4-oxazolidones (pseudohydantoins) (IV) are sometimes formed instead of the isomeric hydantoins, and hydrolysis of the imino group then gives the corresponding 2,4-oxazolidinedione. Replacement of the sulfur atom of 5,5-dimethyl-2-thio-4-oxazolidione (V) (170) by oxygen gave 5,5-dimethyl-2,4-oxazolidinedione and led to recognition of the oxazoli-



dinedione ring system (I) in 1878 (171, 172). Many 2,4-oxazolidinediones (116) were originally regarded as the isomeric tartronimides (VI) (71, 137–142, 145, 165), but with the possible exception of triphenylmalonimide (VII: R = C_6H_5) (156), there appear to be no authentic examples of the 2,4-azetidinedione ring system (VI and VII) (116–118).

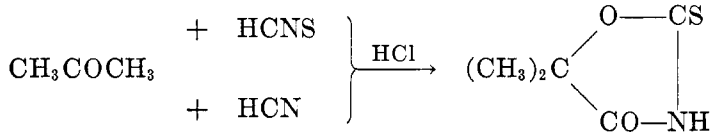
[1] U.S.P. = U. S. Pharmacopoeia.
N.N.R. = New and Nonofficial Remedies.
B.P. = British Pharmacopoeia.

II. Methods of Synthesis of 2,4-Oxazolidinediones

Methods of preparing 2,4-oxazolidinediones from heterocyclic intermediates are considered first, and then the more direct syntheses from acyclic compounds. The latter include two of the most satisfactory general methods: viz., condensations of esters of α-hydroxy acids with urea and of amides of α-hydroxy acids with a dialkyl carbonate (methods 4 and 5).

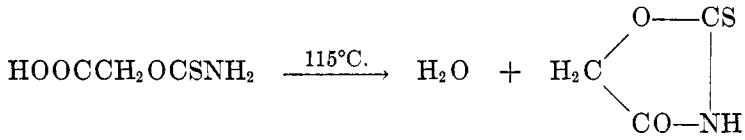
A. Method 1: Oxidation of 2-thio-4-oxazolidones

Acetone, potassium cyanide, and potassium thiocyanate in the presence of concentrated hydrochloric acid give 5,5-dimethyl-2-thio-4-oxazolidone (170).



Replacement of acetone by its cyanohydrin and use of ammonium thiocyanate are reported to give a better yield of 5,5-dimethyl-2-thio-4-oxazolidone (70, 112, 113), but the original method (170) has been improved and gives yields of 62–75 per cent (87, 174). The reaction has been extended to formaldehyde (87, 173), acetaldehyde (87), benzaldehyde (174), and ethyl methyl ketone (87, 93, 174), but fails with some higher ketones, possibly because of limited solubility of the ketones or intermediate cyanohydrins in the aqueous medium (87).

2-Thio-4-oxazolidone (90 per cent yield) was obtained by heating thiocarbamoylglycolic acid at 115°C. for 30 min. (3).



The required acid was obtained indirectly from sodium glycolate.

$$^{-}OOCCH_2OH + CS_2 + OH^- \rightarrow H_2O + {}^{-}OOCCH_2OCS_2^-$$

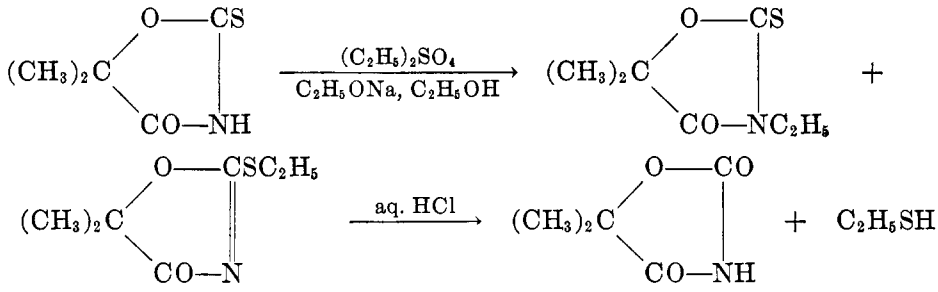
$$\xrightarrow{ClCH_2CONH_2} Cl^- + {}^{-}OOCCH_2OCSSCH_2CONH_2 \xrightarrow{NH_3}$$

$$^{-}OOCCH_2OCSNH_2$$

N-Ethylthiocarbamoylglycolic acid (104), $C_2H_5NHCSOCH_2COOH$, cyclized so readily that 3-ethyl-2-thio-4-oxazolidone was isolated directly after reaction of ethylamine with the above acetamide intermediate (ca. 80 per cent yield) or with the corresponding acetic acid (4). 3-Phenyl-2-thio-4-oxazolidone was obtained similarly (105).

3-Alkyl-2-thio-4-oxazolidones are more conveniently prepared by the alkylation (85, 87) of 2-thio-4-oxazolidones; *N*-alkylation (30–50 per cent yield) is accompanied by *S*-alkylation, but the products are easily separated as the 2-

alkylthioöxazol-4-ones are readily hydrolyzed by acids to mercaptans and 2,4-oxazolidinediones, which are soluble in aqueous ammonia (87), e.g.:



The proportion of *N*-alkylation compared with *S*-alkylation decreases with increasing size of the alkyl group (85). The *S*-alkyl derivatives are so readily hydrolyzed that 2,4-oxazolidinediones may be formed during alkylation unless conditions are strictly anhydrous, and the products then undergo alkylation to 3-alkyl-2,4-oxazolidinediones. 3-Benzyl- and 3-ethyl-5,5-dimethyl-2,4-oxazolidinedione were obtained in this way from 5,5-dimethyl-2-thio-4-oxazolidone (85).

Conversion of 2-thio-4-oxazolidones into 2,4-oxazolidinediones (table 1) is effected (*a*) with bromine water (2, 85, 93, 106), (*b*) by passing chlorine through a water–carbon tetrachloride solution of the thio compound (85, 87), (*c*) by oxidation with hydrogen peroxide at 70–100°C. (70), (*d*) by oxidation with acid

TABLE 1

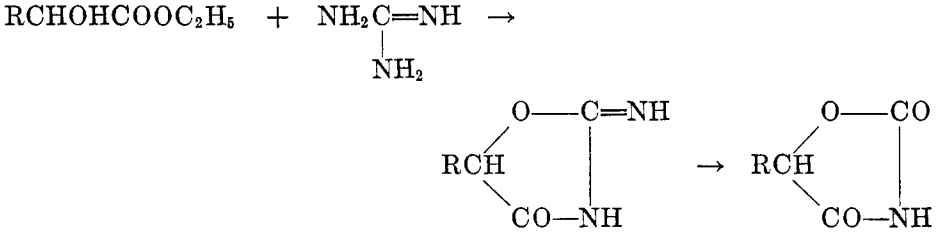
2,4-Oxazolidinediones from 2-thio-4-oxazolidones

Source	Substituent in the 2-Thio-4-oxazolidone (and Yield)	Yield of 2,4-Oxazolidinedione in Oxidation and Method of Oxidation	References
		per cent	
NH_2CSOCH_2COOH	—	72%; method a	(5)
$C_2H_5NHCSOCH_2COOH$	3-Ethyl	85%; method a	(6)
$C_6H_5NHCSOCH_2COOH$	3-Phenyl (90%)	ca. 95%; method a	(106)
Formaldehyde	— (40%)	Method a	(87)
	— (48%)	Not converted	(173)
Acetaldehyde	5-Methyl (47–54%)	Not converted	(87)
Benzaldehyde	5-Phenyl (64%)	Not converted	(174)
Acetone	5,5-Dimethyl (73%; 62%)	Not converted	(87, 174)
	5,5-Dimethyl (61%)	50%; method a	(132)
	5,5-Dimethyl	Method f	(171, 172)
α-Hydroxyisobutyronitrile	5,5-Dimethyl (77%)	ca. 100%; method c	(70)
	5,5-Dimethyl	Method f	(112)
	5,5-Dimethyl (90–95%)	Not converted	(113)
Ethyl methyl ketone	5-Ethyl-5-methyl	Methods a and f	(93)
	5-Ethyl-5-methyl (35%)	Not converted	(87, 174)
Alkylation of 2-thio-4-oxazolidone	3,5-Dimethyl (38%)	71%; method b	(85, 87)
	3,5,5-Trimethyl (49%)	ca. 100%; methods a and d	(85, 87)
	3-Ethyl-5,5-dimethyl (52%)	90%; methods b and a	(85, 87)
	3,5-Dimethyl-5-ethyl (46%)	67%; method b	(85, 87)
	3,5-Diethyl-5-methyl (41%)	76%; method b	(85, 87)
Aldehyde and 2-thio-4-oxazolidone	5-Benzylidine-3-phenyl	Method e	(150)
	5-*o*-Chlorobenzylidine-3-phenyl	Method e	(150)

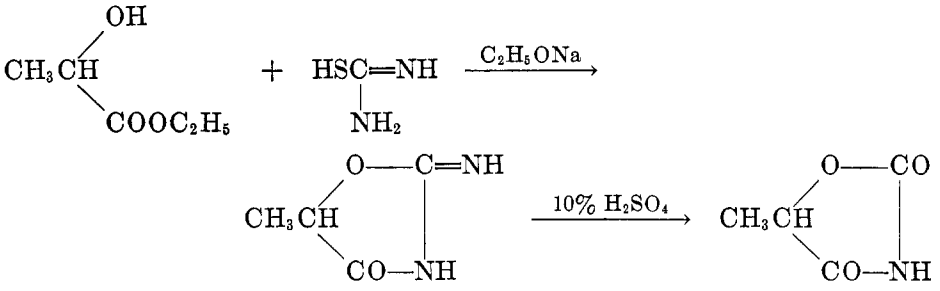
permanganate (87), or (*e*) by oxidation with nitric acid (150), and (*f*) less satisfactorily by heating the thio compounds with aqueous lead acetate (93, 112, 171) or by oxidation with alkaline permanganate (2, 103).

B. METHOD 2: HYDROLYSIS OF 2-IMINO-4-OXAZOLIDONES

Esters of α-hydroxy acids condense with guanidine (50 per cent solution in ethanol) to yield 2-imino-4-oxazolidones (169), which are isomeric with hydantoins and are frequently termed pseudohydantoins; the imino compounds are readily hydrolyzed to 2,4-oxazolidinediones (e.g., R = H, CH_3, C_6H_5) (169).

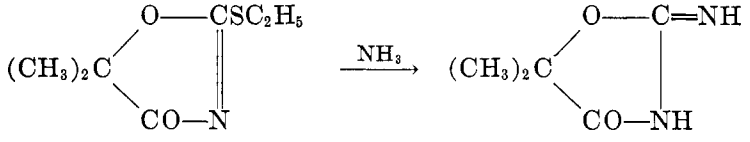


Guanidine can be replaced by its nitrate and one equivalent of sodium ethoxide, or by thiourea with sodium ethoxide as condensing agent, as in the preparation of 2-imino-5-methyl- and 2-imino-5-phenyl-4-oxazolidone (30).

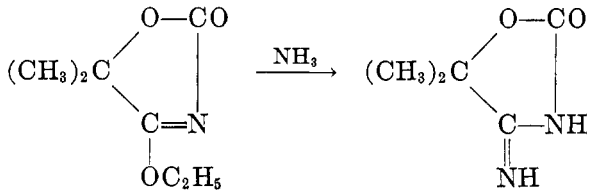


The intermediate 2-imino compounds obtained from thiourea were formerly regarded as α-hydroxyacylcyanamides, and the 2,4-oxazolidinediones as 1,3-di(α-hydroxyacyl)ureas (80, 81; *cf.* 29 and 30). The compound obtained (133) from lactide and alcoholic potassium cyanamide is presumably 2-imino-5-methyl-4-oxazolidone (30, 81).

2-Imino-5,5-dimethyl-4-oxazolidone has also been prepared by the action of cold aqueous ammonia on 2-ethylthio-5,5-dimethyloxazol-4-one (87),



and 4-imino-5,5-dimethyl-2-oxazolidone was obtained by ammonolysis of 4-ethoxy-5,5-dimethyloxazol-2-one in ethanol (84).



Acid hydrolysis of both imino compounds gave 5,5-dimethyl-2,4-oxazolidinedione (84, 87).

2-Imino-4-oxazolidones are also obtained by the action of alkali on α-bromoureides and 5-bromobarbituric acids (16), and by the condensation of esters of α-chloro acids with substituted ureas, as described below (method 7).

Hydrolysis of 2-imino-4-oxazolidones to 2,4-oxazolidinediones (ca. 80 per cent yield) occurs very readily with aqueous mineral acids, e.g., with boiling 10 per cent sulfuric acid for 15–30 min. (30, 80, 81) (table 2). Alcoholic hydrogen chloride (169) appears less satisfactory than the aqueous acid (84), and 30 per cent sulfuric acid was used to convert 5,5-diethyl-2-imino-4-oxazolidone into 5,5-diethyl-2,4-oxazolidinedione (91). The condensation product obtained from ethyl mandelate and dicyandiamide in the presence of sodium methoxide was hydrolyzed to 5-phenyl-2,4-oxazolidinedione with 67 per cent sulfuric acid (89).

C. METHOD 3: ALKALINE HYDROLYSIS OF DIALURIC ACIDS

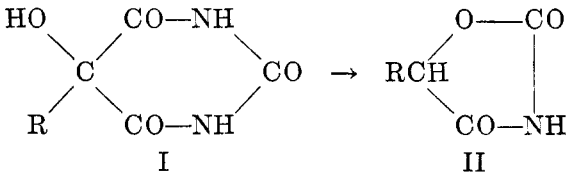
2,4-Oxazolidinediones (29–31, 116) are formed from dialuric acids (I) by the action of aqueous sodium hydroxide either at room temperature or at 100°C. for 20–30 min., and in many cases (especially when R = aryl) the products (II)

TABLE 2

2,4-Oxazolidinediones from 2-imino-4-oxazolidones

Substituent in the 2-Imino-4-oxazolidone	Yield of Imino Compound and Method	Yield of Oxazolidinedione	Reference
		per cent	
—	40–50% from guanidine	40	(84)
—	60% from thiourea	81	(81)
5-Methyl	70% from guanidine	32	(169)
	From guanidine and thiourea	Not stated	(30)
	70% from thiourea	83	(81)
5-Ethyl	70% from thiourea	ca. 80	(81)
5-Isopropyl	77% from thiourea	ca. 80	(81)
5-Phenyl	90% from guanidine	Not stated	(169)
	From guanidine and thiourea	Not stated	(30)
5,5-Dimethyl	73% from thiourea	ca. 80	(80)
5,5-Diethyl	83% from thiourea	ca. 80	(80)
	From guanidine	Not stated	(91)
5,5-Di-*n*-propyl	81% from thiourea	ca. 80	(80)
5,5-Pentamethylene (spirocyclohexane)	From guanidine	80 (overall)	(151)

crystallize from the acidified solutions:



I II

Optimum results are achieved with 2–3 equivalents of alkali and, if less than 2 equivalents is used, fission of the pyrimidine ring occurs but formation of the oxazolidinedione is incomplete (29, 30). *N*-Alkyl(or aryl)- and *N*,*N'*-dialkyl(or diaryl)dialuric acids also yield oxazolidinediones (see below and table 4), but

TABLE 3

2,4-Oxazolidinediones from dialuric acids

Aromatic Component for Preparation of Dialuric Acid	Yield of Dialuric Acid	Reference	5-Substituent in the Dialuric Acid and in the 2,4-Oxazolidinedione	References
	per cent			
Aniline	—	(137)	5-*p*-Aminophenyl	(71, 137)
Methylaniline	60	(137)	5-*p*-Methylaminophenyl	(71, 137)
Dimethylaniline	86	(137)	5-*p*-Dimethylaminophenyl	(71, 137)
o-Toluidine	—	(137)	5-(4-Amino-3-methylphenyl)	(71, 137)
Pseudocumidine(5-amino-1,2,4-trimethylbenzene?)	—	(138)	5-(2-Amino-3,5,6-trimethylphenyl)?	(138)
Diphenylamine	—	(137)	5-*p*-Phenylaminophenyl	(137)
Ethylaniline	—	(71)	5-*p*-Ethylaminophenyl	(71)
Diethylaniline	—	(71)	5-*p*-Diethylaminophenyl	(71)
o-Anisidine	—	(71)	5-(4-Amino-3-methoxyphenyl)	(71)
Anisole	32	(116)	5-*p*-Methoxyphenyl (47% yield)	(116)
1,3-Dimethoxybenzene	57	(116)	5-(2,4-Dimethoxyphenyl) (65–70% yield)	(116)
1,2,4-Trimethoxybenzene	—	(165)	5-(2,4,5-Trimethoxyphenyl)	(165)
3-Methyl-1-phenylpyrazol-5-one	92	(140)	5-(3-Methyl-5-oxo-1-phenylpyrazolin-4-yl)	(139–142)
2,3-Dimethyl-1-phenylpyrazol-5-one	97	(140)	5-(2,3-Dimethyl-5-oxo-1-phenylpyrazolin-4-yl)	(139–142)
Pyrrole	—	(78)	5-(2-Pyrryl)	(78)

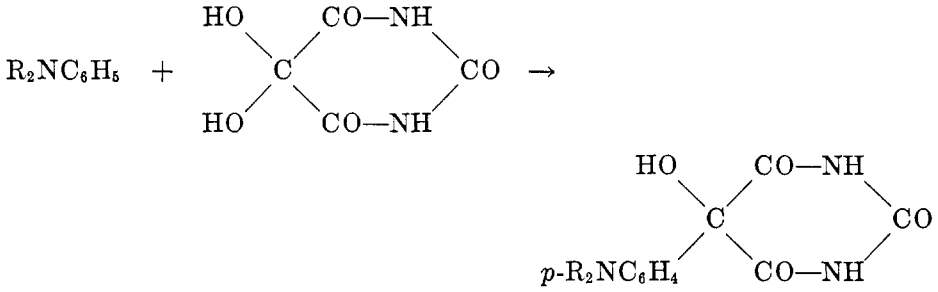
TABLE 4

Comparative yields of oxazolidinediones from N-substituted dialuric acids

Substituent in Dialuric Acid	Substituent in 2,4-Oxazolidinedione	Yield	Reference
		per cent	
5-Ethyl	5-Ethyl	90	(14)
5-Ethyl-1-methyl	5-Ethyl	33	(27)
5-Ethyl-1-phenyl	5-Ethyl	Poor	(31)
5-Benzyl	5-Benzyl	71	(12)
5-Benzyl-1-methyl	5-Benzyl	63	(25)
5-Benzyl-1-phenyl	5-Benzyl	56	(23)
5-Phenyl	5-Phenyl	86	(20)
1-Methyl-5-phenyl	5-Phenyl	67–94	(33)
1,5-Diphenyl	5-Phenyl	83	(32)
5-Benzyl-1,3-dimethyl	5-Benzyl-3-methyl	40–80	(28)
5-Benzyl-1-methyl-3-phenyl	5-Benzyl-3-methyl	55	(53)
	5-Benzyl-3-phenyl	15	(54)

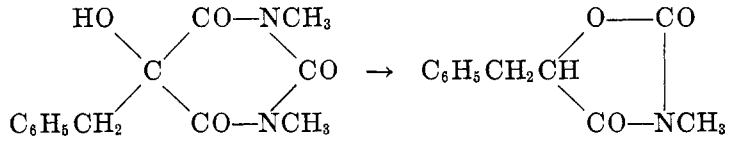
the reaction proceeds most satisfactorily with 5-monosubstituted dialuric acids (I) (table 3).

Alloxan hydrate reacts with aromatic amines (71, 73, 137), such as aniline, methylaniline, and dimethylaniline (137), to give 5-*p*-aminophenyldialuric acids (R = H or CH_3).

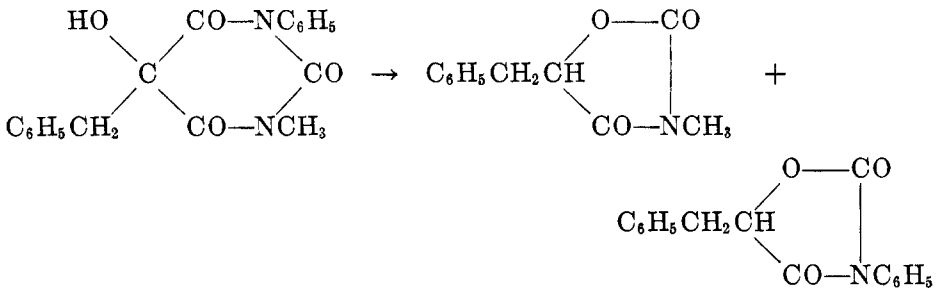


Substitution occurs para to the amino group; if this position is occupied, as in *p*-toluidine, reaction usually does not occur, although a pseudocumidine, thought to be 5-amino-1,2,4-trimethylbenzene (138), gave a dialuric acid in the usual way. Phenols (72, 74, 75, 147) and phenol ethers (116, 165) react similarly with alloxan, which substitutes para to an activating group or, if this position is occupied, in the ortho position; e.g., *p*-cresol yields 5-(2-hydroxy-5-methylphenyl)-dialuric acid (72). A considerable number of dialuric acids have been prepared in this way, including a few from heterocyclic compounds (78, 139–142), and some of the dialuric acids have been converted into 2,4-oxazolidinediones (table 3) which, however, were described as tartronimides (71, 137–142, 165).

Dialuric acids can also be prepared by the oxidation of 5-alkyl- or 5-aryl-barbituric acids with potassium dichromate or with hydrogen peroxide (22, 31). *N*-Substituted dialuric acids prepared in this way were used to investigate the influence of *N*-substitution on the formation of 2,4-oxazolidinediones (22, 31, 52); the latter compounds were described as 1,3-di(α-hydroxyacyl)ureas in earlier papers (11, 19, 22). 1,5-Dialkyl(or aryl)dialuric acids give 5-alkyl(or aryl)-2,4-oxazolidinediones and 3-substituted oxazolidinediones were not isolated; any 3-substituted oxazolidine formed by the alternative ring closure would probably be hydrolyzed further, as these compounds are labile in aqueous alcoholic alkali (see Section IV,C). Alkaline degradation of 5-benzyl-1,3-dimethyldialuric acid gave a low yield of 5-benzyl-3-methyl-2,4-oxazolidinedione, and a better yield was obtained when the dialuric acid was merely boiled in aqueous solution (28).



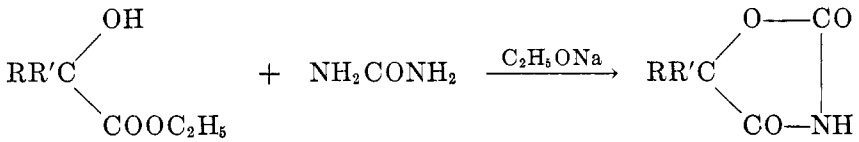
Dialuric acids bearing different *N*-alkyl substituents can lead to mixtures of two oxazolidinediones, but the course of the reaction is not simple (52).



N,N'-Dialkyl-5-bromobarbituric acids yield hydantoins, but other 5-bromobarbituric acids yield 2,4-oxazolidinediones when treated with aqueous alkali. This method is considered together with syntheses from α-bromoacylureas (method 7), since these compounds have been isolated as intermediates in the reaction.

D. METHOD 4: CONDENSATION OF ESTERS OF α-HYDROXY ACIDS WITH UREA

Esters of α-hydroxy acids condense with urea in the presence of sodium ethoxide to yield sodium salts of 2,4-oxazolidinediones.



Yields are about 80 per cent (157), and the reaction has been used extensively since interest has developed in 2,4-oxazolidinediones as medicinal substances. This method is convenient because of the accessibility of the esters and permits the preparation of a wide range of 5-monosubstituted and 5,5-disubstituted 2,4-oxazolidinediones (table 5). Acetone derivatives of α-hydroxy acids (i.e., 1,3-dioxolan-4-ones) can be used instead of the alkyl esters (98), and urea can be replaced by urethans (98, 115).

The interaction of urea, esters of α-hydroxy acids, and sodium ethoxide was reported in 1908 to give 1,3-di(α-hydroxyacyl)ureas (80, 81); thirty years elapsed before the products were recognized as 2,4-oxazolidinediones and the yields were improved by using molecular equivalents of reactants (29, 30, 157). Condensation is usually effected by heating the reactants with one equivalent of alcoholic sodium ethoxide on a steam bath for periods up to 15 hr., and the alcohol is then removed under reduced pressure (157). The residue of sodium salt (or the solution, after aspiration to remove ammonia) may be *N*-alkylated directly (84), or the 2,4-oxazolidinedione is liberated by acidification with mineral acid, and collected by filtration or by extraction into ether; the product is purified by distillation under reduced pressure or by crystallization (157). Heating urea with ethyl lactate, or ethyl glycolate, without a condensing agent at 175–180°C. and in a current of air gives satisfactory yields of 5-methyl-2,4-oxazolidinedione and 2,4-oxazolidinedione (134). The progress of the reaction can be followed by estimation of the ammonia liberated; unchanged urea is then

TABLE 5

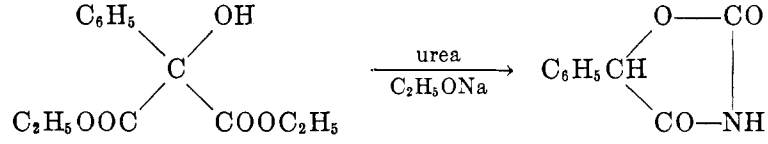
2,4-Oxazolidinediones from α-hydroxy acid esters and urea

Substituent in the 2,4-Oxazolidinedione	Yield; Reference in Parentheses
	per cent
5-Monosubstituted derivatives:	
Parent compound	67 (30); 70–80 (134); 35 (81)
5-Methyl	67 (30); 50–70 (134); — (81)
5-Ethyl	66 (81); 41 (30)
5-*n*-Propyl	— (155)
5-Isopropyl	77 (81); — (155)
5-*n*-Hexyl	— (158)
5-Phenyl	77 (116); 67.5, 75 as sodium salt (148)
5-Phenyl	17
5-*p*-Tolyl	9
5-*p*-Ethylphenyl	24
5-(2′,5′-Dimethylphenyl)	37 from tartronic esters (145)
5-Mesityl	6
5-*p*-*sec*-Butylphenyl	38
5,5-Disubstituted derivatives:	
5,5-Di-*n*-amyl	ca. 80 (157); 80 (159)
5,5-Di-*n*-butyl	ca. 80 (157); — (158, 159)
5,5-Diisobutyl	ca. 80 (157); — (159)
5,5-Diethyl	80 (80, 157); — (30)
5,5-Dimethyl	90 (30); 83 (80); ca. 80 (157)
5,5-Di-*n*-propyl	ca. 80 (157); 75–80 (158, 159); 70 (80)
5,5-Diisopropyl	— (158, 159)
5,5-Diphenyl	95 (55); ca. 80 (157); 70–90 (162); — (99)
5-*n*-Amyl-5-methyl	ca. 80 (157); — (158–160)
5-*n*-Amyl-5-phenyl	ca. 80 (157)
5-Isoamyl-5-ethyl	— (158, 160)
5-Isoamyl-5-methyl	— (159)
5-*n*-Butyl-5-methyl	ca. 80 (157); — (158–160)
5-*n*-Butyl-5-phenyl	ca. 80 (157)
5-Isobutyl-5-phenyl	ca. 80 (157)
5-Di-*n*-butylaminomethyl-5-methyl	71 (163)
5-Diethylaminomethyl-5-methyl	44 (163)
5-(3-Diethylaminopropyl)-5-methyl	60 as hydrochloride (163)
5-Ethyl-5-heptyl	— (160)
5-Ethyl-5-cyclohexyl	— (159, 159, 161)
5-Ethyl-5-phenyl	ca. 80 (157)
5-*n*-Heptyl-5-methyl	ca. 80 (157); — (158, 159, 161)
5-*n*-Hexyl-5-methyl	ca. 80 (157); — (158, 159, 161)
5-Methyl-5-(3-methylhexyl)	ca. 80 (157); — (159)
5-Methyl-5-(4-morpholinylmethyl)	42 (163)
5-Methyl-5-*n*-nonyl	ca. 80 (157)
5-Methyl-5-*n*-octyl	ca. 80 (157)
5-Methyl-5-neopentyl	ca. 80 (157)
5-Methyl-5-phenyl	ca. 80 (157)
5-Methyl-5-(1-piperidinylmethyl)	61 (163)
5-Methyl-5-*n*-propyl	— (155)
5,5-Pentamethylene (spirocyclohexane)	46 (132)
5-Phenyl-5-*n*-propyl	ca. 80 (157)

removed as the oxalate or decomposed with the theoretical quantity of nitrous acid before isolation of the product by distillation under reduced pressure (134).

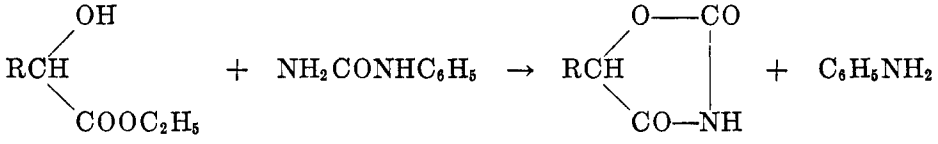
The esters of α-hydroxy acids are usually prepared by esterification of the acids obtained, via the amides, by hydrolysis of aldehyde or ketone cyanohydrins. Some sterically hindered amides resist hydrolysis, but the amides can be converted into 2,4-oxazolidinediones with diethyl carbonate or ethyl chloroformate (method 5). The esters can also be obtained by the interaction of diethyl oxalate and two equivalents of an alkylmagnesium halide (158–161).

Esters of aryltartronic acids were found to condense with urea to give products (145) which were later recognized as 2,4-oxazolidinediones (116).



Dialuric acids apparently are not formed as intermediates in this reaction, as 5-(2,4-dimethoxyphenyl)dialuric acid is stable and not converted into the oxazolidinedione under similar reaction conditions (116). This modification of the α-hydroxy ester method has little practical importance because the yields of 2,4-oxazolidinediones are low and the tartronic esters are not easily prepared.

The behavior of three substituted ureas with ethyl mandelate and ethyl α-hydroxybutyrate has been investigated, 5-phenyl-2,4-oxazolidinedione (74 per cent yield) and 5-ethyl-2,4-oxazolidinedione (41 per cent yield) being obtained from phenylurea (45).



R = C_6H_5 or C_2H_5.

1-Acetyl-3-methylurea similarly gave 5-phenyl-2,4-oxazolidinedione (42 per cent yield) from ethyl mandelate, but 1-methyl-3-phenylurea did not yield an oxazolidinedione with either ester (46), so that 3-substituted 2,4-oxazolidinediones cannot be prepared by this method. Anilides and methylamides isolated from these reactions were possibly formed from intermediate 3-phenyl- or 3-methyl-2,4-oxazolidinediones as well as directly from the esters and aniline or methylamine (45). Ethyl benzilate and urea gave 5,5-diphenyl-2,4-oxazolidinedione (95 per cent yield), also obtained in 65 per cent yield from 1-acetyl-3-methylurea (55).

E. METHOD 5: CONDENSATION OF AMIDES OF α-HYDROXY ACIDS WITH ALKYL CARBONATES OR CHLOROFORMATES

Amides of α-hydroxy acids condense with alkyl chloroformates (10, 149), or with dialkyl carbonates (178, 179), to yield 2,4-oxazolidinediones.

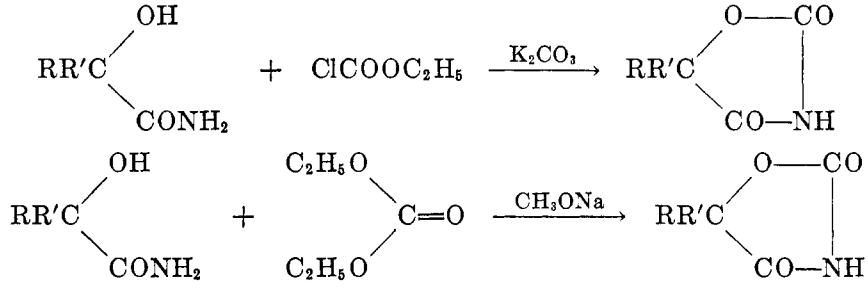


TABLE 6

2,4-Oxazolidinediones from amides and alkyl carbonates or chloroformates

Substituents in the 2,4-Oxazolidinedione	Yield; Reference in Parentheses	Substituents in the 2,4-Oxazolidinedione	Yield; Reference in Parentheses
	per cent		*per cent*
Parent compound	Crude product 95 (178); 95 (179)	5-*n*-Amyl-5-ethyl	85 (160)
5-*n*-Amyl	82 (178, 179)	5-Benzyl-5-ethyl	79 (178, 179)
5-(1-Ethylamyl)	78 (178, 179)	5-*tert*-Butyl-5-methyl	77 (178, 179); 65† (157)
5-*p*-Methoxyphenyl	63 (116)	5-Ethyl-5-*n*-heptyl	65 (161)
5-Methyl	78.5 (178, 179)	5-Ethyl-5-*n*-hexyl	80 (161, 178, 179)
5-Phenyl	86.5 (178, 179)	5-Ethyl-5-phenyl	ca. 100† (10, 149); 82 (178, 179)
5,5-Diphenyl	90 (178, 179)	5-Methyl-5-phenyl	ca. 100† (10, 149)
5,5-Di-*n*-propyl	72, 88.6* (178); 96 (179)		
5,5-Diisopropyl	85.4 (178, 179); 50† (157)		

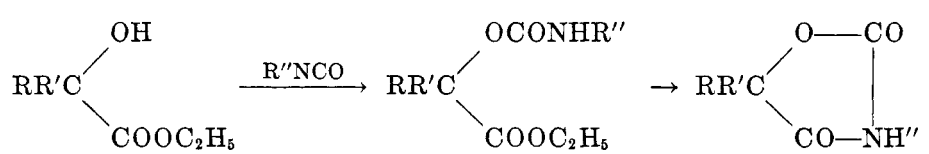
* Magnesium methoxide.

† Ethyl chloroformate.

In the former method an alkyl chloroformate is simply heated with the α-hydroxy acid amide or is added slowly to a solution of the amide in an inert solvent (e.g., boiling toluene) containing potassium carbonate (10, 149, 157). The more widely used condensation of α-hydroxy acid amides with dialkyl carbonates (usually ethyl carbonate) is effected with a sodium, potassium, or magnesium alkoxide (178, 179) under conditions similar to those used for condensing esters with urea (method 4), and optimum yields are obtained with sodium methoxide as condensing agent. The amides of α-hydroxy acids are obtained as intermediates in the hydrolysis of cyanohydrins to α-hydroxy acids (157), and the dialkyl carbonate–amide method therefore provides a convenient alternative to the ester–urea method for preparing 2,4-oxazolidinedione (table 6). It is particularly useful for sterically hindered amides which are difficult to hydrolyze: e.g., 2-hydroxy-2-isopropyl-3-methylbutyramide and 2-hydroxy-2,3,3-trimethylbutyramide (179).

F. METHOD 6: CYCLIZATION OF URETHANS OF α-HYDROXY ACIDS AND THEIR ESTERS

Interaction of alkyl or aryl isocyanates and esters of α-hydroxy acids yields the corresponding urethans, which are cyclized to 2,4-oxazolidinediones when heated (121) and in other ways (110, 121, 123, 126–128, 130, 143, 175, 176) (table 7).



The reaction has been known since 1898 (123, 126) but, apart from its application to the preparation of benzilic acid anilide (143), has attracted little further attention until recently (121). The outstanding advantage of this method is that 3-alkyl(or aryl)-2,4-oxazolidinediones are formed directly, the nature of the

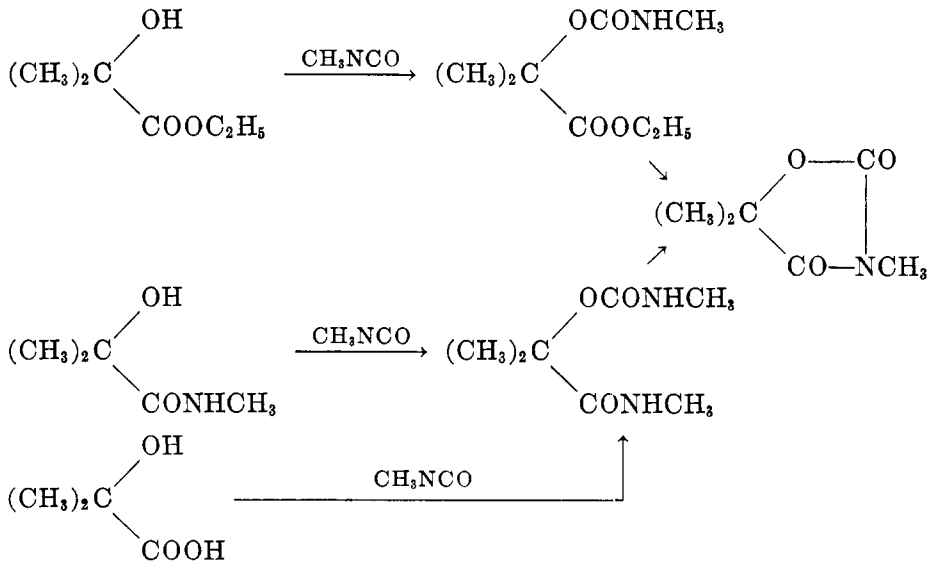
TABLE 7

2,4-Oxazolidinediones from urethans

Components	Substituent in the 2,4-Oxazolidinedione	References
Chloral cyanohydrin or ethyl α-hydroxy-β-trichloropropionate and phenyl isocyanate	5-Dichloromethylene-3-phenyl	(110, 123, 126)
Ethyl α-hydroxyisobutyrate and methyl isocyanate	3,5,5-Trimethyl (60% by heating)	(121)
	3,5,5-Trimethyl (69.4% with sodium in ether)	(121)
	3,5,5-Trimethyl (86% with aqueous Na_2CO_3)	(121)
N-Methyl-α-hydroxyisobutyramide	3,5,5-Trimethyl (50% overall)	(121)
Ethyl-α-hydroxyisobutyrate and phenyl isocyanate	5,5-Dimethyl-3-phenyl	(123, 126, 176)
Ethyl glycolate and phenyl isocyanate	3-Phenyl	(123, 126, 127)
Ethyl lactate and phenyl isocyanate	5-Methyl-3-phenyl	(123, 126, 127, 175)
Ethyl mandelate and phenyl isocyanate	3,5-Diphenyl	(123, 126)
Ethyl α-hydroxybutyrate and phenyl isocyanate	5-Ethyl-3-phenyl	(128)
Ethyl α-hydroxyvalerate and phenyl isocyanate	3-Phenyl-5-*n*-propyl	(128)
Ethyl α-hydroxyisovalerate and phenyl isocyanate	3-Phenyl-5-isopropyl	(128)
Methyl benzilate and phenyl isocyanate	3,5,5-Triphenyl (70%)	(143)
Ethyl lactate and menthyl isocyanate	3-Menthyl-5-methyl	(175)

N-substituent (R″) depending on the isocyanate component (R″NCO). 3-Aryl-2,4-oxazolidinediones are best prepared by this method.

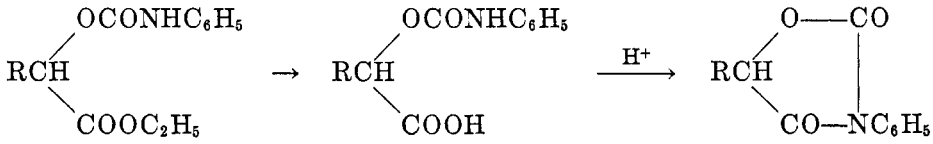
3,5,5-Trimethyl-2,4-oxazolidinedione was obtained by treating ethyl α-hydroxyisobutyrate or *N*-methyl-α-hydroxyisobutyramide with methyl isocyanate, and cyclizing the intermediate urethans by heating them alone, or with aqueous carbonate, or with sodium in ether (121).



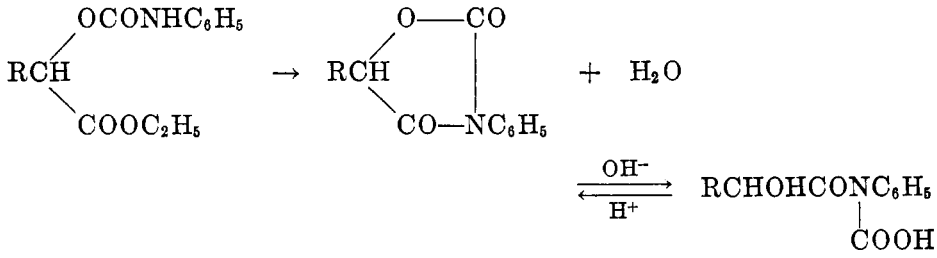
3,5,5-Trimethyl-2,4-oxazolidinedione (60 per cent yield) was also obtained from *N*-propyl-α-(*N*-methylcarbamoyloxy)isobutyramide, which lost *n*-propylamine

when heated (121). These methods of preparation avoid difficulties encountered in methylating 5,5-dimethyl-2,4-oxazolidinedione (112, 121, 151), but the difficulties are mainly due to alkylating in an aqueous medium and are overcome by methylating under anhydrous conditions (*cf.* Section III,C).

In the original isocyanate method for preparing oxazolidinediones, the ester-urethans (124, 125, 128) were hydrolyzed with aqueous alkali and the free acids were heated in aqueous solution (123, 127, 128) or the esters were merely boiled with water (126).

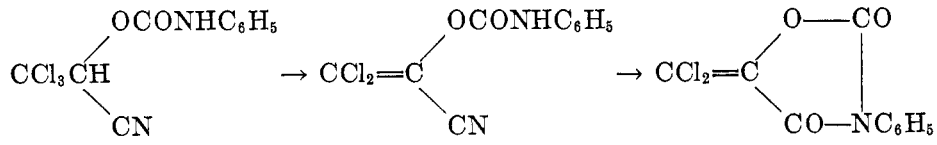


Although the reaction was formulated in this way, the urethans probably cyclize directly (*cf.* 126), so that the acids obtained with aqueous alkali may have been formed from the 2,4-oxazolidinediones; some of the supposed phenylurethans of α-hydroxy acids are therefore probably carbamic acids (see Section IV,C).



Cyclizations were later effected by heating the urethans alone (121) or with sodium in ether (121, 175, 176); ring closure with sodium ethoxide has apparently not been tried.

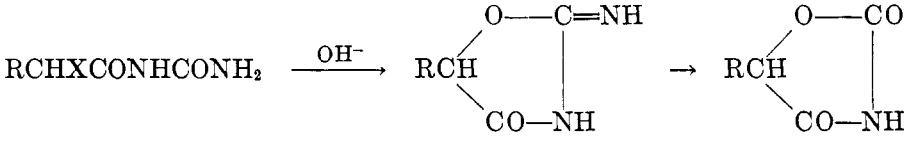
The phenylurethan derivative of chloral cyanohydrin loses hydrogen chloride when treated with alkali, and heating the product with acids yields 5-dichloromethylene-3-phenyl-2,4-oxazolidinedione (110) and not the supposed 5-dichloromethyl compound (123, 126).



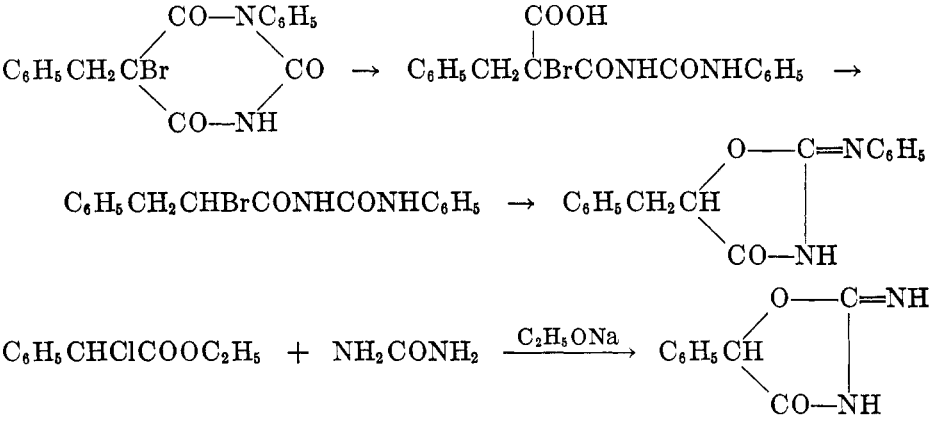
The dichloromethylene-2,4-oxazolidinedione was also obtained by heating chloral cyanohydrin phenylurethan with concentrated hydrochloric acid in a sealed tube, and by heating ethyl trichloroacetate phenylurethan with aqueous alkali (123, 126).

G. METHOD 7: PREPARATION FROM ESTERS OF α-HALOGENO ACIDS AND FROM α-HALOGENOUREIDES OR 5-BROMOBARBITURIC ACIDS

Alkali induces cyclization of α-halogenoureides to 2-imino(or substituted imino)-4-oxazolidones (pseudohydantoins), which can be isolated or converted into 2,4-oxazolidinediones.

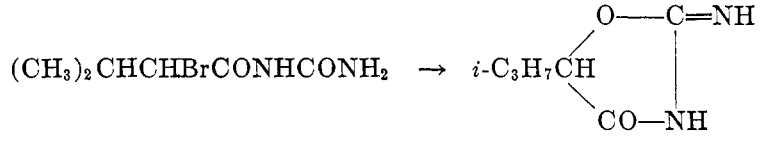


5-Bromobarbituric acids when treated with aqueous alkali give bromoureides as intermediates in this conversion (34, 56), and the condensation of esters of α-halogeno acids with urea (or substituted ureas) leads to 2-imino-4-oxazolidones (47), presumably via the chloroureides.



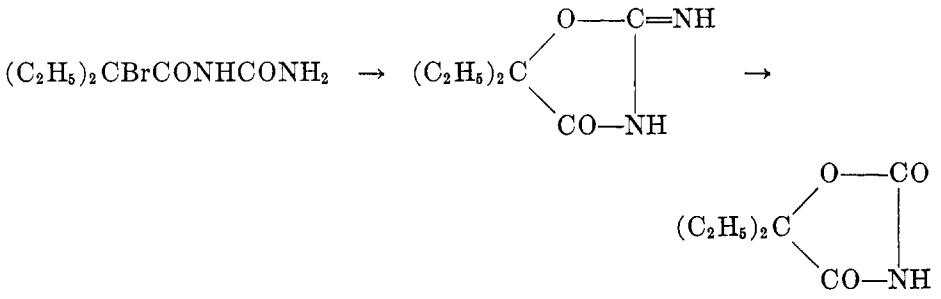
The 2-alkyl(or aryl)imino-4-oxazolidones are converted satisfactorily into 2,4-oxazolidinediones by acid hydrolysis (see method 2), but the overall yield of a 2,4-oxazolidinedione by this method is usually poor because of inefficiency in the initial cyclization (table 8). The imino compounds are also hydrolyzed by alkali, although more slowly (34), so that a small proportion of 2,4-oxazolidinedione is formed directly.

Dehydrobromination of bromural (α-bromoisovalerylurea) with alcoholic potassium hydroxide gives a 45 per cent yield of 2-imino-5-isopropyl-4-oxazolidone (21), formerly regarded as dimethylacryloylurea (182).



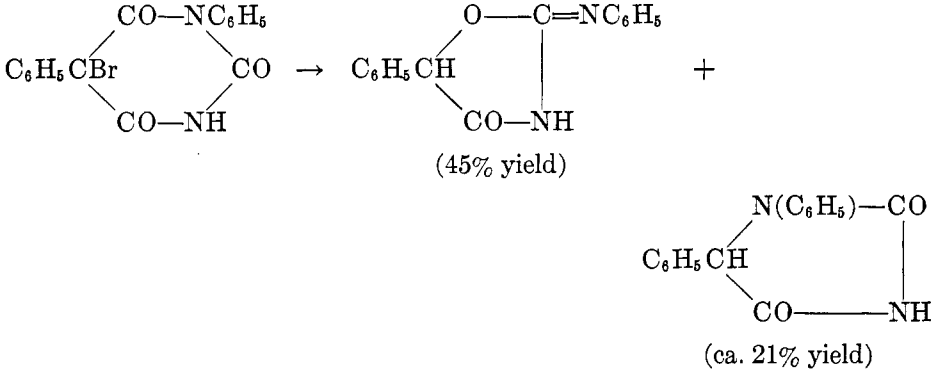
The same product was obtained from the iodoureide (182). The yield was increased to 65 per cent when the bromoureide was boiled with aqueous ammonium

carbonate instead of potassium hydroxide (21), but similar conditions did not improve yields in the cyclization of N'-alkyl- or N'-arylbromoacylureas. α-Bromo-α-ethylbutyrylurea (adalin, carbromal) gave 5,5-diethyl-4-oxazolidone when treated with alkali (135).



If this change occurs also under physiological conditions, as seems possible (*cf.* 182), the sedative properties of these bromoureides may be due to the pseudohydantoins or oxazolidinediones so formed.

Boiling aqueous or alcoholic alkali converts 5-bromo-1-phenylbarbituric acids into mixtures of 2-phenylimino-4-oxazolidones (pseudohydantoins) and 1-phenylhydantoins, in which the former predominate (36, 38, 40):



(45% yield)

(ca. 21% yield)

The preferential cyclization to oxazolidone derivatives accounts for the very poor yields of hydantoins in this type of reaction (*cf.* 181). 1,3-Disubstituted bromobarbituric acids under similar conditions, however, yield only the hydantoin, or mixtures of two hydantoins if the 1,3-substituents are different (44). The lability of 3-substituted 2,4-oxazolidinediones under alkaline conditions, and the isolation of anilides or methylamides of α-hydroxy acids from some of these reaction mixtures (34), suggest that any 3-substituted derivative which is formed is subsequently decomposed.

The reaction of esters of α-chloro acids with urea and substituted ureas (47) yields 2-imino-4-oxazolidones, together with minor quantities of 2,4-oxazolidinediones formed by alkaline hydrolysis of the 2-imino compounds. Reaction pre-

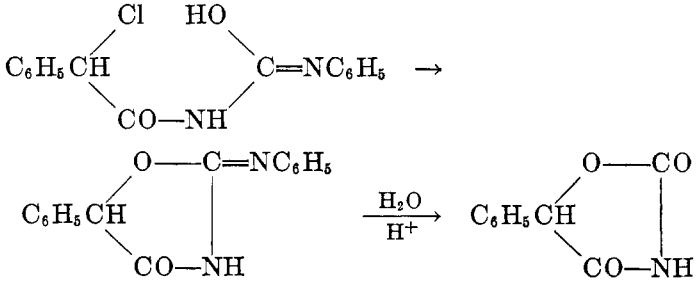
TABLE 8

2,4-Oxazolidinediones from esters or ureides of α-halogeno acids

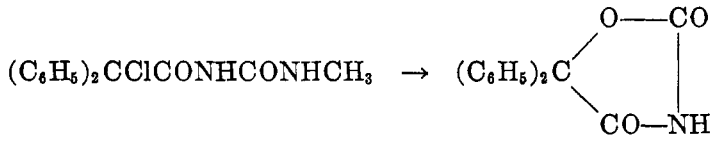
Source	Substituent in the 2,4-Oxazolidinedone	2-Substituent and Yield of Intermediate 4-Oxazolidone	References
α-Halogeno ureides:			
(1-Bromo-2-phenylpropionyl)urea	5-Benzyl	2-Imino; 5%; —	(17, 35)
α-Bromobutyroylurea	5-Ethyl	2-Imino	(18)
α-Bromo-α-ethylbutyroylurea (carbromal)	5,5-Diethyl	2-Imino (not isolated); 39% of oxazoiidinedione overall	(135)
α-Bromoisovaleroylurea	5-Isopropyl	2-Imino; 45–65%; —	(21, 182)
α-Iodoisovaleroylurea	5-Isopropyl	2-Imino	(182)
1-(1-Bromo-2-phenylpropionyl)-3-methylurea	5-Benzyl	2-Methylimino; 32%	(57)
1-(1-Bromo-2-phenylpropionyl)-3-phenylurea	5-Benzyl	2-Phenylimino; 13–29%	(37, 58)
1-α-Bromobutyroyl-3-phenylurea	5-Ethyl	2-Phenylimino; 34%	(59)
1-α-Bromobutyroyl-3-methylurea	5-Ethyl	2-Methylimino; 65%	(60)
1-Diphenylchloroacetyl-3-methylurea	5,5-Diphenyl	2-Methylimino (not isolated); 91% of oxazolidinedione overall	(108)
1-Phenylchloroacetyl-3-phenylurea	5-Phenyl	2-Phenylimino; 40%	(41)
Phenylchloroacetylurea	5-Phenyl	2-Imino; 22%	(42)
5-Bromobarbituric acids:			
5-Benzyl-5-bromo-1-phenylbarbituric acid	5-Benzyl	2-Phenylimino; 22%	(36)
5-Bromo-5-ethyl-1-phenylbarbituric acid	5-Ethyl	2-Phenylimino; 13%	(38)
5-Bromo-5-methyl-1-phenylbarbituric acid	5-Methyl	2-Phenylimino; 7%	(39)
5-Bromo-1,5-diphenylbarbituric acid	5-Phenyl	2-Phenylimino; 45%	(40)
5-Bromo-1-methyl-5-phenylbarbituric acid	5-Phenyl	2-Methylimino; ca. 50%	(43)
Acid chlorides and ureas:			
Phenylchloroacetyl chloride and 1-methyl-3-phenylurea	3-Methyl-5-phenyl	2-Phenylimino	(48)
Diphenylchloroacetyl chloride and phenylurea or 1-methyl-3-phenylurea	3,5,5-Triphenyl	—	(55)
Diphenylchloroacetyl chloride and methylurea	3-Methyl-5,5-diphenyl	2-Diphenylchloroacetylimino; 22%	(108)
Diphenylchloroacetyl chloride and methylurea	5,5-Diphenyl	2-Methylimino (not isolated); 12.5% of oxazolidinedione overall	(108)
α-Chloro esters and ureas:			
Ethyl phenylchloroacetate and urea	5-Phenyl	2-Imino	(49)
Ethyl phenylchloroacetate and 3-methylacetylurea	5-Phenyl	2-Methylimino	(49)
Ethyl phenylchloroacetate and phenylurea	5-Phenyl	2-Phenylimino	(50)
Ethyl chloroacetate and phenylurea	—	2-Phenylimino	(51)

sumably proceeds by cyclization of an intermediate α-chloroacylurea in the enolic form.

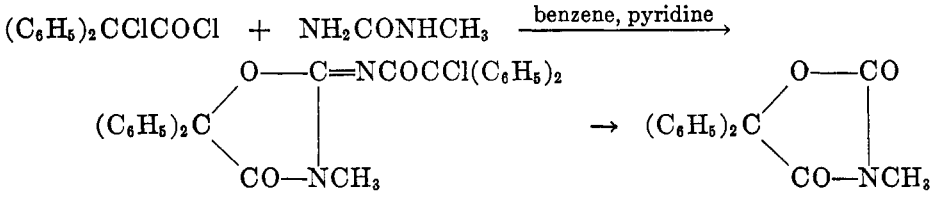
$$C_6H_5CHClCOOC_2H_5 + NH_2CONHC_6H_5 \rightarrow$$



1-Diphenylchloroacetyl-3-methylurea was converted into 5,5-diphenyl-2,4-oxazolidinedione (91 per cent yield) when heated with pyridine in benzene (108).



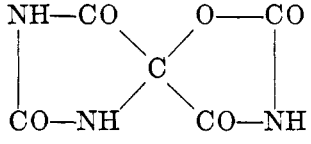
Heating the chloro acid chloride with methylurea in benzene gave only 12.5 per cent of the same oxazolidinedione, but in benzene containing pyridine the product was 2-diphenylchloroacetylimino-3-methyl-5, 5-diphenyl-4-oxazolidone (22 per cent yield), which on hydrolysis gave 3-methyl-5,5-diphenyl-2,4-oxazolidinedione (72 per cent yield) (108).



Acid chlorides with alkyl(or aryl)ureas normally yield 1-acyl-3-alkyl(or aryl)-ureas (47), and addition of pyridine to the above reaction mixture apparently induced acylation of both nitrogen atoms (108).

H. CAFFOLIDES

Caffolide is the spiro compound composed of a hydantoin and a 2,4-oxazolidinedione ring system; all the mono-, di-, and tri-*N*-methyl derivatives (62) and a number of *N*-ethyl- and *N*-acetyl derivatives are known (63). The compounds, which are obtained from uric acid and its derivatives, have been reviewed (63).

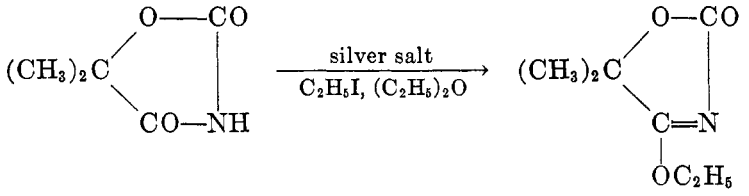


Caffolide

III. Alkylation of 2,4-Oxazolidinediones

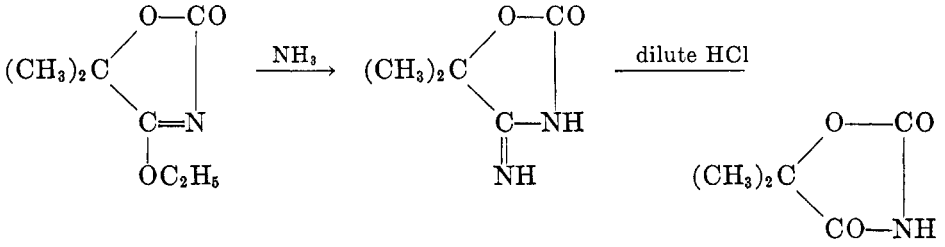
A. 4-alkoxy-2-oxazolones

The silver salt of 5,5-dimethyl-2,4-oxazolidinedione yields 4-ethoxy-2-oxazolone when treated with ethyl iodide in ether at room temperature (84, 109); methyl iodide and benzyl bromide yield the corresponding enol ethers (84).



Increase in reaction temperature results in simultaneous formation of *N*-alkyl derivatives, and the 4-alkoxy-2-oxazolones also isomerize slowly to 3-alkyl-2,4-oxazolidinediones when heated at 180°C. alone or in the presence of the corresponding alkyl halide. 4-Ethoxy-5,5-dimethyl-2-oxazolone thus yields 3-ethyl-5,5-dimethyl-2,4-oxazolidinedione, and when heated with benzyl bromide or methyl iodide it gives the 3-benzyl or 3-methyl derivative by alkyl exchange (84). Substituents in the 5-position promote *O*-alkylation of the silver salts, and 2,4-oxazolidinedione, 5,5-dimethyl-2,4-oxazolidinedione, and 5,5-diphenyl-2,4-oxazolidinedione gave increasing ratios of *O*-alkyl to *N*-alkyl derivatives (83).

4-Alkoxy-2-oxazolones react with cold ethanolic ammonia to give 4-imino-2-oxazolidones, and both the *O*-ethers and the imines are readily hydrolyzed to the parent 2,4-oxazolidinedione by dilute hydrochloric acid.

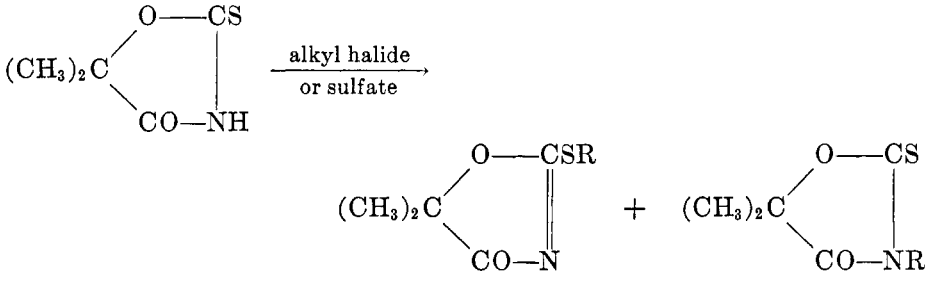


The 4-imino-5,5-dimethyl-2-oxazolidone prepared in this way differed from the 2-imino isomer obtained by the guanidine method, thus establishing the enol ethers as 4-alkoxy-2-oxazolones (84). The formation of enol ethers is apparently inhibited by alcohols, as the silver salt of 5,5-dimethyl-2,4-oxazolidinedione failed to react with ethanolic ethyl iodide (151). The ethyl derivative of undetermined structure obtained by the action of ethyl iodide on the silver salt of 5,5-diethyl-2,4-oxazolidinedione derived from carbromal (135) is probably 3,5,5-triethyl-2,4-oxazolidinedione.

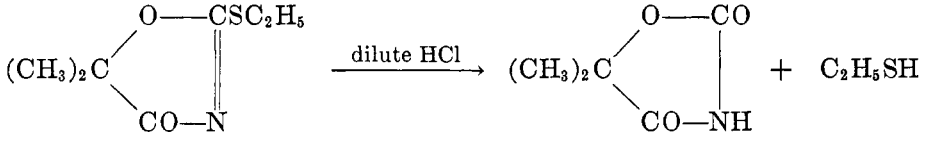
B. 2-ALKYLTHIO-4-OXAZOLONES AND 3-ALKYL-2-THIO-4-OXAZOLIDONES

Alkylation of 2-thio-4-oxazolidones in the presence of bases gave mixtures of *N*- and *S*-alkyl derivatives, although in the absence of base 5,5-dimethyl-2-thio-4-oxazolidone underwent partial *S*-alkylation only. Alkylation under various conditions (87) showed that optimum yields of *N*-alkyl derivatives are obtained with anhydrous solvents (e.g., acetone) and with bases yielding large cations. The best yield (49 per cent) of 3,5,5-trimethyl-2-thio-4-oxazolidone was obtained by methylation of the barium salt with dimethyl sulfate in acetone in the presence

of barium carbonate (87). The proportion of *N*-alkylation decreased with increase in size of the alkyl group (85).



2-Alkylthio-4-oxazolones with aqueous ammonia yield 2-imino-4-oxazolidones identical with those prepared by the guanidine method; unlike the 4-alkoxy analogs the 2-alkylthio compounds do not undergo thermal rearrangement to 3-alkyl derivatives (87). 2-Ethylthio-5,5-dimethyl-4-oxazolone is unstable in moist air and is readily hydrolyzed by dilute hydrochloric acid to ethanethiol and 5,5-dimethyl-2,4-oxazolidinedione, which is soluble in aqueous ammonia.



3-Alkyl-2-thio-4-oxazolidones are conveniently isolated from the mixture of *N*- and *S*-alkyl derivatives obtained by alkylation after removing the 2-alkylthio-4-oxazolones in this way (87). If alkylation is not conducted under strictly anhydrous conditions, hydrolysis of *S*-alkyl groups may occur and 3-alkyl-2,4-oxazolidinediones are then obtained directly (examples 8 and 9 of reference 85).

C. 3-ALKYL-2,4-OXAZOLIDINEDIONES

3-Alkyl-2,4-oxazolidinediones have been obtained from 4-alkoxy-2-oxazolones as noted above and also by direct synthesis (methods 1, 3, 6, and 7) (3, 22, 48, 52, 87, 108, 121, 175); presumably they could be obtained also from *N*-alkylamides of α-hydroxy acids by method 5. With the exception of the isocyanate method, however, yields in direct syntheses of 3-alkyl-2,4-oxazolidinediones are poor, and the compounds are more conveniently prepared by alkylation (97, 151).

Methylation was originally effected with dimethyl sulfate and aqueous sodium hydroxide, and a number of 3-methyl-2,4-oxazolidinediones were prepared in yields of 50–65 per cent (151). 3-Alkyl-2,4-oxazolidinediones are readily hydrolyzed by aqueous alkali, and this imposes an obvious limitation on the use of aqueous solvents; e.g., 3,5,5-trimethyl-2,4-oxazolidinedione, which was obtained in only 30–40 per cent yield, is hydrolyzed rapidly by 0.1 *N* sodium hydroxide to *N*-methyl-α-hydroxyisobutyramide (151). Ethylation with ethyl sulfate and aqueous alkali was even less satisfactory (84, 151), but by alkylating

TABLE 9

Alkylating agents used in preparing 3-substituted 2,4-oxazolidinediones and 2-thio-4-oxazolidones

3-Substituent	Alkylating Agent	References
Acetic acid	Chloroacetic acid	(132, 155)
	tert-Butyl bromoacetate	(148)
2-Acetoacetoxyethyl	2-Chloroethyl acetoacetate	(84)
Allyl	Allyl bromide	(86)
	Allyl iodide	(84, 97)
	Allyl halide	(83, 155)
n-Amyl	*n*-Amyl bromide	(86)
	n-Amyl iodide	(84)
	n-Amyl halide	(83)
sec-Amyl	*sec*-Amyl halide	(155)
Isoamyl	Isoamyl bromide	(86)
	Isoamyl iodide	(84)
	Isoamyl halide	(155)
Benzyl	Benzyl bromide	(84, 86, 87)
	Benzyl chloride	(85, 87, 97)
n-Butyl	*n*-Butyl iodide	(83, 84, 86)
Isobutyl	Isobutyl iodide	(84, 86)
tert-Butyloxycarbonylmethyl	*tert*-Butyl bromoacetate	(148)
2-Di-*n*-butylaminoethyl	2-Di-*n*-butylaminoethyl chloride	(163)
3-Di-*n*-butylaminopropyl	3-Di-*n*-butylaminopropyl chloride	(163)
2-Diethylaminoethyl	2-Diethylaminoethyl chloride	(84, 115, 132, 155, 163)
3-Diethylamino-2-hydroxypropyl	3-Diethylamino-2-hydroxypropyl chloride	(84)
2-Diethylaminopropyl	2-Diethylaminopropyl chloride	(163)
2-Dimethylaminoethyl	2-Dimethylaminoethyl chloride	(163)
2-Ethoxyethyl	2-Ethoxyethyl halide (?)	(84)
Ethyl	Diethyl sulfate	(8, 84–87, 109)
	Ethyl bromide	(136)
	Ethyl iodide	(86, 109, 135)
	Not stated	(83, 155)
2-Hydroxyethyl	Not stated	(84)
Methyl	Dimethyl sulfate	(70, 85–87, 112, 132, 151–155, 163)
	Methyl iodide	(83, 86, 112, 136)
	Diazomethane	(111, 114, 115, 116)
	Not stated	(1, 69, 78, 154)
2-Methylallyl	2-Methylallyl iodide	(83, 84)
2-Methylthioethyl	Not stated	(84)
2-(4-Morpholinyl)ethyl	2-(4-Morpholinyl)ethyl chloride	(163)
2-Oxopropyl	Not stated	(83)
2-(1-Piperidinyl)ethyl	2-(1-Piperidinyl)ethyl chloride	(163)
n-Propyl	*n*-Propyl bromide	(86, 136)
	n-Propyl iodide	(84)
	Not stated	(83, 155)
Isopropyl	Isopropyl bromide	(136)
	Isopropyl iodide	(84, 86)
Trichloromethylthio	CCl_3SCl	(82, 102, 119, 120)

the sodium or potassium salts with dialkyl sulfates or alkyl halides under anhydrous conditions good yields of 3-alkyl-2,4-oxazolidinediones were obtained (84, 86, 136, 153, 155), and a wide variety of alkylating agents has been used (table 9). The sodium salts of 2,4-oxazolidinediones are obtained directly in syntheses with sodium alkoxide as condensing agent, and these salts may be alkylated, without prior isolation of the 2,4-oxazolidinedione, after removal of ammonia by aeration (84, 86). Alkylation proceeds most satisfactorily in anhydrous acetone or an anhydrous alcohol, and methylation is effected with

dimethyl sulfate. Other alkyl groups are usually introduced with alkyl halides, and chlorides, bromides, and iodides give substantially similar yields (155).

The reaction of diazomethane with 2,4-oxazolidinediones apparently yields only *N*-methyl derivatives and is a convenient method for small-scale methylation (111, 114, 115, 116).

Perchloromethanethiol (CCl_3SCl) reacts with sodium salts of imides, including 2,4-oxazolidinediones (82, 102, 119, 120), to give *N*-trichloromethylthio derivatives which are useful as parasiticides.

D. 3-ARYL-2,4-OXAZOLIDINEDIONES

Aryl substituents cannot be introduced into the 2,4-oxazolidinedione ring system; hence the 3-aryl derivatives must be prepared by direct synthesis. A number of 3-phenyl-2,4-oxazolidinediones (table 7) have been obtained from phenylurethans (Section II,F).

IV. Physical Properties and Chemical Reactions of 2,4-Oxazolidinediones

A. GENERAL PHYSICAL AND CHEMICAL PROPERTIES

Most 2,4-oxazolidinediones with aliphatic substituents are crystalline solids of low melting point (30–100°C.) although some, especially the *N*-alkyl derivatives, are oils; they can be distilled without decomposition under reduced pressure or, in some cases, even at atmospheric pressure. 5-Aryl-2,4-oxazolidinediones have higher melting points (100–200°C.) and crystallize readily from hot water. The lower 5-alkyl-2,4-oxazolidinediones are moderately soluble in water but can be extracted into organic solvents; they are associated in benzene (30). The 3-aryl derivatives are very sparingly soluble in water (122–130), and the 3-alkyl-2,4-oxazolidinediones are more soluble than the parent compounds in aprotic solvents. The solubility of 3,5,5-trimethyl-2,4-oxazolidinedione in water (5 per cent) is increased by urethan (151).

2,4-Oxazolidinediones with a free imide-hydrogen atom are weak monobasic acids (pK_A ca. 6.0) and form stable salts with metals, e.g., calcium, magnesium, zinc, copper, mercury, and silver (80). The sparingly soluble silver salts, which dissolve in aqueous ammonia and are photostable, are obtained by addition of silver nitrate to neutral solutions of the sodium salts. The water-soluble alkali, alkaline earth, and magnesium salts have a slightly bitter taste (10, 149); urea increases the solubility of the sodium salts (134). The sodium and calcium salts of 5,5-di-*n*-propyl-2,4-oxazolidinedione (propazone) have been described, and the alkali and alkaline earth metal salts of other 2,4-oxazolidinediones mentioned in the patent literature (158, 159). Sodium or potassium salts are generally used in alkylating 2,4-oxazolidinediones.

Organic bases similarly form salts with 2,4-oxazolidinediones, and 5-ethyl-5-methyl-2,4-oxazolidinedione has been resolved into the two enantiomorphs by means of the brucine salt (66).

Infrared data are so far not available for 2,4-oxazolidinediones; a few un-

published observations are mentioned below in connection with acetyl derivatives (Section IV,E).

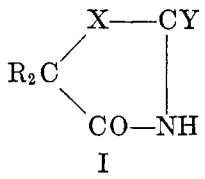
B. ACIDITY OF 2,4-OXAZOLIDINEDIONES

Dissociation of the imide-hydrogen atom of 2,4-oxazolidinediones permits quantitative estimation of the compounds by titration with 0.1 *N* sodium hydroxide and use of a suitable indicator, e.g., phenolphthalein (30, 103, 116, 134, 151, 157). Sodium salts of oxazolidinediones are stable in aqueous solution, except on prolonged boiling, so that the mesomeric anions have considerable stability. *N*-Alkylation reduces the stability of the ring system to such an extent that ring fission occurs rapidly with consumption of one equivalent of alkali, and this is utilized in the quantitative estimation of 3,5,5-trimethyl-2,4-oxazolidinedione (151; see below).

The dissociation constants of three 2,4-oxazolidinediones have been determined and the values compared with those for the corresponding hydantoins and thiazolidinediones (93). The oxazolidinediones resemble hydantoins and

Compound	pK_A
5,5-Dimethyl-2,4-oxazolidinedione	6.1
5-Ethyl-5-methyl-2,4-oxazolidinedione	5.9
5,5-Diethyl-2,4-oxazolidinedione	5.7

differ from barbituric acids in that changing the substituents in the 5-position has little effect upon the dissociation constant. In the series of compounds represented by formula I (X = O, S, or NH; Y = O or S),



I

the acidity was found (92) to fall in the sequence:

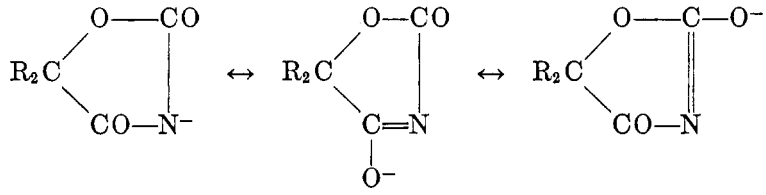
$$\text{—SCSNH— > —OCONH— > —SCONH— > —NHCONH—}$$

The acidity of the 2,4-oxazolidinediones is therefore second only to that of the 2-thio-4-thiazolidones in this series and is greater than that of the corresponding hydantoin.

C. HYDROLYSIS OF 2,4-OXAZOLIDINEDIONES

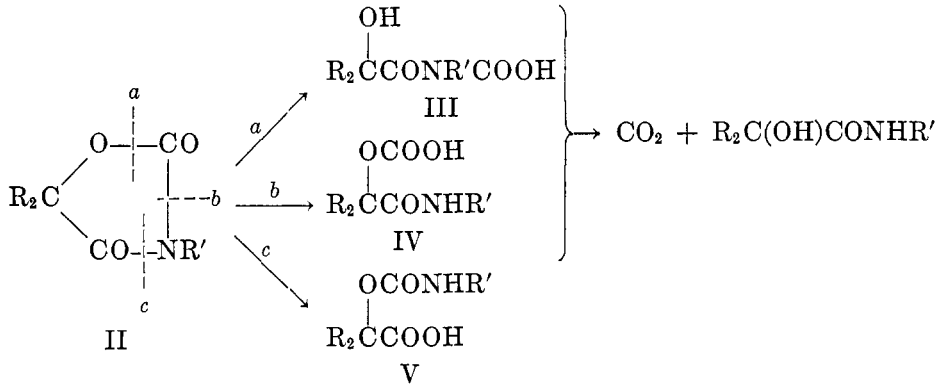
2,4-Oxazolidinediones possessing an imide-hydrogen atom are stable towards boiling water or dilute mineral acids and are recovered from their *O*-alkyl and 2(or 4)-imino derivatives, and from 2-alkylthio-4-oxazolones, by acid hydrolysis. The 3-alkyl-2,4-oxazolidinediones are also moderately stable towards dilute mineral acids. Sodium salts of oxazolidinediones are stable in aqueous solution,

except on prolonged boiling, but are degraded by an excess of alkali to amides, and ultimately to α-hydroxy acids. The comparative stability of the salts may be attributed to resonance stabilization of the mesomeric anion, e.g.,



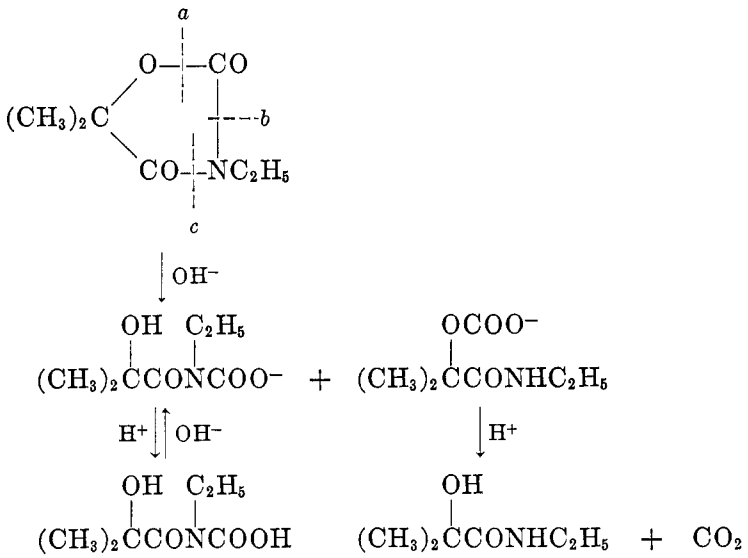
and the pronounced lability towards aqueous alkali of 3-alkyl(and aryl)-2,4-oxazolidinediones, in which formation of this mesomeric anion is prevented, has many analogies among *N*-alkylimides, e.g., dialuric acids (19, 31), 1,3-dimethylalloxan (64, 144), 1,3-dimethylalloxazine (144), and *N*-methylpteridones (9).

The 2,4-oxazolidinedione ring system (II) formally represents a cyclic urethan (1,2,3-positions) and a cyclic amide (3,4,5-positions), so that hydrolysis could lead to amides (via carboxylic acids III and IV) or to urethans (V) (30, 96). Hydrolysis of 3-alkyl-2,4-oxazolidinediones leads to amides (84, 151) by fission at *a* and *b*, and there is little or no formation of urethans by fission at *c*. Hydrolysis of 3-phenyl-2,4-oxazolidinediones, however, has generally been thought to yield phenylurethans (i.e., fission at *c*) (96, 123, 127, 128). Formation of urethans from 3-phenyl-2,4-oxazolidinedione and from its 5-methyl and 5-ethyl derivatives is well substantiated, but reinvestigation of the remaining compounds appears desirable.



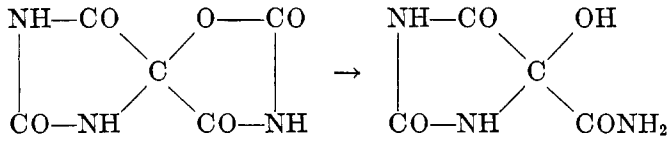
3,5,5-Trimethyl-2,4-oxazolidinedione is rapidly hydrolyzed by cold aqueous-alcoholic sodium hydroxide to *N*-methyl-α-hydroxyisobutyramide (151), and 3-ethyl-5,5-dimethyl-2,4-oxazolidinedione similarly yields the *N*-ethylamide (84). Hydrolysis is quantitative and the 3-alkyl-2,4-oxazolidinediones are assayed (151) by addition of standard 0.1 *N* sodium hydroxide and back titration with standard acid (phenolphthalein as indicator) (84, 151). The neutral solution thus obtained contains sodium salts of the acids (III and IV, above) and the proportion of these may be determined by addition of further standard acid,

removal of carbon dioxide liberated from the carbonate (IV), and titration to neutrality (phenolphthalein) with standard alkali (84).

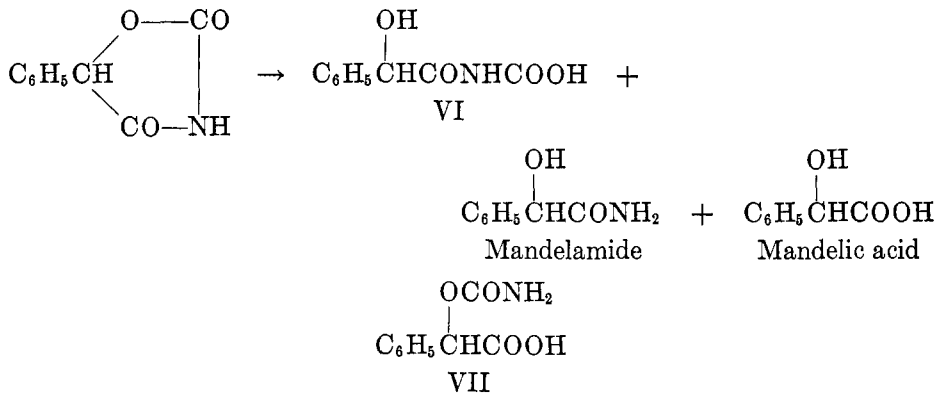


The ratio of hydrolyses (*a*:*b*) for 3-alkyl-5,5-dimethyl-2,4-oxazolidinediones was, in per cent: 3-methyl (60:40), 3-ethyl (69:31), and 3-isopropyl (85:15); the ratios varied slightly with the strength of alkali (84). The figure for fission at *a* will include any fission at *c*, but the proportion of the latter is evidently small because decarboxylation (75–88 per cent) gave the *N*-ethylamide expected from *N*-α-hydroxyisobutyryl-*N*-ethylcarbamic acid (84). The carbamic acid cyclized slowly in aqueous solution to 3-ethyl-5,5-dimethyl-2,4-oxazolidinedione, which crystallized from the solution (84). β-Phenyllactic acid, its *N*-methylamide, and the corresponding carbamic acid were isolated after hydrolysis of 5-benzyl-3-methyl-2,4-oxazolidinedione with aqueous alkali (26).

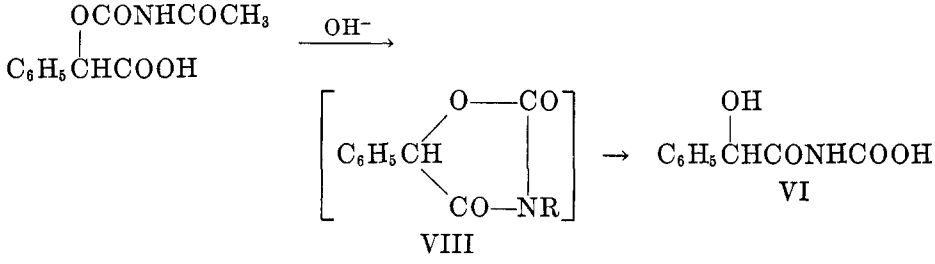
Data for the hydrolysis of other 2,4-oxazolidinediones are less precise, but reaction appears to follow a similar course. 2,4-Oxazolidinedione-5-spiro-5′-hydantoin (caffolide) when boiled with water undergoes fission of the oxazolidinedione ring (61), and *N*-alkylcaffolides can also be converted into alloxanic acid amides (63).



Hydrolysis of 5-phenyl-2,4-oxazolidinedione under various conditions (30) gave an acidic substance (A) and smaller quantities of mandelamide and mandelic acid.



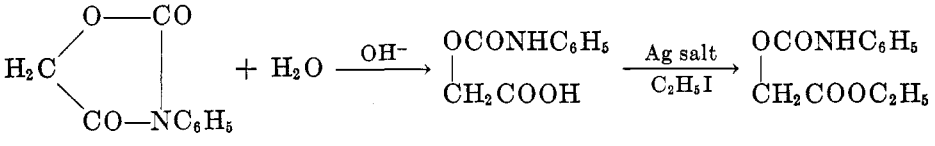
The primary hydrolysis product (A) was regarded (30) as *N*-mandeloylcarbamic acid (VI), because on pyrolysis it gave a mixture of mandelamide (decarboxylation) and 5-phenyl-2,4-oxazolidinedione (cyclization). Structure VI was later rejected (31) because of the identity of the primary product (A) with "*O*-carbamoylmandelic acid" (VII) (95); however, the latter may well be the isomeric *N*-mandeloylcarbamic acid (VI), formed from an intermediate 2,4-oxazolidinedione (VIII: R = H or CH_3CO) as follows:



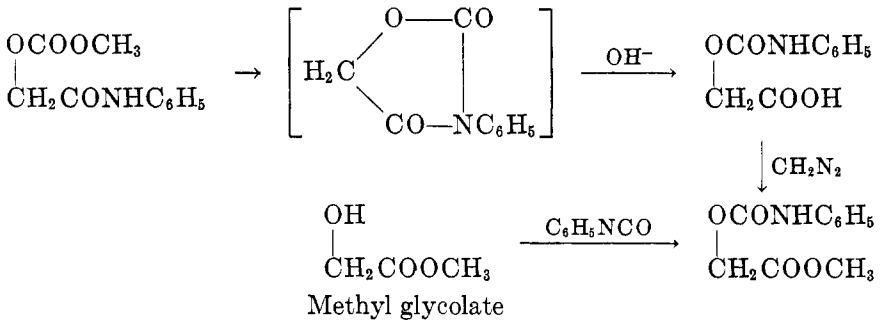
Alkaline hydrolysis of 5-benzyl- (13) and 5-ethyl-2,4-oxazolidinedione (15) gave unchanged oxazolidinedione and the α-hydroxyacylcarbamic acids and amides; β-phenyllactamide was also obtained by thermal decarboxylation of the carbamic acid from 5-benzyl-2,4-oxazolidinedione.

1. Hydrolysis of 3-phenyl-2,4-oxazolidinediones

Alkaline hydrolysis of 3-phenyl-2,4-oxazolidinedione (123, 127) gave the phenylurethan of glycolic acid. The structure of the product was established by treating the silver salt with ethyl iodide (127), which gave an ester identical with that obtained from ethyl glycolate and phenyl isocyanate.



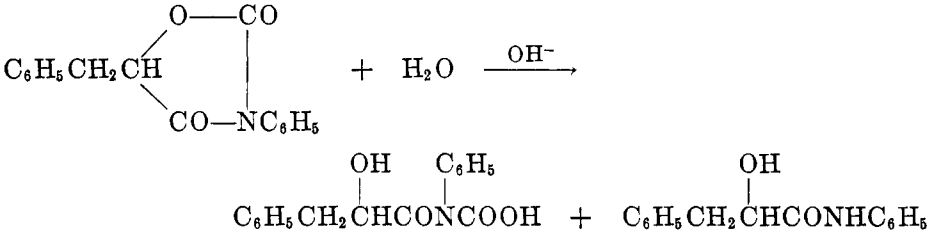
Alkaline hydrolysis of methoxycarbonyloxyacetanilide (96) similarly gave glycolic acid phenylurethan:



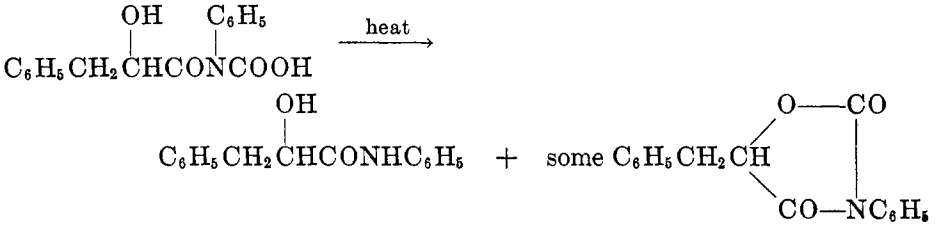
Methyl glycolate

Rearrangement was assumed to proceed through the oxazolidinedione, and the structure of the methyl ester, obtained from the acid with diazomethane, was confirmed by its preparation from methyl glycolate and phenyl isocyanate (96). Hydrolysis of 5-methyl- (123, 127) and 5-ethyl-3-phenyl-2,4-oxazolidinediones (128) gave the phenylurethans of lactic acid and α-hydroxybutyric acid. Lactic acid phenylurethan was converted by the action of ethyl iodide on the silver salt into the ethyl ester (127), also obtained from ethyl lactate and phenyl isocyanate. 3-Phenyl-2,4-oxazolidinedione was considered to give an equilibrium mixture of the acid (40 per cent) and dione (60 per cent) after being boiled with water for 10 hr. (127). 5-Methyl-3-phenyl-2,4-oxazolidinedione in contact with water at room temperature developed an acid reaction, but the equilibrium in this case lies far over on the side of the oxazolidinedione (127).

The above observations have been taken to apply generally, without proof, to the hydrolysis of other 3-phenyl-2,4-oxazolidinediones (31, 123, 128) and ester-phenylurethans (122, 124, 125, 128), but the properties of the remaining "α-hydroxy acid phenylurethans" are more easily accommodated on the alternative carbamic acid structure. Hydrolysis of 5-benzyl-3-phenyl-2,4-oxazolidinedione, for example, was considered to give a mixture of the anilide and the carbamic acid (24; see, however, reference 31).



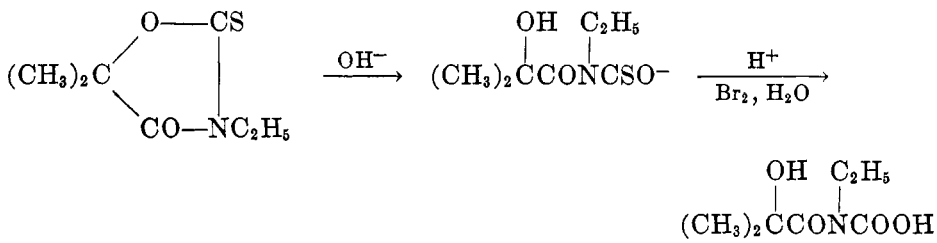
Pyrolysis of the carbamic acid gave mainly the corresponding anilide and some oxazolidinedione (24).



5-*n*-Propyl- (128), 5-isopropyl- (128), 5-phenyl- (123), and 5,5-dimethyl-3-phenyl-2,4-oxazolidinediones (123) resemble 5-benzyl-3-phenyl-2,4-oxazolidinedione in the simultaneous formation of acids and anilides on hydrolysis, so that the acids are probably carbamic acids rather than the supposed phenylurethans. The available evidence does not, however, preclude the occurrence of ring fission of these compounds at all three positions *a*, *b*, and *c* (see page 86). Hydrolysis of the phenylurethans of ethyl benzilate and ethyl α-ethyl-α-hydroxybutyrate led only to anilides, presumably via the oxazolidinediones, and no intermediate acids were isolated (129). Heating methyl benzilate on a steam bath with phenyl isocyanate gave 3,5,5-triphenyl-2,4-oxazolidinedione directly (70 per cent), and on hydrolysis with 20 per cent aqueous sodium hydroxide the dione gave benzilanilide (65 per cent yield), $HOC(C_6H_5)_2CONHC_6H_5$ (143).

2. Hydrolysis of 2-thio-4-oxazolidones

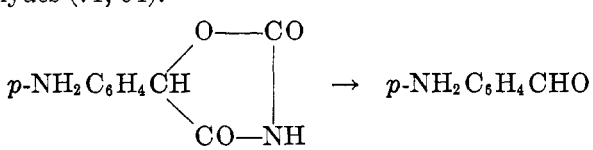
Alkaline hydrolysis of 3-ethyl-5,5-dimethyl-2-thio-4-oxazolidone followed by desulfurization with bromine gave *N*-α-hydroxyisobutyryl-*N*-ethylcarbamic acid (84), identical with the product obtained from 3-ethyl-5,5-dimethyl-2,4-oxazolidinedione.



Hydrolysis of 3-ethyl-2-thio-4-oxazolidone and subsequent desulfurization gave an acid regarded as *N*-ethylcarbamoylglycolic acid (3) but, by analogy with the 5,5-dimethyl compound, the product is probably the isomeric *N*-α-hydroxyacetylcarbamic acid (84).

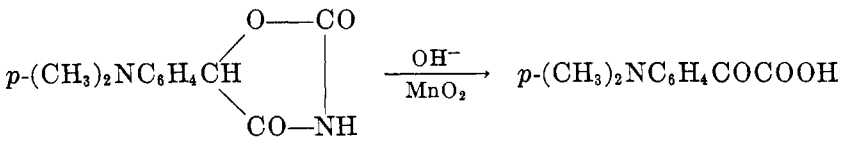
D. AROMATIC ALDEHYDES FROM 2,4-OXAZOLIDINEDIONES

Aromatic amines and alloxan yield 5-*p*-aminophenyldialuric acids which are converted by aqueous alkali to 5-*p*-aminophenyl-2,4-oxazolidinediones. When the dialuric acids, or the oxazolidinediones, are stirred with sulfuric acid (d = 1.5–1.84) at 150–160°C. for 10 min., they are converted into the corresponding aromatic aldehydes (71, 94).



p-Aminobenzaldehydes were prepared in this way from aniline, methylaniline, ethylaniline, diethylaniline, *o*-toluidine, and *o*-anisidine (71). A small yield of 2,4-bis(dimethylamino)benzaldehyde was similarly obtained from tetramethyl-*m*-phenylenediamine via the dialuric acid (146).

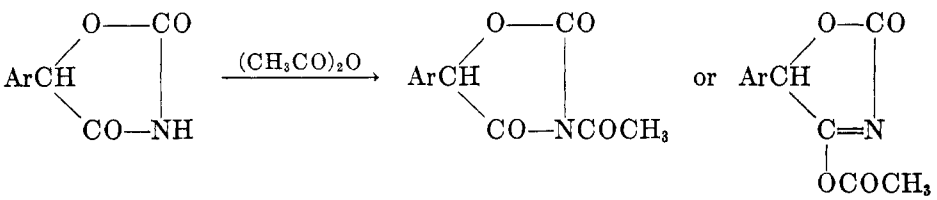
Aminophenyltartronic acids are converted by mild oxidizing agents (e.g., manganese dioxide, lead dioxide, silver oxide) to aminophenylglyoxylic acids (76), which may also be obtained from the dialuric acids and the corresponding 2,4-oxazolidinediones by alkaline hydrolysis in the presence of these oxidants (77).



Heating the glyoxylic acids with *p*-toluidine causes decarboxylation and formation of anils which can then be hydrolyzed to the aromatic aldehyde (*cf.* preparation of vanillin) (147).

E. ACYLATION OF 2,4-OXAZOLIDINEDIONES

During experiments designed to distinguish between the tartronimide and 2,4-oxazolidinedione structures for the hydrolysis products from dialuric acids it was found that 5-(2,4-dimethoxyphenyl)-2,4-oxazolidinedione gave an acetyl derivative which was insoluble in alkali (116).

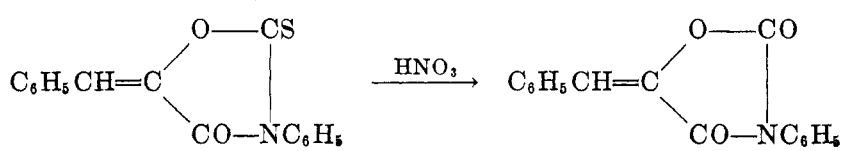


Ar = 2,4-dimethoxyphenyl.

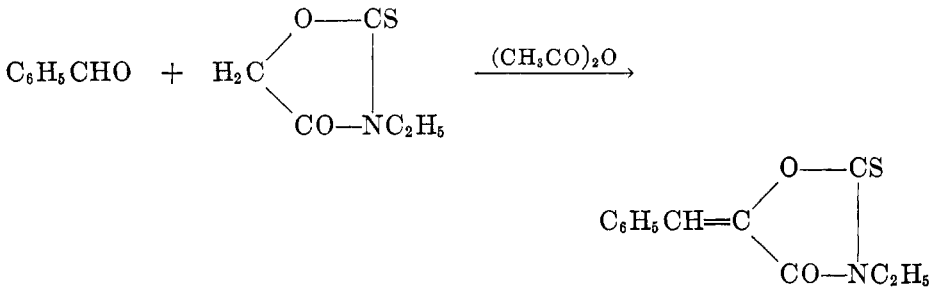
5-(2,4-Dimethoxyphenyl)-3-methyl-2,4-oxazolidinedione showed carbonyl absorption at 5.45 μ (urethan) and 5.73 μ (amide), and the above acetyl compound absorbed at 5.45, 5.62, 5.70, and 5.75 μ (both examined as Nujol mulls) (79). The complexing of the amide band suggests that the acetyl derivative is 3-acetyl-5-(2,4-dimethoxyphenyl)-2,4-oxazolidinedione, but examination of related compounds, such as the 4-enol ethers, is clearly necessary before excluding the alternative 4-acetoxy-5-(2,4-dimethoxyphenyl)-2-oxazolone structure. Caffolides have been acetylated (63), but acyl derivatives of other 2,4-oxazolidinediones have not been reported.

F. SUBSTITUTION IN THE METHYLENE GROUP

The 5-benzylidene and 5-*o*-chlorobenzylidene derivatives of 3-phenyl-2,4-oxazolidinedione were prepared from the 2-thio-4-oxazolidone analogs by oxidation with nitric acid (150).



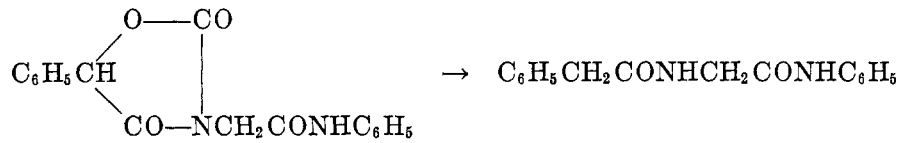
These two compounds appear to be the only known arylidene-2,4-oxazolidinediones, and the methylene group in the parent compound is insufficiently reactive for condensation with aromatic aldehydes. Benzylidene acetate was the sole product isolated after heating 3-ethyl-2,4-oxazolidinedione with benzaldehyde and acetic anhydride for 5 hr. (7), whereas 3-ethyl- and 3-phenyl-2-thio-4-oxazolidones gave the 5-benzylidene derivatives under similar conditions (107).



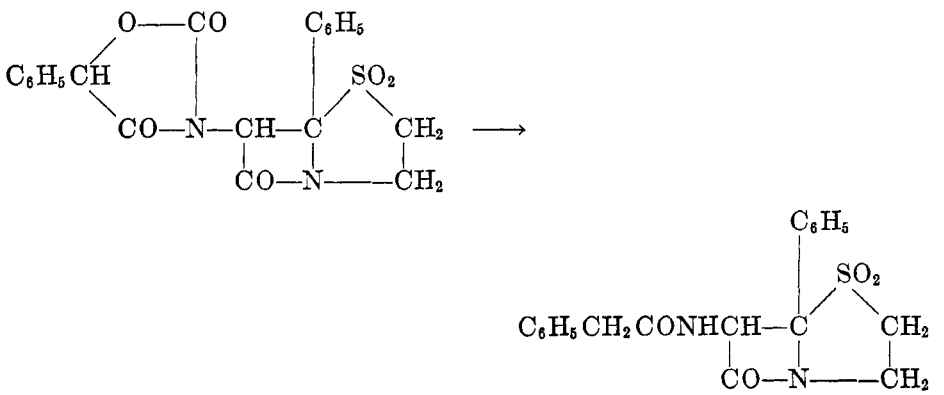
Benzylidene and other arylidene derivatives have been prepared under milder conditions from 2-thio-4-oxazolidone (173), and corresponding derivatives of 2,4-thiazolidinedione and 2-thio-4-thiazolidone (rhodanine) are well known (65).

G. HYDROGENOLYSIS OF 5-ARYL-2,4-OXAZOLIDINEDIONES

The 5-phenyl-2,4-oxazolidinediones can be regarded as cyclic esters of substituted benzyl alcohols and, as expected, are amenable to hydrogenolysis (148). 5-Phenyl-3-phenylcarbamoylmethyl-2,4-oxazolidinedione was converted by hydrogenolysis over palladized charcoal at room temperature to *N*-(phenylcarbamoylmethyl)phenylacetamide, which was also obtained by reducing the dione with aluminum amalgam (148).



The reduction was applied to the preparation of a 3-phenylacetamido-β-lactam (148) containing some of the structural features of benzylpenicillin.



V. Applications of 2,4-Oxazolidinediones

A. Medicinal Uses and Pharmacology

The most important application of this class of compound is the use of the 3-methyl derivatives of the lower 5,5-dialkyl-2,4-oxazolidinediones as anticonvulsants, especially in the treatment of petit mal epilepsy. Oxazolidinediones not bearing *N*-alkyl substituents have mild hypnotic, sedative, and narcotic properties (10), and pharmacologically they are classed with the barbiturates and hydantoins (90, 92, 100, 101). 5,5-Di-*n*-propyl-2,4-oxazolidinedione (propazone) has been studied clinically as a hypnotic and antiepileptic agent (101, 164).

The discovery that 3-methyl-2,4-oxazolidinediones differ from the parent compounds in having analgesic and anticonvulsant properties, with little or no hypnotic action (131, 151, 152, 155), led to the preparation and pharmacological testing of a large number of 2,4-oxazolidinediones covered by patents. 3,5,5-Trimethyl-2,4-oxazolidinedione (trimethadione, U.S.P.; troxidone, B.P.) is the compound most widely used in the symptomatic treatments of petit mal epilepsy; it prevents the appearance of the clinical symptoms and the characteristic electroencephalogram associated with petit mal. The pharmacology of trimethadione and other medicinally useful oxazolidinediones has been reviewed (101) and is still being actively investigated. The specific action of trimethadione in alleviating petit mal epilepsy is unparalleled by other classes of compounds, but 5-ethyl-3,5-dimethyl-2,4-oxazolidinedione (paramethadione) and 3-allyl-5-methyl-2,4-oxazolidinedione (malidone) have similar therapeutic properties. Some petit mal cases that initially fail to respond or cease to benefit from trimethadione respond to paramethadione. The reverse is also true, and these compounds are therefore a valuable complementary pair (101). The structural factors important for anticonvulsant activity in 2,4-oxazolidinediones and other classes of antiepileptic agents have been discussed (167, 168).

The primary action of trimethadione is on the central nervous system, but the mechanism and the site of the cerebral action responsible for its dramatic benefit in petit mal are unknown (101). Trimethadione is the most specific antagonist that is known towards seizures induced by pentylenetetrazole (leptazol; metrazole), and it is thought that this antagonism may provide a fundamental clue to the reason for the efficacy of trimethadione in petit mal epilepsy (101). In rats, dogs, and man trimethadione is completely demethylated to 5,5-dimethyl-2,4-oxazolidinedione, which is devoid of anticonvulsant activity and is slowly excreted in the urine (67, 68, 166). The *d*- and *l*-forms of 5-ethyl-3,5-dimethyl-2,4-oxazolidinedione were excreted by mice at about the same rate, and no significant difference was found in the physiological activity of the enantiomorphs (69).

The oxazolidinediones are generally well tolerated but occasional toxic effects, particularly blood disorders such as agranulocytosis and aplastic anemia, make medical supervision of their use necessary (101). Blurring of vision is caused by trimethadione in 50–75 per cent of the cases, especially in adults; this effect, which is observed in viewing brightly lighted objects, is unpleasant but not harmful and is less pronounced with paramethadione, and not shown by malidone

(101). Dark adaptation is not affected and the glare sensation is due to specific action on the retinal cones (88).

5,5-Diphenyl-2,4-oxazolidinedione is ineffective in petit mal but resembles 5,5-diphenylhydantoin in controlling grand mal seizures, for which trimethadione and paramethadione alone are ineffective. The latter are sometimes useful in conjunction with diphenylhydantoin therapy for control of grand mal or psychomotor seizures (101). The 5,5-diaryl-2,4-oxazolidinediones do not possess the hypnotic and sedative properties which characterize the 5,5-dialkyl compounds (162). 2,4-Oxazolidinediones with dialkylaminoalkyl substituents also differ from the simple alkyl derivatives in having little or no hypnotic or sedative action, but some have analgesic properties of a much higher order than the simpler trialkyl derivatives (163) such as trimethadione.

B. OTHER USES OF 2,4-OXAZOLIDINEDIONES

2,4-Oxazolidinedione and its 5-methyl derivative are claimed to prevent the denaturation of protein glues by formaldehyde; the glue solutions can be kept for a long time and give firm joints without perforations, especially when heat and pressure are applied (134).

Trichloromethylthio derivatives of 2,4-oxazolidinediones (82, 102, 119, 120) and other imides have recently been found useful as parasiticides.

Reference has already been made (Section IV) to the use of 3-phenyl-2,4-oxazolidinediones for the preparation of anilides of α-hydroxy acids, to the formation of aromatic aldehydes from 5-aryl-2,4-oxazolidinediones, and to the hydrogenolysis of 5-phenyl-2,4-oxazolidinediones to phenylacetamides.

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