THE OXAZOLIDINES

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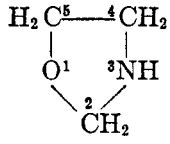
CONTENTS

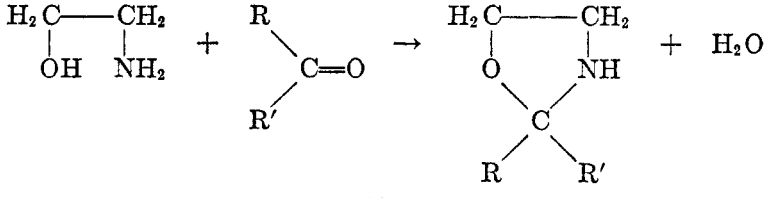
I. INTRODUCTION

The oxazolidine ring system

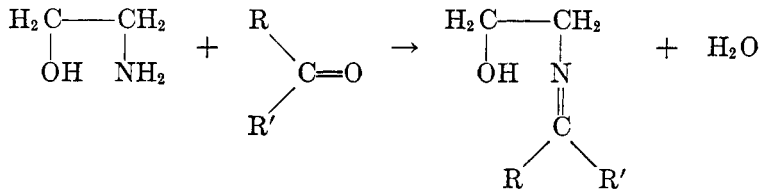


has had a remarkable history. Knorr and coworkers (75, 76) ascribed the cyclic structure to products which were obtained, e.g., from ethanolamine and aldehydes or ketones with the loss of one molecule of water (scheme A), without taking into account the possibility that the condensation products might simply be Schiff bases (scheme B).

Scheme A:



Scheme B:



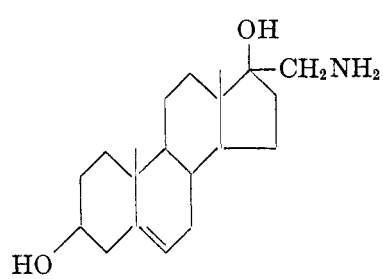
From time to time, doubts as to the structure of some particular products of such reactions were expressed, but the existence of oxazolidines as such has not been questioned until recently. In 1951, McCasland and Horswill (83), who were investigating some complex cases, arrived at the conclusion that no "simple oxazolidine (without substituent on the $N_{(3)}$ nitrogen atom) of well-established structure and purity is now known."

It seemed, therefore, worthwhile to present the existing data on the oxazolidine system, in order to parallel the review on the related group of oxazoles which was published in 1945 by Wiley (117). A comprehensive survey of the parallel class of thiazolidines has been published by Cook and Heilbron (33). The conclusion may be anticipated that oxazolidines do indeed exist, but that they form a sometimes very mobile tautomeric system with the corresponding Schiff bases. It will be shown that it is possible to determine accurately the structure of a given condensation product between a β-aminoalcohol and a carbonyl compound. It should further be borne in mind that obviously a β-aminoalcohol in which the nitrogen atom is of secondary nature must, if reaction occurs at all, give an oxazolidine derivative with a carbonyl compound.

II. SYNTHESIS OF OXAZOLIDINES

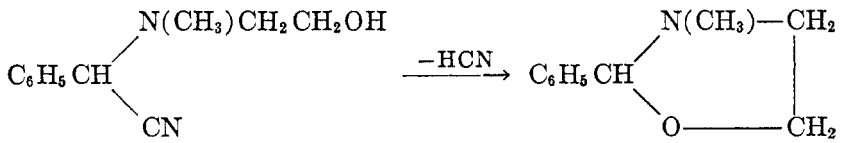
Without going into the question of the structure of the condensation products between β-aminoalcohols and carbonyl compounds, the methods employed for the preparation of these products will be reviewed briefly.

Knorr and coworkers (75, 76) condensed the reactants in boiling ether in the presence of solid potassium carbonate; they pointed out, however, that some stable compounds, such as those derived from aromatic aldehydes or ketones, form as soon as the reagents are mixed. Indeed, the condensation can be carried out without any catalyst. As reaction media the following have been suggested: ether (19, 120), chloroform (120), alcohol (61, 80, 83, 89), butyl ether or its mixture with butyl alcohol (85), and even water, which has been recommended especially for formaldehyde (70, 120). Δ⁵-3β,17β-Dihydroxy-17α-aminoethylandrostene



condenses with acetone when the compounds are refluxed together (62). The best and most common method, however, is azeotropic distillation, in which benzene is used as the water-entraining agent (18, 19, 24, 28, 34, 35, 44, 56–59, 92, 106, 120); occasionally, toluene or xylene has been proposed for this purpose (92, 120). The condensation reactions, especially with complex ketones, are often accelerated by a trace of iodine (7, 18, 120), a method which has proven useful in a number of similar reactions (12, 115). Nevertheless, catalysts have been added by some authors to the reaction mixtures,—unnecessarily, as it seems: thus, 2-(α-hydroxyethyl)piperidine has been condensed with benzaldehyde in the presence of aqueous hydrochloric acid (65), and Knorr's original method, employing potassium carbonate, has been applied by a number of more recent investigators (e.g., 113). Sometimes it has been found advisable to add a small quantity of acetic acid to the reaction mixture which was subjected to azeotropic distillation (57, 58). In condensing 2-methylaminoethanol with benzaldehyde, acetaldehyde, or acetone, Kiprianov and Rashkovan (74) used potassium cyanide as catalyst; they assumed that the nitriles of hydroxy-(alkylamino) acids were formed, which split off hydrocyanic acid and thus formed the heterocyclic compounds:

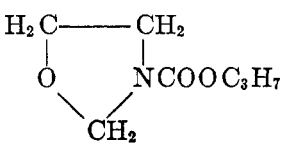
$$C_6H_5CHO + HCN + CH_3NHCH_2CH_2OH \longrightarrow$$



However, Bergmann, Zinkin, and Pinchas (19) have shown that these condensations can be carried out equally well without the addition of potassium cyanide.

The condensation with carbonyl compounds takes place with both primary and secondary β-hydroxyethylamines; obviously, tertiary amines are incapable of entering into reaction. Indeed, the use of formaldehyde has been (23) suggested occasionally as a means of separating tertiary from secondary β-hydroxyethylamines; only the latter react to form oxazolidines, which are separated.

Although *N*-acyl-β-aminoalcohols should be capable of reacting with carbonyl compounds, only the reaction between *N*-carbopropoxyethanolamine and formaldehyde has been studied (64). It gives a product which may be 3-carbopropoxyoxazolidine (I), although its discoverers had originally assigned to it the formula (II) of *N*-carbopropoxy-*N*-methylaminoacetaldehyde. An analogous



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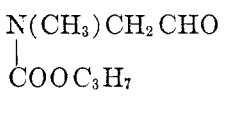


II

product is obtained from *N*-carbethoxy-1-phenyl-2-aminoethanol; its structure has not been definitely elucidated.

The comparative ease with which different aminoalcohols and different car-

TABLE 1

Aminoalcohols capable of undergoing condensation with carbonyl compounds

	AMINOALCOHOL	REFERENCES
C_2	Ethanolamine	(7, 8, 9, 10, 11, 13, 14, 18, 28, 35, 38, 39, 53, 55, 57 75, 76, 85, 87, 88, 89, 106)
C_3	*N*-Methylethanolamine	(14, 18, 19, 53, 74, 75)
	1-Amino-2-propanol	(34)
	2-Amino-1-propanol	(58)
	1-Amino-2,3-propanediol	(20, 83)
	2-Amino-1,3-propanediol	(100)
	1-Amino-3-chloro-2-hydroxypropane	(22, 23, 103)
C_4	Diethanolamine	(19, 56)
	N-Ethylethanolamine	(38, 56)
	2-Amino-2-methyl-1-propanol	(58, 106)
	2-Amino-1-butanol	(8, 58, 88a)
	2-Amino-2-methyl-1,3-propanediol	(1, 34, 59, 106)
	Aminotrimethylolmethane	(1, 91, 92, 106)
C_5	1-Amino-3-methyl-2-butanol	(113)
	1-(β-Hydroxyethylamino)-2-propanol	(56)
	2-Amino-3-ethyl-1,3-propanediol	(1, 106)
	2-Amino-3-methyl-3-butanol	(7, 10, 11, 13, 14, 18, 70, 87, 88)
C_6	3-Methyl-1-methylamino-2-butanol	(113)
	N-Isobutylethanolamine	(75, 106)
	2-Amino-3-propyl-1,3-propanediol	(106)
	2-Amino-3-isopropyl-1,3-propanediol	(106)
	2-Aminocyclohexanol (*cis* and *trans*)	(83)
	2-Amino-3-methyl-3-pentanol	(18)
C_7	2-(α-Hydroxyethyl)piperidine	(65)
	2-Amino-2-methyl-3-hexanol	(106)
	γ-(2-Hydroxyisobutylamino)propylamine	(110a)
C_8	*N*-Phenylethanolamine	(14, 78, 120)
	2-Amino-3,5-dimethyl-3-hexanol	(18)
	1-(α-Aminoethyl)cyclohexanol	(18)
C_9	2-Amino-1-indanol	(80)
	1-Amino-2-indanol	(80)
	N-(*p*-Methoxyphenyl)ethanolamine	(78)
	1-Anilino-2-propanol	(78)
	Norephedrine (2-amino-1-phenol-1-propanol)	(44, 106)
	Pseudonorephedrine (2-amino-1-phenyl-1-propanol)	(44)
	3,4-Dihydroxynorephedrine	(44)
	3-Hydroxynorephedrine	(44)
	4-Hydroxynorephedrine	(44)
	3-Aminonorephedrine	(44)
	2-Amino-1-*p*-nitrophenyl-1,3-propanediol (*threo*)	(32a, 70)
C_{10}	*N*-(*p*-Ethoxyphenyl)ethanolamine	(23)
	2-(β-Ethylbutylamino)-2-methyl-1-propanol	(106)
	2-Methyl-2-propylamino-3-hexanol	(106)
	Ephedrine	(40a, 44, 103a, 116)
	Pseudoephedrine	(103a)
	2-Amino-5-methoxy-1-indanol	(61)
	2-Amino-6-methoxy-1-indanol	(61)
	2-Amino-7-methoxy-1-indanol	(61)
C_{11}	1-(*p*-Ethoxyanilino)-2,3-propanediol	(23)
	2-Benzylamino-2-methyl-1-propanol	(106)
	2-Isobutylamino-2-methyl-3-hexanol	(106)
	2-Methyl-3-(α,γ-dimethylbutylamino)-3-butanol	(14)
	Ethyl *p*-nitrophenylserinate (*erythro* and *threo*)	(6, 8, 40)
	2-Amino-5,6-dimethoxy-1-indanol	(61)
	2-Amino-4,5-dimethoxy-1-indanol	(61)
C_{13}	*N*-(β-Naphthyl)ethanolamine	(78)
C_{14}	2-Benzylamino-2-methyl-3-hexanol	(106)
	α-Amino-β-hydroxybibenzyl (both isomers)	(23, 45a, 45b, 45d, 95a, 95b)
C_{16}	2-Benzylamino-1-phenyl-1-propanol	(106)
C_{20}	Δ^5-3β,17β-Dihydroxy-17α-aminomethylandrostene	(62)

bonyl compounds enter into the reaction has not been studied very systematically. In table 1 the aminoalcohols are enumerated which have been shown to

give a positive response; there seems to be no structural limitation to the condensation reaction.

Regarding the ability of the carbonyl component to enter into reaction with these aminoalcohols, the following general conclusions can be drawn from the material listed in tables 11–16: all aldehydes condense with aminoalcohols containing primary and secondary amino groups; ketones are much less reactive, condensing easily only with primary β-hydroxyalkylamines. If the amino group is secondary, the substituent present on the nitrogen atom appears to exert a decisive influence. *N*-Phenylethanolamine does not condense with ketones even under the most stringent conditions (120); *N*-methylethanolamine, on the other hand, condenses with the more active ketones, such as acetone, cyclohexanone,

TABLE 2

Relative reactivity of different carbonyl compounds with aminoalcohols

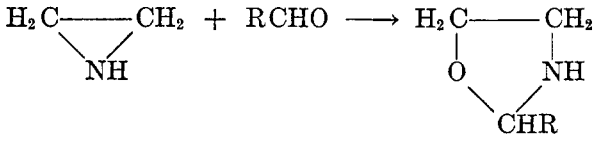
AMINOALCOHOL	CARBONYL COMPOUND	TIME REQUIRED FOR COMPLETE REACTION
2-Amino-3-methyl-3-butanol	Cyclohexanone	10 min.
	3-Methyl-3-butanol-2-one	15 min.
	2-Ethyl-2-hexenal	20 min.
	2-Ethylhexanal	25 min.
	Benzaldehyde	25 min.
	Mesityl oxide epoxide	35 min.
	Cyclopentanone	2 hr.
	4-Methyl-4-phenyl-2-pentanone (in the presence of iodine)	2 hr.*
	Isobutyl methyl ketone	3 hr.
	Pinacolone (in the presence of iodine) (7,18)	7 hr.
Ethanolamine	Cyclopentanone	2.5 hr.
	4-Methyl-4-phenyl-2-pentanone	2.5 hr.
	Pinacolone (in the presence of iodine only) (7)	15 hr.
***N*-Methylethanolamine**	2-Ethyl-2-hexenal	45 min.
	Benzaldehyde	45 min.
	Cyclohexanone	105 min.
	Acetone	2 hr.
	Anisaldehyde	2.5 hr.
	Cyclopentanone	4.5 hr.
	Isobutyl methyl ketone	13 hr.
2-Amino-2-methyl-1-propanol	Isovaleraldehyde	1.2 hr.
	Amyl methyl ketone	5 hr.
	Cyclohexanone (in the presence of acetic acid)	8 hr.
	Ethyl methyl ketone (in the presence of acetic acid)	67 hr.

* In the absence of iodine, reaction is 50 per cent complete in 90 min.

cyclopentanone, isobutyl methyl ketone, and acetophenone; diisobutyl ketone, however, proved refractory (see page 329) (19). M. Bergmann, Ulpts, and Camacho (23) claim that *N*-(*p*-ethoxyphenyl)ethanolamine condenses with aldehydes *and* ketones; however, their experiments were limited to two aldehydes, formaldehyde and benzaldehyde.

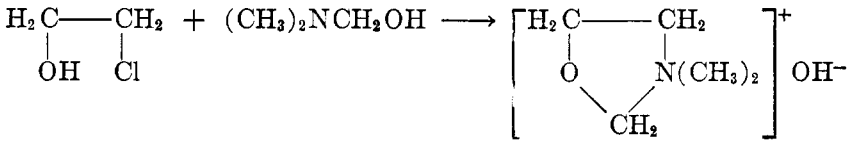
Some crude quantitative estimation of the *relative reactivity of different carbonyl compounds* is possible on the basis of the times required for reaction under the conditions of azeotropic distillation (table 2). The reactivity in parallel series seems to follow a parallel sequence; the difference in reactivity between cyclohexanone and cyclopentanone should be emphasized (see page 332). Similar observations have been made regarding the tendency of various carbonyl compounds to acetal formation with ethylene glycol by Sulzbacher, E. Bergmann, and Pariser (109).

In comparison with the condensation of carbonyl compounds with amino-alcohols, very few other methods appear to be of preparative interest. Attention is, however, drawn to the fact that, according to Doughty, Lazzell, and Collett (42), ethylenimine condenses smoothly with aliphatic aldehydes to form 2-substituted oxazolidines:



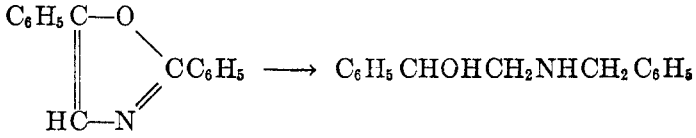
The yields were as follows: acetaldehyde, 56 per cent; propionaldehyde, 28 per cent; butyraldehyde, 57 per cent; isobutyraldehyde, 55 per cent; heptaldehyde, 95 per cent; with benzaldehyde, however, only a 10 per cent yield was obtained. The two aliphatic ketones studied (acetone and amyl methyl ketone) gave yields of 6 and 5 per cent, respectively.

A substance described as 3,3-dimethyloxazolidinium hydroxide has been obtained (46) from dimethylaminomethanol and ethylene chlorohydrin in a reaction which can be formulated as follows:



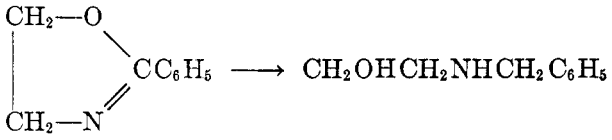
but no proof for this structure has been offered.

In any event, the preparation of oxazolidines by the reduction of oxazoles and oxazolines does not seem to offer any promise. As will be shown later (page 318), the oxazolidines are so prone to reductive fission that it is understandable that E. Fischer (47) obtained 2-benzylamino-1-phenyl-1-propanol by the action of sodium and alcohol on 2,5-diphenyloxazole,



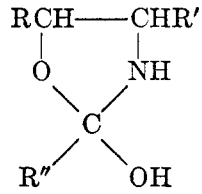
2,5-Diphenyloxazole 2-Benzylamino-1-phenyl-1-propanol

and Gabriel and Stelzner (51) obtained *N*-benzylethanolamine from 2-phenyl-oxazoline by the action of sodium and amyl alcohol.

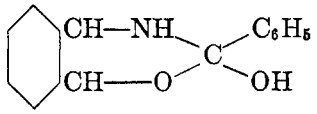


2-Phenyloxazoline *N*-Benzylethanolamine

For the sake of completeness, it should be mentioned that M. Bergmann, Brand, and Weinmann (21) have suggested an oxazolidine derivative

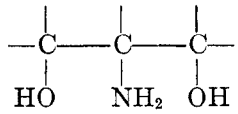


as intermediate in the O → N migration of acyl groups in acylated β-hydroxy amines (see also 50, 54, 90, and 118). Crawhall and Elliott (37) proposed a similar intermediate for the analogous thiazolidine derivative. Analogously, McCasland, Clark, and Carter (82) postulated the formation of a substituted oxazolidine as an intermediate in the transformation of one isomer of *dl*-2-aminocyclohexanol (in the form of its *N*-benzoyl-*O*-(*p*-toluenesulfo) derivative) into the other (in the form of its *N*-benzoyl derivative) upon treatment with sodium acetate in aqueous acetic acid or in dry ethyl alcohol:

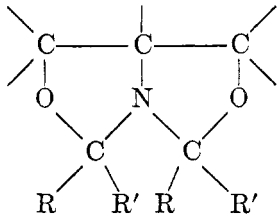


Synthesis of 1-aza-3,7-dioxabicyclo[3.3.0]octanes

Primary amines of the general structure



are capable of reacting with either one or two molecules of a carbonyl compound. In the latter case, substituted 1-aza-3,7-dioxabicyclo[3.3.0]octanes are formed (1, 91, 92, 106; *cf.* 111):

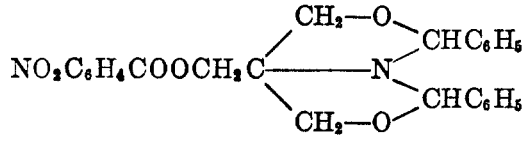


III. CHEMICAL REACTIONS OF THE INTACT OXAZOLIDINE RING

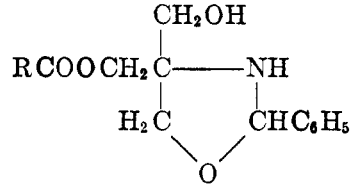
A. Stability toward hydrolysis

The oxazolidines are liquids or solids of basic character; their stability to hydrolysis is generally low, but appears to be significantly influenced by substituents, in a manner which cannot as yet be assessed on the strength of the available

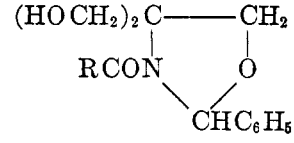
experimental material. Some representatives of the group are hydrolyzed even by water (e.g., the ethanolamine derivative of cyclopentanone (7)); all of them are hydrolyzed by acids. In the case of oxazolidines derived from *N*-methylethanolamine, nitrogen analyses were performed by hydrolysis and titration of the aminoalcohol in the presence of methyl orange (19). The acetone derivative of Δ^5-3β,17β-dihydroxy-17α-aminomethylandrostene is hydrolyzed by cold dilute acetic acid into its components (62). In a number of cases stable picrates have been obtained; some, however, can be prepared only in ether, and even recrystallization from alcohol causes hydrolysis and formation of the picrate of the corresponding aminoalcohol (58, 65, 75, 113). In several instances, on the other hand, stable hydrochlorides of the condensation products have been described; *viz.*, the hydrochlorides of the condensation products of aminotrimethylolmethane with cyclohexanone and benzaldehyde (92), of 2-amino-1-indanol and various aromatic aldehydes (61), and of the bicyclic compound (91):



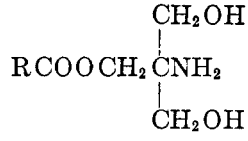
On substances of the last type (with various acyl groups), the stepwise hydrolysis of the ring system has been studied (91). Hydrochloric acid gives one molecule of benzaldehyde and the hydrochloride of the oxazolidine:



Also, the relatively water-insoluble nitrates of these oxazolidines are fairly stable. When these salts are treated with alkali, migration of the acyl radical from oxygen to nitrogen takes place and—*via* an alkali-soluble intermediate product—*N*-acyloxazolidines of the general formula



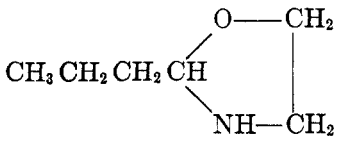
are obtained. In certain cases (*p*-nitrobenzoyl, phenoxyacetyl) alcoholic hydrochloric acid causes fission of the ring and an inverse migration of the acyl group, leading to the hydrochloride of



These reactions are of some importance in connection with the general study of the acylation of oxazolidines (see page 321).

B. Polymerization

There is yet another limitation to the stability of the oxazolidine ring. The condensation products of ethanolamine with acetaldehyde (75) and propionaldehyde (10), as well as that of aminotrimethylolmethane and butyraldehyde (92), resinify upon standing. The mechanism of this polymerization reaction has not been completely elucidated, although Paquin (89) has studied the condensation between ethanolamine and butyraldehyde. Three products were obtained, which upon distillation showed a relatively low boiling point, low viscosity, and low solubility in water, but were reversibly transformed, upon standing, into highly viscous, water-soluble products. Paquin claimed that the three products were derived, respectively, from butyraldehyde, 2-ethyl-2-hexenal, and 2,4,6-triethyl-2,4,6-decatrienal and ascribed oxazolidine structures (III–V) to the forms of low viscosity and the *isomeric* Schiff base formulas to those of high viscosity (VI–VIII):



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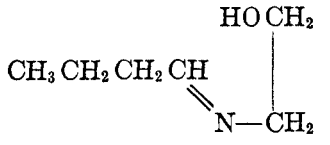

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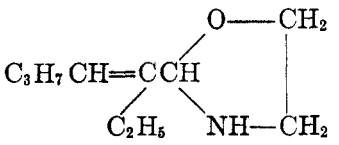

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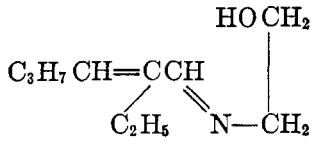

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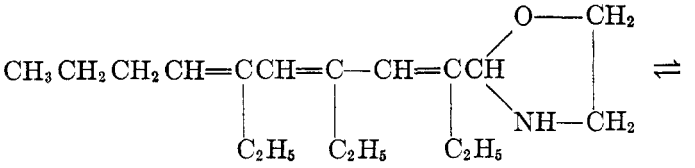
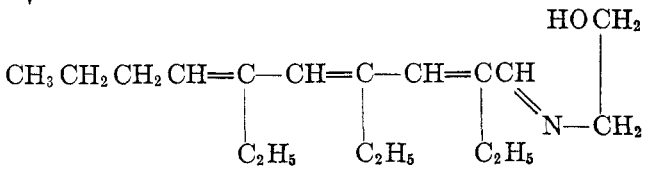


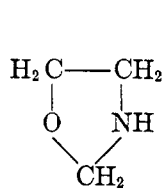
V



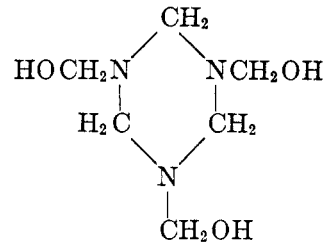
VIII

Also from formaldehyde and ethanolamine a highly viscous, water-soluble product was obtained; this gave, upon distillation (b.p. 100°C./6–7 mm.), a mobile distillate which polymerized spontaneously and with liberation of heat.

The author assumed that the polymer was 1,3,5-tri(hydroxymethyl)hexahydro-1,3,5-triazine (X) and that the monomer was the oxazolidine (IX).



IX



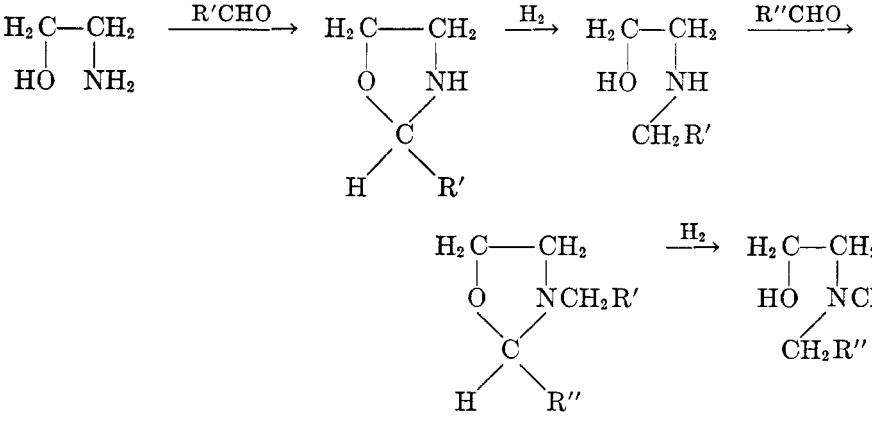
X

It is unlikely that this explanation is correct, since the boiling point of the monomeric oxazolidine could not be as high as 100°C./6–7 mm. (2,2-dimethyloxazolidine boils at 64–65°C./100 mm. (10)). Probably also in the case of the reaction with butyraldehyde, the products are not isomers but polymers. However, the question of the mechanism of the polymerization must remain unsettled for the time being, whilst that of the isomerization of the oxazolidine structure will be discussed below (page 321).

C. Reduction

Apart from the reversal of the condensation reaction, the oxazolidine ring undergoes *fission* between O and $C_{(2)}$ upon treatment with Grignard compounds or reducing agents.

Reducing agents convert the oxazolidines into aminoalcohols with the same number of carbon atoms and thus permit the defined *N*-alkylation of the aminoalcohols from which the oxazolidines have been prepared. If the aminoalcohol has a primary amino group, the process can be repeated and leads to di-*N*-alkyl derivatives, in which the two alkyl groups may be identical or different:

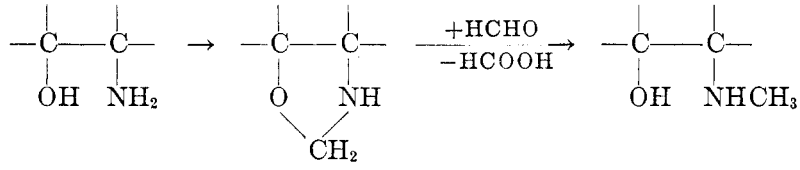


The reduction of the oxazolidine system can be carried out by various means: with sodium and alcohol (57; see also page 314), with aluminum amalgam (30),

with catalytically activated hydrogen (9, 34, 25, 53, 58, 106), and with lithium aluminum hydride (14, 62). Occasionally, formic acid has been used for this purpose (29, 30).

This method for the alkylation of aminoalcohols, which consists in the preparation and subsequent fission of oxazolidines, has been used in recent years for the preparation of substituted aminoalcohols without isolation of the primary condensation product; an aminoalcohol and a carbonyl compound are subjected to coreduction (29, 30, 34, 35, 44, 58, 73).

The observation of M. Bergmann, Ulpts, and Camacho (23) that an aminoalcohol gives with an excess of formaldehyde not the oxazolidine but the *N*-methyl derivative can be explained in an analogous manner,

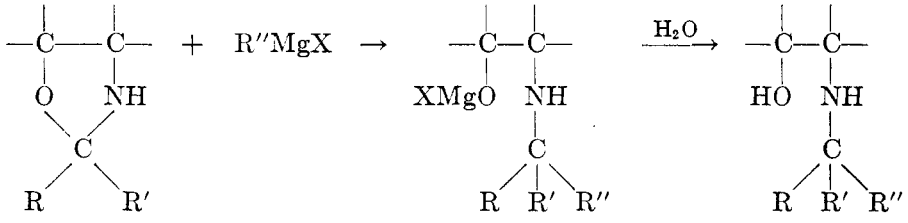


although the authors assumed that the formation of the oxazolidine is reversed and the aminoalcohol is methylated directly. The same explanation applies to the observation of Heinzelmann, Kolloff, and Hunter (61) that substituted 2-amino-1-indanols are converted by formaldehyde not into oxazolidines, but directly into the *N*,*N*-dimethyl derivatives of the starting materials.

It has been pointed out that in such reductions the configuration on the carbon atom of the original aminoalcohol is not affected (44, 61). Thus it is possible that the well-known method for the alkylation of amines with formaldehyde and formic acid, proceeds, as far as it is applied to β-hydroxy amines, *via* oxazolidines which are eventually reduced by the formic acid (68, 69; *cf.* 12).

D. Reaction with Grignard reagents

Analogously, Grignard reagents cleave the oxazolidine ring according to the general scheme (56, 106):

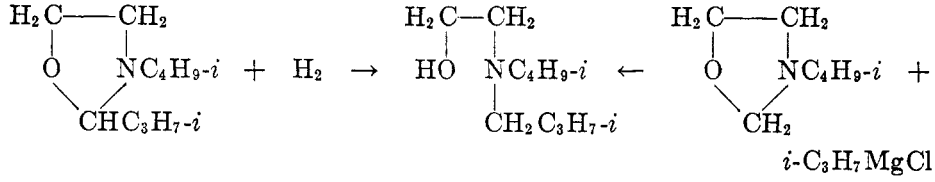


This reaction recalls the observation of Robinson and Robinson (101) that (dialkylamino)alkoxymethanes react with Grignard compounds according to the following scheme:

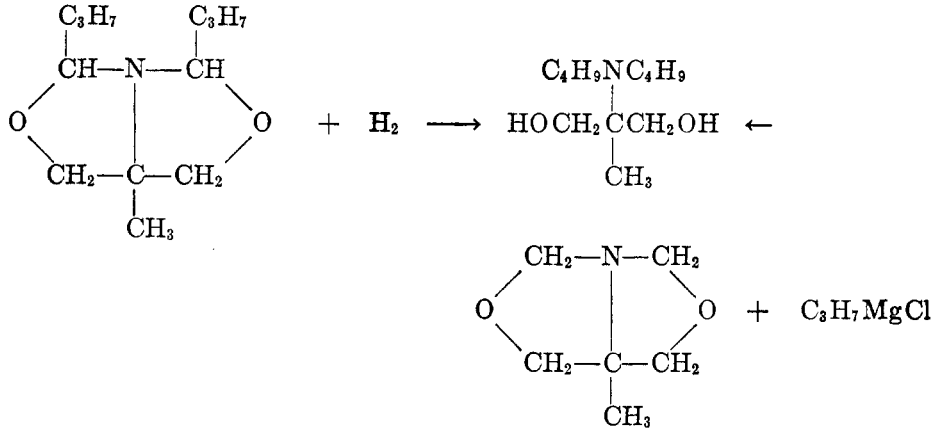
$$R_2NCH_2OR + R'MgCl \rightarrow R_2NCH_2R' + ROMgCl$$

The relationship between the hydrogenation of oxazolidines and the Grignard reaction with these compounds has been demonstrated very elegantly by Senkus

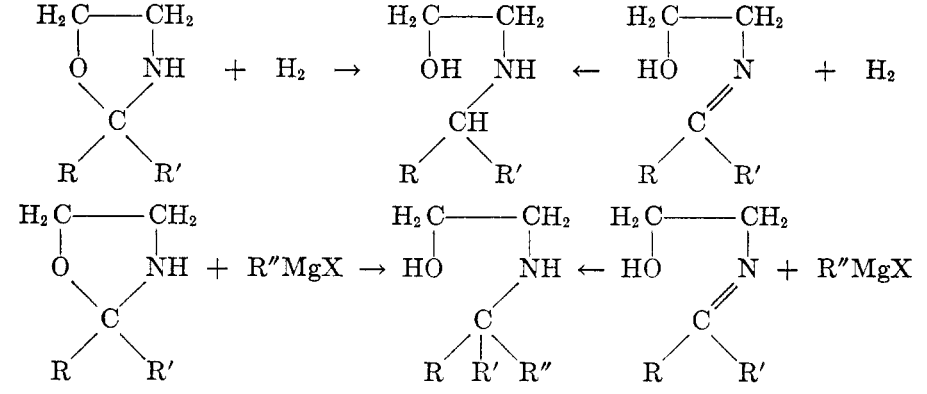
(106), who obtained the same 2-(diisobutylamino)ethanol by the hydrogenation of 3-isobutyl-2-isopropyloxazolidine and by the reaction between 3-isobutyl-oxazolidine and isopropylmagnesium chloride:



Also, the same 2-(dibutylamino)-2-methyl-1,3-propanediol was obtained by the catalytic hydrogenation of 5-methyl-2,8-dipropyl-1-aza-3,7-dioxabicyclo[3.3.0]-octane and by the reaction of *n*-propylmagnesium chloride with 5-methyl-1-aza-3,7-dioxabicyclo[3.3.0]octane:

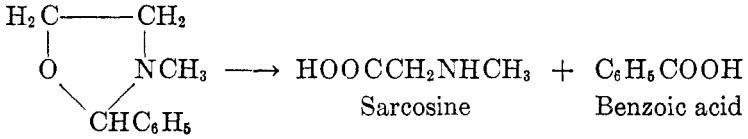


For the elucidation of the structure of the condensation products between aminoalcohols and carbonyl compounds, it is of considerable interest that the above two reactions, hydrogenation and reaction with the Grignard reagent, cannot differentiate between the oxazolidine and the Schiff base structures, as the following reaction schemes demonstrate:



E. Oxidation

The oxidation of oxazolidines has scarcely been studied. Only Knorr and Mathes (75) reported the oxidation of 3-methyl-2-phenyloxazolidine to sarcosine and benzoic acid:

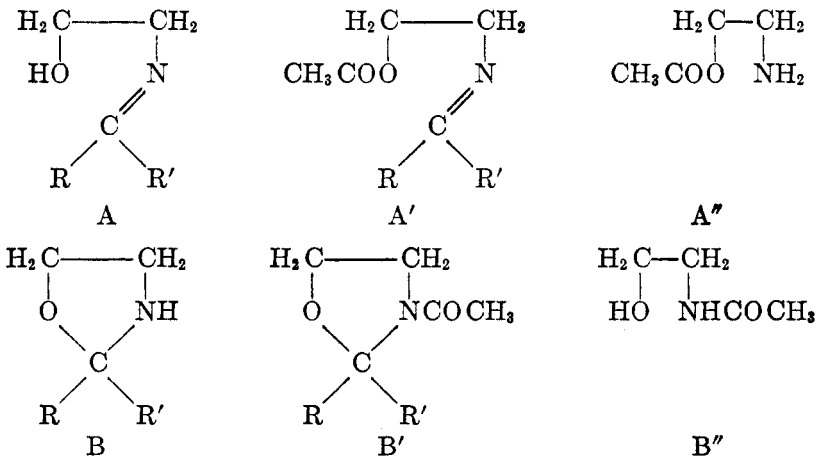


Milder oxidants are capable of oxidizing only the (potential) alcoholic group in these condensation products. Thus, it has been suggested that α-amino acids may be made by oxidation of the condensation products of primary β-amino-alcohols with saturated aliphatic or aromatic aldehydes (24).

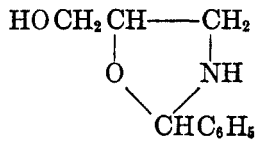
F. Substitution

Substitution in the oxazolidine ring system is possible at the nitrogen atom. However, apart from the condensation with ethylene oxide or glycidol, which gives high-polymeric derivatives (28), and the nitrosation of 4-ethyl-2-propyl-oxazolidine (88a; see page 334), only acylation has been studied. Indeed, M. Bergmann and coworkers (20, 22, 23) believed that this reaction would permit a differentiation between oxazolidines and the isomeric Schiff bases, but it will be shown that the situation is much more complex than these authors had anticipated. No chemical method appears to exist which can definitely establish the structure of the condensation products formed by reaction between amino-alcohols and carbonyl compounds.

It would appear that a Schiff base (A) can only be acylated at the hydroxyl group (A′) and the corresponding oxazolidine (B) at the nitrogen atom (B′). Splitting off the aldehyde radical would lead to an ester and an amide, respectively (A″ and B″), provided none of the operations caused a molecular rearrangement.

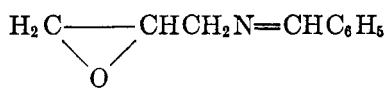


Thus, it was concluded that the benzaldehyde derivative of Erlenmeyer's (45) "isodiphenyloxyethylamine" (β-amino-α-hydroxybibenzyl) is an oxazolidine, as benzoylation in pyridine and subsequent treatment with concentrated hydrochloric acid gives α-hydroxy-β-benzoylaminobibenzyl, which had been prepared by an unambiguous method by v. Auwers and Sonnenstuhl (4). An additional argument appeared to present itself in the observation that the benzaldehyde derivative of 1-amino-2,3-propanediol

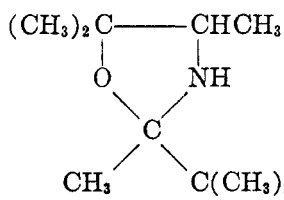


(which contains two asymmetric carbon atoms and represents, therefore, in spite of its tendency to form well-shaped crystals, a mixture of diastereoisomers) gives on benzoylation two dibenzoates, but that the isomerism disappears when the benzaldehyde molecule is split off and O^2,N-dibenzoyl-1-amino-2,3-propanediol is formed. However, the nature of these two dibenzoates is somewhat obscured by the fact that their separation had to be carried out in the presence of $N/10$ hydrochloric acid and alcohol; no explanation was given for the part which the acid plays in this operation.

Similarly, the 3-amino-2-hydroxypropyl chloride which is formed from epichlorhydrin and ammonia was claimed to give with benzaldehyde an oxazolidine derivative, as benzoylation and removal of the benzaldehyde moiety gave the N-benzoyl derivative of the original chlorinated aminoalcohol. Here, too, the argument is somewhat invalidated by the observation of the authors that the oxazolidine gives with sodium ethoxide (apart from replacement of the chlorine atom by the ethoxy group) a Schiff base of the presumable formula:



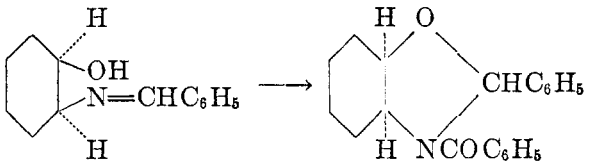
It is true that oxazolidines can be acylated at the nitrogen atom. Thus, the compound from 2-amino-3-methyl-3-butanol and 3-methyl-3-butanol-2-one



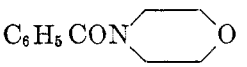
is acylated on the nitrogen atom, as the acylation product shows not only the characteristic infrared absorption of the oxazolidine system, but also an absorption at 1634 cm.$^{-1}$, characteristic of the disubstituted amide group (18; see 79, 97). (The use of the infrared spectrum for the differentiation between O-acyl and N-acyl groups would recommend itself in cases of the above type.) Also, the acetone derivative of Δ^5-3β,17β-dihydroxy-17α-aminomethylandrostene gives

with acetic anhydride in pyridine a diacetyl derivative which should contain one of the acyl groups at $C_{(3)}$ of the steroid system and the other at the NH group of the oxazolidine ring. The former is preferentially split off upon alkaline hydrolysis (the monoacetyl derivative so obtained is converted by aluminum *tert*-butoxide into an α,β-unsaturated ketone); the position of the latter follows from the observation that reduction of the monoacetyl derivative with lithium aluminum hydride both cleaves the ring and reduces the acetyl to an ethyl group, giving the *N*-ethyl-*N*-isopropyl derivative of the original aminoalcohol (62). On the other hand, acylation of the condensation product between ethanolamine and isobutyl methyl ketone (which is largely the Schiff base, see page 328) gives with *p*-methoxybenzoyl chloride only the *O*,*N*-di(*p*-methoxybenzoyl) derivative of ethanolamine (18), and in the series of the closely related thiazolidines the observation has been made that one and the same product can under suitable conditions be acylated either to the *N*-acylthiazolidine or to the *S*-acyl Schiff base (95, 105, 118, 119); similar observations have been made in the imidazoline series (86).

This very complex situation has been clarified by McCasland and Horswill (83), who found that the benzaldehyde derivatives of *cis*- and *trans*-2-aminocyclohexanol, which have the ultraviolet absorption spectrum expected of a Schiff base (see page 325), give with benzoyl chloride the corresponding *N*-benzoyloxazolidines:

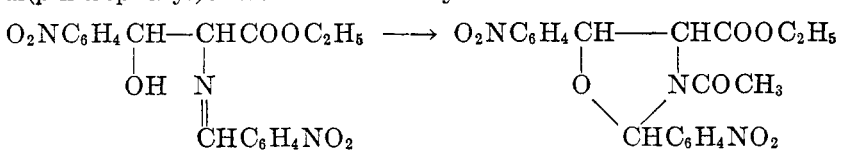


The spectrum of the latter is very similar to that of *N*-benzoylmorpholine:



Ethereal hydrochloric acid splits the *N*-benzoyloxazolidines to benzaldehyde and the corresponding 2-benzoylaminocyclohexanols. These authors also showed that the benzaldehyde derivative of 1-amino-2,3-propanediol of M. Bergmann and coworkers has the ultraviolet absorption of a Schiff base, although acylation gives an *N*-acyloxazolidine.

An analogous case has recently been studied by E. Bergmann, Bendas, and Resnick (5): both the *threo*- and the *erythro*-forms of ethyl *p*-nitrophenylserinate condense with *p*-nitrobenzaldehyde; the two well-crystallized derivatives have the structure of Schiff bases, as their ultraviolet and infrared spectra indicate. Acylation, however, converts them both into diastereoisomeric ethyl 3-acetyl-2,5-di(*p*-nitrophenyl)oxazolidine-4-carboxylates:



The infrared spectra of the reaction products prove the presence of the disubstituted amide group (see page 322), and in the ultraviolet spectra the absorbing system ArC(=N)— is no longer apparent. Incidentally, the maintenance of the configuration in the transformations is interesting in view of the explanation suggested by McCasland, Clark, and Carter (see page 315) for the interconversion of certain derivatives of the isomeric 2-aminocyclohexanols through a common intermediate of oxazolidine structure.

In conclusion, it is obvious that chemical methods are not delicate enough for the elucidation of the structure of the fairly mobile condensation products of aminoalcohols and carbonyl compounds; hence physical methods of studying the molecular structures have been applied.

IV. PHYSICAL PROPERTIES

A. Boiling point

The condensation products of aminoalcohols with carbonyl compounds are distillable liquids or solids; their boiling points have occasionally been used as an indication of the structure. The argument has been that the aminoalcohol formed by catalytic hydrogenation of the condensation product would have a boiling point similar to that of the corresponding Schiff base but higher than that of the isomeric oxazolidine; the latter would not tend to associate as much as the compounds containing free hydroxyl groups. Thus, it has been correctly concluded (35) that the products from ethanolamine and cyclohexanone (b.p. 89–90°C./16 mm.), amyl methyl ketone (b.p. 88–90°C./7 mm.), and methyl propyl ketone (b.p. 62–62.5°C./16 mm.) are oxazolidines, but that the one obtained with diisobutyl ketone (b.p. 110–111°C./8 mm.) is a Schiff base, since the corresponding aminoalcohols boil at 122–124.5°C./13 mm., 115–116°C./10 mm., 98–99°C./15 mm., and 113–114°C./7 mm., respectively. Conversely, one can safely conclude that the two substances formed from 2-amino-1-butanol and butyraldehyde and boiling at 38–40°C./2 mm. and 78.5–80°C./1 mm., respectively (88a), cannot be isomeric, as the discoverers have assumed.

The value of such observations is, however, limited, since these condensation products sometimes represent mixtures in spite of their sharp boiling points, so that other factors appear to play a part in determining the associative tendency of the condensation product. The products formed from aminoalcohols of the general formula $(CH_3)_2CHCHOHCH_2NHR$ and aldehydes have been described as glycerol-like fluids, while the corresponding ketone derivatives are more mobile liquids (113). (For a discussion of the pertinent observations of Paquin (89), see page 317.)

B. Dipole moment

The dipole moments of the condensation products have only a qualitative value. Owing to the uncertainty in the relative direction of the polar bonds in the oxazolidine system, the theoretical calculation of the dipole moments of the condensation products has not been possible; it has, however, been found that

oxazolidines generally have lower dipole moments than the Schiff bases (7) (see table 3).

C. Magnetic susceptibility

The magnetic susceptibilities (K) have been suggested as a means of differentiation between the two isomeric structures (Metzger and Pacault (88)). For the four substances studied, the results are in accord with those obtained by other methods, but the method is at best capable of differentiating between a pure oxazolidine, a pure Schiff base, and a mixture in which both isomers are present to an appreciable extent (see table 4).

TABLE 3

Dipole moments

PRODUCT FORMED FROM	SCHIFF BASE	OXAZOLIDINE
	Debyes	*Debyes*
Ethanolamine and 2-ethylhexanal		1.53 ± 0.03
2-Amino-3-methyl-3-butanol and isobutyl methyl ketone		1.63 ± 0.03
2-Amino-3-methyl-3-butanol and cyclopentanone		1.51 ± 0.03
N-Methylethanolamine and cyclohexanone		1.85 ± 0.03
Ethanolamine and isobutyl methyl ketone	2.50 ± 0.05	
Ethanolamine and diisobutyl ketone	2.80 ± 0.05	

TABLE 4

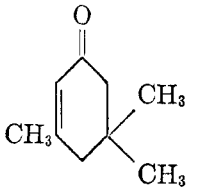
Magnetic susceptibilities (K)

PRODUCT FROM	$K_{obsd.}$	K_{open}	K_{cyclic}	CONCLUSION
Ethanolamine and benzaldehyde	91.0	91.2	97.8	Schiff base
2-Amino-3-methyl-3-butanol and benzaldehyde	132.0	128.0	133.4	Mixture
2-Amino-3-methyl-3-butanol and isobutyl methyl ketone	144.0	136.6	143.5	Oxazolidine
2-Amino-3-methyl-3-butanol and 2-ethyl-2-hexenal	153.9	149.6	155.0	Mixture

D. Ultraviolet spectra

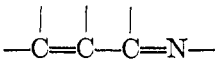
A similar limitation applies to the evaluation of the ultraviolet spectra of the condensation products. It can be expected, and has been verified experimentally (120), that the oxazolidine system itself (without chromophoric substituents) has no absorption in the near ultraviolet, but also that the aliphatic C=N double bond absorbs only in the very far ultraviolet (1900 Å. (13, 26, 81, 84, 93)). A difference in the absorption spectra of the cyclic and the open forms can, however, be expected, if the carbonyl compound employed in the synthesis is either aromatic or α,β-unsaturated. The conjugated system in the ethylimide or cyclohexylimide of benzaldehyde shows a maximum at 2450 Å. ($\log E_m = 4.14$), which appears in the cyclohexylimide of acetophenone at 2400 Å. and is obliterated by substitution in the *o*-positions of the benzene nucleus. This same maximum must appear in Schiff bases of the formula $ArCH{=}NCH_2CH_2OH$ or $ArCR{=}NCH_2CH_2OH$, as the introduction of the hydroxyl group in the β-position of the aliphatic side chain is not likely to affect the spectrum (especially since it can be shown (9) that no hydrogen bonds exist between the hydroxyl group and the azomethine nitrogen atom). Indeed, this expectation has been

substantiated by experiment (13). Thus, the product from ethanolamine and benzaldehyde is *N*-benzylideneëthanolamine and not 2-phenyloxazolidine (and the identity of its spectrum with that of the condensation product with *o*-chlorobenzaldehyde proves that the latter, too, is a Schiff base; see reference 55). The use of the ultraviolet spectrum for the elucidation of the products which form from benzaldehyde and the 2-aminocyclohexanols (83) has already been mentioned (see page 323). Analogously, it could be shown that the products obtained from isophorone



Isophorone

by reaction with ethanolamine and 2-amino-3-methyl-3-butanol, respectively, are Schiff bases; they absorb at about 2400 Å. (the same wave length as the α,β-unsaturated ketone itself) and must thus contain the chromophoric system



Apart from the limitation to derivatives of the aromatic or α,β-unsaturated carbonyl compounds, the ultraviolet spectrum suffers from the drawback that it can even in these cases hardly be used for direct estimation of the cyclic form in a mixture; the oxazolidine system, as already pointed out, has no absorption of its own. The *indirect* estimation (from the extinction coefficient of the characteristic peak) is ambiguous, not only as a difference method, but also because of the dependence of this extinction coefficient on a number of unknown or variable factors.

E. Infrared spectra

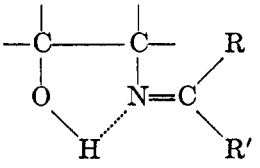
The infrared spectrum is much freer from these uncertainties. It is possible, on the one hand, to determine the presence of a carbon–nitrogen double bond in purely aliphatic compounds and to verify the observation by the determination of the hydroxyl absorption which must appear in the open form of the condensation products. On the other hand, the cyclic form has a characteristic infrared spectrum and can, therefore, be detected independently of the Schiff base structure. The result can be verified by the determination of the NH absorption (in those cases in which the formation of the oxazolidine ring implies the presence of the NH group). However, the NH stretching frequency (at 3350 cm.$^{-1}$) is generally very weak and has only been observed in undiluted samples of oxazolidines, not in their solutions (18).

The O—C—N system in the oxazolidine system is characterized by a triplet of bands in the 1080–1200 cm.$^{-1}$ region (1149–1185, 1116–1139, and 1080–1114

cm.$^{-1}$, respectively), whilst the aliphatic C=N group absorbs at 1670 cm.$^{-1}$ (72); this frequency is shifted by conjugation with a phenyl ring to about 1640 cm.$^{-1}$ and in more extended conjugated systems as far as 1618 cm.$^{-1}$ (18).

In 3-phenyloxazolidines this same band triplet has been observed (at 1115–1122 cm.$^{-1}$, 1155–1160 cm.$^{-1}$, 1174–1188 cm.$^{-1}$); in the case of 2-methyl-3-phenyloxazolidine the first band is split into three, at 1099, 1109, and 1122 cm.$^{-1}$ (120). In 3-methyloxazolidines the same type of absorption has been found (19); however, the split of the three absorption peaks into five (some of them usually of minor intensity) is here a general feature of the spectrum; the bands found in ten representatives of the class can be characterized as follows: 1049–1078, 1095–1120, 1135–1155, 1159–1165, 1178–1181 cm.$^{-1}$

It should be noted that the isopropyl group also has a strong absorption in the 1080–1200 cm.$^{-1}$ region (at about 1160 cm.$^{-1}$ (107)). As to the hydroxyl absorption, it has been found that on the whole there is no hydrogen bonding in the Schiff bases of the following type:



However, for *N*-(α-naphthylmethylene)aminoethanol, a shift of the hydroxyl absorption into the 3350–3450 cm.$^{-1}$ region (3420 cm.$^{-1}$) has been observed; as this shift persists in dilute solution, it can be ascribed to hydrogen bonding of the above type (9). Several authors (38, 39) have studied the infrared C=N— absorption and have concluded that the presence of this respective band proves the presence of a Schiff base only. This is evidently not justified theoretically and does, indeed, not represent the facts correctly.

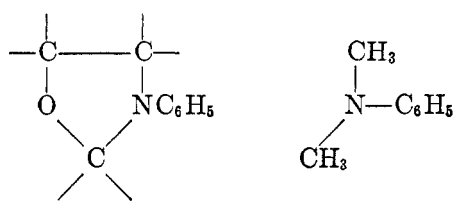
Unfortunately, the infrared spectrum also can only serve as a *qualitative* criterion for the structure of a given condensation product between an aminoalcohol and a carbonyl compound (in those cases in which both an open and a cyclic structure are possible). The reason for that lies in the fact (10) that the two isomeric forms between which one has to differentiate represent a fairly mobile tautomeric system which is dependent on the concentration. The solutions of the "oxazolidines" do *not* follow Beer's law. The product from acetone and ethanolamine showed a drop in the extinction coefficient of the C=N absorption band of 60 per cent when the concentration was reduced from 1.2 to 0.6 mole/liter, and the corresponding ethyl methyl ketone derivative a decrease by 40 per cent when the concentration was diminished from 1.05 to 0.1 mole/liter (solvent, carbon tetrachloride).

Nevertheless, the infrared spectrum has given a great deal of information about the actual structure of the condensation products and about the influence of substituents on this structure. Since the results are in good agreement with those obtained from the evaluation of the molecular refraction of these substances, they will be summarized in the following section.

F. Molecular refraction

The molecular refraction has been used by a number of authors (7, 10, 18, 19, 42, 55, 58, 59, 106, 120) for the characterization of the liquid "oxazolidines." The basis of this method can be stated as follows: The secondary amino-nitrogen in the oxazolidine has a lower atomic refraction (2.50) (43) than the azomethine nitrogen in the Schiff base (4.10) (2, 112). The difference between the two forms would thus be 1.60, and taking into account the difference (0.10) in the atomic refractions of the oxygen in the hydroxyl and the ether groups (114), the corrected value would be 1.50. In addition, it has already been suspected (35, 59) that the oxazolidine ring has a specific depression of the molecular refraction (see also page 334), and an evaluation of those cases in which the infrared spectrum had established the *absence* of a Schiff base, i.e., the presence of a pure oxazolidine, has permitted this depression to be estimated as 0.50. The molecular refraction of an oxazolidine would thus be 2.00 units smaller than that of the isomeric Schiff base in those cases in which the C=N double bond of the latter is not conjugated with a C=C double bond or an aromatic nucleus. Such conjugation would cause exaltation and the difference would be still greater.

The situation is very much more complex in the 3-phenyloxazolidines; fortunately, in this series the presence of Schiff base structures is excluded and no doubt arises as to the correct formulation of the condensation products. In the case of the 3-phenyl compounds, a considerable exaltation has been observed, which has probably the same cause as the well-known exaltation of the molecular refraction of dimethylaniline (3):



In the 3-methyloxazolidine series, on the other hand, the depression characteristic of the oxazolidine system is very pronounced; it appears to be reduced in size somewhat in the 3-methyl-2-phenyloxazolidine (not in 2,3-dimethyl-2-phenyloxazolidine), so that a certain amount of conjugation between the phenyl and the oxazolidine rings may exist. This effect, if real, cannot be traced in the 3-unsubstituted oxazolidines, as in this series no pure 2-phenyl compound exists (see below).

The following general conclusions can be drawn from the molecular refractions of the condensation products between *primary* β-hydroxy amines and carbonyl compounds:

(*1*) Ethanolamine and aliphatic aldehydes and ketones give liquid condensation products predominantly of oxazolidine structure; this is not correct for ketones which contain an isobutyl group (isobutyl methyl ketone, diisobutyl ketone) and which yield 50 per cent or more of the Schiff base. Explanation of this deviation, based on the bulkiness of the isobutyl group, is not supported

by models and is invalidated by the fact that pinacolone (in spite of the tertiary butyl group) behaves like a "normal" aliphatic ketone. Amongst the products derived from the various aliphatic ketones, there exists a very definite gradation, as table 5 shows, which is based on the molecular refraction of the condensation products.

It is likely that the position of the equilibrium is dependent less on steric factors than on effects of electrostatic nature and on hyperconjugation, but the material available is still too scanty to warrant a more quantitative evaluation. It should be added that the condensation of aliphatic aldehydes with ethanolamine (106) or ethylenimine (42) leads to products which, according to their molecular refraction, contain certain amounts (5–15 per cent) of Schiff bases.

TABLE 5

Per cent of Schiff base in some aliphatic oxazolidines (7, 10, 18)

KETONE	SCHIFF BASE IN PRODUCT FROM	
	Ethanolamine	2-Amino-3-methyl-3-butanol
	per cent	*per cent*
Acetone	40*	0(?)
Ethyl methyl ketone	20	0
Methyl propyl ketone	20†	
Isobutyl methyl ketone	70	10
tert-Butyl methyl ketone	25	0
Dipropyl ketone	10	
Diisobutyl ketone	80	6
4-Methyl-4-phenyl-2-pentanone	35	50

* The product obtained from acetone and ethylenimine in very low yield (42) appears to contain 14 per cent of the open form.

† The product obtained from amyl methyl ketone and ethylenimine (42) appears to be wholly cyclic.

(*2*) Replacement of the hydrogen atoms in ethanolamine by methyl groups favors formation of the cyclic form in the condensation with aliphatic carbonyl compounds. This is particularly obvious from the results obtained in the series with 2-amino-3-methyl-3-butanol; the effect may well be due to a deflection of the valency angles caused particularly by the *gem*-dimethyl group (see, e.g., 71). In table 5 the pertinent figures are recorded in comparison with those for the corresponding derivatives of ethanolamines. The only exception is the product formed from 4-methyl-4-phenyl-2-pentanone. The corresponding aldehyde derivatives appear to be fully cyclic; the formaldehyde product appears to contain (according to the infrared spectrum) a slight amount of the Schiff base.

(*3*) α,β-Unsaturated aldehydes and ketones tend to form Schiff bases, stabilized by the conjugation between the C=C and the C=N double bonds. The observed molecular refractions are higher than those calculated for the pure Schiff bases.

An interesting case arises in the reaction of cyclopropyl methyl ketone with ethanolamine and with 2-amino-3-methyl-3-butanol, respectively (11). Both compounds are largely Schiff bases; in the infrared they show C=N absorption (as well as the hydroxyl absorption), and the molecular refraction has, at least for the former, a very much higher value than that calculated for the oxazolidine. It is well known (see, e.g., 60, 108) that the cyclopropyl radical resembles a double

bond, so that the Schiff base would be stabilized by conjugation between the three-membered ring and the C=N double bond.

(*4*) Aromatic aldehydes show the same effect. From table 6 one can see that the molecular refractions are considerably higher than those calculated for the oxazolidines; however, in some cases, they do not show the exaltation over and above the values calculated for the Schiff base structure which one would expect from the conjugation between the aryl nucleus and the C=N double bond. One has, therefore, to conclude that these products are mixtures of the isomeric compounds; in view of the uncertainty as to the absolute value of the theoretical

TABLE 6

Presence of Schiff bases in some 2-aryloxazolidines (18)

ALDEHYDE	MOLECULAR REFRACTION (CALCULATED FOR OXAZOLIDINE* AND FOUND) OF PRODUCT FROM					
	Ethanolamine			2-Amino-3-methyl-3-butanol		
	Calculated	Found	Exaltation over molecular refraction of Schiff base	Calculated	Found	Exaltation over molecular refraction of Schiff base
Benzaldehyde	42.69	45.87	1.18	56.55	58.67	0.12
2-Hydroxybenzaldehyde	44.20	48.53	2.33			
2-Chlorobenzaldehyde	47.50	50.57	1.07			
2-Bromobenzaldehyde				64.32	66.04	−0.28
3-Bromobenzaldehyde				64.32	65.97	−0.35
4-Bromobenzaldehyde				64.32	66.70	0.28
α-Naphthaldehyde				71.90	76.14	2.24

* The molecular refraction for the Schiff base—without exaltation—is 2.00 units higher.

TABLE 7

Presence of Schiff bases in some 2-methyl-2-aryloxazolidines (14)

KETONE	MOLECULAR REFRACTION (CALCULATED FOR OXAZOLIDINES AND FOUND) OF PRODUCT FROM					
	Ethanolamine			2-Amino-3-methyl-3-butanol		
	Calculated	Found	Exaltation over molecular refraction of Schiff base	Calculated	Found	Exaltation over molecular refraction of Schiff base
Acetophenone				60.16	61.49	−0.67
4-Fluoroacetophenone	47.12	48.85	−0.27	60.96	61.31	−1.65

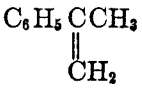
exaltation, it is impossible to indicate the relative proportions of the two constituents. The study of the infrared spectrum has led to the same results.

Table 6 also indicates qualitatively that the derivatives of 2-amino-3-methyl-3-butanol contain relatively more of the cyclic form than the corresponding ones of ethanolamine.

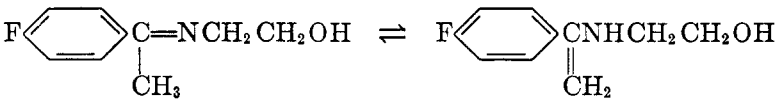
(*5*) An analogous regularity prevails in the condensation products of acetophenone or substituted acetophenones, as table 7 shows. The products must be mixtures which contain in the derivatives of 2-amino-3-methyl-3-butanol even considerable amounts of the cyclic form. Obviously, an additional methyl group in the 2-position also favors the cyclic structure.

The infrared spectrum permits a more quantitative statement as to the struc-

ture of the condensation products in a number of cases (18); it is further applicable to the solutions of the solid condensation products which are not accessible to measurements of the molecular refraction. Thus it has been found that the following are pure Schiff bases: the products formed from ethanolamine and the three bromobenzaldehydes, 4-nitrobenzaldehyde, salicylaldehyde, *o*-methoxybenzaldehyde, α- and β-naphthaldehyde, and benzophenone, whilst the products from 2-amino-3-methyl-3-butanol, 3-nitroacetophenone, and 4-fluoroacetophenone are pure oxazolidines. The presence of mixtures has been ascertained by the infrared spectra of the products from 2-amino-3-methyl-3-butanol and the three bromobenzaldehydes, benzaldehyde, and acetophenone, and of the products from ethanolamine and 3-nitroacetophenone and 4-fluoroacetophenone. In the last-mentioned case, the interesting observation has been made that a band exists at 1682 cm.$^{-1}$, i.e., at a wave length beyond the range of aromatic Schiff bases. In view of the existence of a similar band in α-methylstyrene

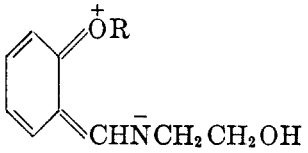


it is concluded that the Schiff base in question isomerizes largely to a substituted styrene:



An analogous shift has been observed in the condensation product of ethylenediamine and two moles of *p*-fluoroacetophenone (15).

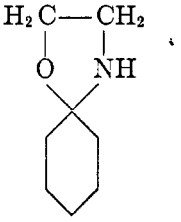
It is to be hoped that the systematic study of the condensation products between primary β-hydroxy amines and substituted aromatic aldehydes and ketones will shed light on the nature of the factors which determine the structure of the condensation products. Thus, all those substituents which are capable of extending the conjugated system should favor the formation of Schiff bases. Indeed, the fact that the products formed from salicylaldehyde and 2-methoxybenzaldehyde, respectively, and ethanolamine are pure Schiff bases may possibly be ascribed to formulas such as:



Analogously, it has been found (11) that the condensation product of ethanolamine and 4-dimethylaminobenzaldehyde is a pure Schiff base.

(*6*) Cyclic ketones react very easily with aminoalcohols. Cyclohexanone gives in all cases studied (ethanolamine, 2-amino-3-methyl-3-butanol, 2-amino-3-ethyl-3-butanol, 2-amino-3-isobutyl-3-butanol, 1-(α-aminoethyl)cyclohexanol, 2-am-

ino-2-methyl-1,3-propanediol, and probably also 2-amino-2-methyl-1-propanol (18, 58, 59)) the pure oxazolidine, which has a spirane structure:



Cycloheptanone and ethanolamine, too, give a pure oxazolidine (11). This rule does not apply, however, to cyclopentanone. The latter (7) gives with 2-amino-3-methyl-3-butanol the oxazolidine; with ethanolamine, however, it gives the pure Schiff base, which, incidentally, proved to be a very unstable compound.

TABLE 8

Molecular refraction of oxazolidines from methylated cyclohexanones

AMINOALCOHOL	KETONE	MOLECULAR REFRACTION (FOUND)	MOLECULAR REFRACTION (CALCULATED FOR OXAZOLIDINE)	ESTIMATED PER CENT OF SCHIFF BASE
Ethanolamine	Dihydroisophorone	53.83	53.34	25
2-Amino-3-methyl-3-butanol.	*o*-Methylcyclohexanone	58.08	57.96	6
	m-Methylcyclohexanone	58.46	57.96	25
	p-Methylcyclohexanone	58.26	57.96	15
	Dihydroisophorone	67.49	66.75	37

Differences in behavior between corresponding cyclopentane and cyclohexane derivatives are not unknown; they have been ascribed by Brown, Fletcher, and Johannesen (27) to the effect of *I*-strain (for further references, see 7; *cf.* also 49, 100), but the magnitude of the effect in this case is somewhat unexpected. It may be linked to the abnormal infrared absorption of cyclopentanone (17) and the observation that also towards ethylenediamine the two ketones behave differently, cyclohexanone giving an imidazolidine and cyclopentanone forming *N*,*N'*-bis(cyclopentylidene)ethylenediamine. However, in this series, cycloheptanone behaves like cyclopentanone (15).

Methyl-substitution in cyclohexanone changes the situation only slightly. Table 8 shows that the molecular refraction is slightly higher than that calculated for the oxazolidines. It should be added that most of these products are likely to be mixtures of *cis-trans* isomers.

V. CONCLUSIONS

In principle, therefore, the results of these investigations show that the condensation products of primary β-hydroxy amines are apt to consist of mixtures of the two isomeric products, the Schiff base and the oxazolidine. One will, therefore, expect an influence of external conditions on the equilibrium states. Indeed, it has already been stated that the equilibrium shows a dependency on concentration (see page 327); furthermore, it has been observed (18) that the product

from 2-amino-3-methyl-3-butanol and α-naphthaldehyde shows a decrease in the optical density of the infrared C=N absorption when its alcoholic solution is kept at room temperature for 5 days, and Cope and Hancock (35) have shown that the product from ethanolamine and dipropyl ketone changes its refractive index upon standing (increase of the molecular refraction from 37.00 to 37.81) for two months; the phenomenon is reversed by distillation of the product. Of particular interest is the influence of the temperature on the equilibrium, which has been studied in a number of cases by Metzger (87). The compound obtained from 2-ethyl-2-hexenal and 2-amino-3-methyl-3-butanol showed a pronounced increase in the tendency towards the Schiff base structure with increasing temperature. Likewise, an increase in the molecular refraction has been observed (10) for the derivatives of ethanolamine and methyl propyl ketone (increase between 30° and 60°C., 0.43) and dipropyl ketone (0.56) and for the compound obtained from 2-amino-3-methyl-3-butanol and 4-methyl-4-phenyl-2-pentanone (0.47). As the normal increase of the molecular refraction in the temperature interval of 30–60°C. is of the order of magnitude of 0.22 (87), the equilibrium shifts in these cases with rising temperature towards the open (Schiff base) structure.

VI. STEREOCHEMICAL PROBLEMS

It would have been interesting to study systematically the behavior, towards carbonyl compounds, of diastereoisomeric pairs of aminoalcohols. However, only a very few pertinent cases appear to be known. Pairs of diastereoisomeric *N*-acyloxazolidines have been described in the case of the two ethyl *p*-nitrophenylserinates (5) and the two 2-aminocyclohexanols (83). (It should be noted that diastereoisomerism can also arise from condensation of an aldehyde or an unsymmetrical ketone with an aminoalcohol with only one asymmetric carbon atom (20, 61).)

The condensation products of *p*-nitrobenzaldehyde with the two ethyl *p*-nitro-β-phenylserinates are known to be different (see, e.g., 5, 6, 8, 40), but both are Schiff bases, as the infrared and ultraviolet spectra have shown. The same is true of the condensation products of the diastereoisomeric 2-aminocyclohexanols and benzaldehyde (see page 323), and probably of the benzaldehyde and hydroxymethylenecamphor derivatives of the two α-amino-β-hydroxybibenzyls (45a, 45b, 95a). The only case known is, therefore, that of the two benzaldehyde derivatives of ephedrine and pseudoephedrine which—as secondary amines—can give only oxazolidines and not Schiff bases (40a, 103a).

From the investigations of Fodor and Koczka (48) one would, indeed, expect that even in the formation of true oxazolidines, diastereoisomeric aminoalcohols would retain their configuration. However, the structure of the aminoalcohols is likely to influence the course of such reactions. This is indicated by the fact (32) that ephedrine and pseudoephedrine give, upon heating with urea, a 2-imidazolidone and a 2-oxazolidone, respectively, and by similar observations (48).

VII. ANALOGOUS OBSERVATIONS

The features exhibited by the oxazolidines are not without analogy. It seems worthwhile to summarize briefly parallel observations made in similar systems.

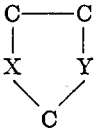
The typical infrared spectrum of the oxazolidines recurs in the analogously built 1,3-dioxolanes, 1,3-thioxolanes, and imidazolidines, as is illustrated in table 9.

It is worthy of note that ethylenediamine and its *N*-alkyl derivatives resemble the β-hydroxy amines in that they show similar regularities regarding the influence of the nature of carbonyl compounds on their reactivity and on the structure of the condensation products (see page 329 and reference 15; also for the literature, see 88, 89, 100). The same applies to the reactions of the imidazolidines (35, 36, 41, 52, 94, 96, 98, 106).

With regard to the specific depression of the molecular refraction, the oxazolidine ring is by no means unique. 1,3-Dioxolanes (16), 1,3-dithiolanes (96), and 1,3-imidazolidines (41, 98) show the same effect; the order of magnitude of the depression is 0.45, 0.50, and 0.80, respectively. Also, for 2-isobutyl-2-methylthioxolane (not, however, for 2-isobutyl-5-mercaptomethyl-2-methylthioxolane) a depression (of 0.4) has been observed (15).[1]

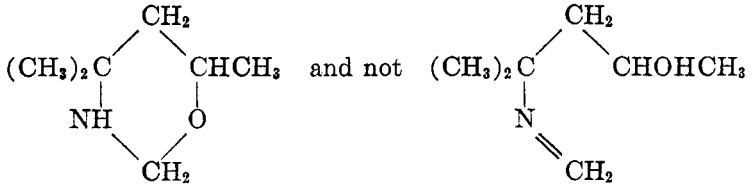
TABLE 9

Infrared spectra of heterocyclic compounds having the structure



X	Y	CHARACTERISTIC ABSORPTION BANDS		
O	O	1158–1190	1124–1143	1063–1097 (16)
O	NH	1149–1185	1116–1139	1086–1114
O	S	1157–1160	1125–1130	1072–1074 (15)
NH	NH	1152–1167	1110–1116	1037–1104 (15)

Furthermore, it should be recalled that the phenomena and problems discussed here for 2-aminoethanol and its derivatives, also occur in the series of 3-amino-1-propanol and even that of 4-amino-1-butanol. Whilst the products from the *N*-phenyl derivatives of these two aminoalcohols and formaldehyde are undoubtedly 3-phenylhexahydro-1,3-oxazine and 3-phenylhexahydro-1,3-oxazepine, respectively (78), a discussion has arisen as to the structure of the formaldehyde and benzaldehyde condensation products of 2-amino-2-methyl-4-pentanol (67, 77, 102). It has been argued in the latter case (but with doubtful validity) that the formation of an *N*-nitroso derivative points to a cyclic structure, e.g.:



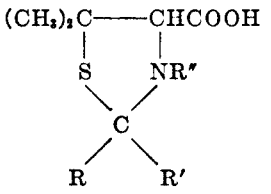
[1] The theoretical value for that compound is 46.79, not 45.6 as indicated in the original paper.

It is also noteworthy (see page 316) that these oxazines give solid picrates, but that the latter do not have sharp melting points (63, 67).

For the structure of the products from benzaldehyde and 2-(β-hydroxyethyl)- and 2-(γ-hydroxypropyl)piperidine[2] (56), the structures of 2-phenyl-3,4-tetramethylenehexahydro-1,3-oxazine and -1,3-oxazepine have been assumed by the authors without proof (for the reaction of 2-(β-hydroxypropyl)piperidine and formaldehyde, see reference 66). In both products the ring is opened by benzylmagnesium chloride in the same manner, as has been shown for the oxazolidines (see page 319). The structures of the condensation products of 3-amino-1-propanol with cyclohexanone, diisobutyl ketone, and dipropyl ketone have been determined by an evaluation of the molecular refraction. It is interesting to note that here, too, the cyclohexanone derivative is cyclic and that of diisobutyl ketone is a Schiff base, while dipropyl ketone gives a mixture of the two possible isomeric forms (59). Also in the series of the 2-aryl-2,3-dihydro-4,5-benzo-1,3-oxazines, an interesting dependence of the stability of the ring on the nature of the substituents has been observed by Witkop, Patrick, and Kissman (118a): the 2-phenyl compound gives a normal salt, whilst in the case of the 2-(*p*-methoxyphenyl) derivative, salt formation is accompanied by isomerization to the corresponding Schiff base. Incidentally, it should be noted that the heterocyclic compounds in question (69a) were considered originally (88b) as Schiff bases of *o*-aminobenzyl alcohol; the final proof, based on the infrared spectra, has been provided only by the above-quoted authors.

TABLE 10

Isomerization of thiazolidines



R	R′	R″	TIME REQUIRED FOR ISOMERIZATION
H	C_6H_5	H	1-2 min.
H	C_6H_5	H	1-2 min.
CH_3	COOH	H	1-2 min.
CH_3	$COCH_3$	H	1-2 min.
CH_3	$CH_2COOC_2H_5$	H	1-2 min.
H	H	H	>3 hr.
CH_3	$COOC_2H_5$	H	>3 hr.
$CH_2COOC_2H_5$	$COOC_2H_5$	H	>3 hr.
Any	Any	$COOCH_3$	>3 hr.

In general, the regularities of the ring fission are qualitatively the same for these analogous ring systems as for the oxazolidines. Even the 1,3-dioxolanes, which represent a fairly stable ring system, undergo hydrogenolysis in the same

[2] The product has been erroneously designated by the authors as 2-(2-hydroxypropyl)-piperidine.

TABLE 11

Condensation products of aliphatic aldehydes with β-hydroxy amines

ALDEHYDE	AMINOALCOHOL	PRODUCT			REFERENCES
		Boiling or melting point	Structure	Remarks	
		°C.			
Formaldehyde	*N*-Methylethanolamine	100/735 mm. 99.5–101.5/760 mm.	Cyclic	Yield, 18%; picrate, m.p. 152°C.	(19, 75)
	2-Amino-3-methyl-3-butanol	48–49/27 mm.	Cyclic, with trace of Schiff base		(18)
	N-Isobutylethanolamine	66–68/30 mm.	Cyclic	Conversion, 80%	(106)
	2-(α-Hydroxyethyl)piperidine	79–81/18 mm.	Not proven	Picrate, m.p. 163°C.	(65)
	N-Phenylethanolamine	94/1.5 mm. 28; 26–27 (m.p.)	Cyclic		(78, 120)
	N-(*p*-Methoxyphenyl)ethanolamine	88 (m.p.)	Cyclic		(78)
	1-Anilino-2-propanol	120/6 mm. 37–38 (m.p.)	Cyclic		(78)
	N-(*p*-Ethoxyphenyl)ethanolamine	140/14 mm.	Cyclic		(23)
	2-(β-Ethylbutylamino)-2-methyl-1-propanol	93–95/10 mm.	Cyclic	Conversion, 94%	(106)
	2-Benzylamino-2-methyl-1-propanol	110–110.5/4 mm.	Cyclic	Conversion, 96%	(106)
	3-(*p* Ethoxyanilino)-1,2-propanediol	135–145/0.3–0.4 mm. 57–59 (m.p.)	Cyclic		(23)
	N-(β-Naphthyl)ethanolamine	91–92 (m.p.)	Cyclic		(78)
	2-Isobutylamino-2-methyl-3-hexanol	97/5 mm.	Cyclic	Conversion, 89%	(106)
	2-Benzylamino-2-methyl-3-hexanol	110/0.3 mm.	Cyclic	Conversion, 84%	(106)
Acetaldehyde	Ethanolamine	140–142/748 mm.*	Cyclic (?)	"Bad yield"; picrate, m.p. 75°C. (unsharp)	(75)
	Ethylenimine	85–85.5/740 mm.*	Cyclic	Yield, 56%	(42)
	N-Methylethanolamine	109/758 mm.	Cyclic	Yield, 41%; picrate, m.p. 75°C. (unsharp)	(74, 75)
	1-Amino-3-methyl-2-butanol	162/760 mm.	Not proven	Yield, 79%; picrate, oily	(113)
	3-Methyl-1-methylamino-2-butanol	151/760 mm.	Cyclic	Picrate, m.p. 88°C.	(113)
	N-Phenylethanolamine	60.5–61 (m.p.)	Cyclic		(120)
Propionaldehyde	Ethylenimine	87.5–88/740 mm.	Cyclic	Yield, 28%	(42)
	N-Phenylethanolamine	112–113/4 mm. 115–116/4 mm.	Cyclic		(14, 120)

Butyraldehyde	Ethanolamine	104–105/12 mm.*	Structure doubtful†		(89)
	Ethylenimine	45–45.5/40 mm.*	Cyclic	Yield, 53%	(42)
	N-Methylethanolamine	90.5/110 mm.	Cyclic		(19, 53)
	2-Amino-2-methyl-1,3-propanediol	65.0 (m.p.)	Not proven	Conversion, 80%	(106)
	2-Amino-1-butanol	38–40/2 mm.	Mixture	Yield, 43.8%	(88a)
	2-Nitrosoamino-1-butanol	54.4–55.5/2 mm.	Cyclic	From the foregoing compound by nitrosation or from 2 amino-1-butanol and nitrous acid	(88a)
	Trimethylolmethylamine	195–206/34 mm.	Not proven	Yield, 45%; becomes pasty on standing	(92)
	2-Amino-3-methyl-3-butanol	113–114/100 mm.	Cyclic		(18)
	2-Amino-2-methyl-3-hexanol	80/2.7 mm.	Cyclic	Conversion, 65%	(106)
	N-Phenylethanolamine	133–133.5/5 mm.	Cyclic		(120)
	Ephedrine	110–112/1 2 mm.	Cyclic	Yield, 89%	(44)
	2-Methyl-3-(α,γ-dimethylbutylamino)-3-butanol	120–122/20 mm.	Cyclic		(14)
Isobutyraldehyde	Ethylenimine	37–39/40 mm.	Cyclic	Yield, 55%	(42)
Isovaleraldehyde	Ethanolamine	62–62.5/30 mm.	Cyclic	Conversion, 92%	(106)
	2-Amino-2-methyl-1-propanol	72–74/17 mm.	Cyclic	Yield, 95%	(58)
	N-Isobutylethanolamine	72–73/30 mm.	Cyclic	Conversion, 90%	(106)
Diethylacetaldehyde	2-Amino-2-methyl-1-propanol	78–79/10 mm.	Cyclic	Conversion, 65%	(106)
Heptaldehyde	Ethylenimine	38–39 (m.p.)	Not proven	Yield, 95%	(42)
2-Ethylhexanal	2-Amino-2-methyl-1-propanol	89–90/4 mm.	Cyclic	Conversion, 98%	(106)
	2-Amino-3-methyl-3-butanol	95–96/5 mm.	Cyclic		(18)
	2-Amino-3-ethyl-3-butanol	101–102/5 mm.	Cyclic		(18)
3-Hydroxymethylenecamphor	α-Amino-β-hydroxybibenzyl	(+) derivative, 146 (m.p.) (−) derivative, not isolated in pure state	Not proven		(95a)
	Iso-α-amino-β-hydroxybibenzyl	168 (m.p.)			(95b)

* The two boiling points indicate that the products are not identical.
† See page 317.

TABLE 12

Condensation of aliphatic and alicyclic ketones with β-hydroxy amines

KETONE	AMINOALCOHOL	PRODUCT			REFERENCES
		Boiling or melting point	Structure	Remarks	
		°C.			
Acetone	Ethanolamine	64–65/100 mm.	40% Schiff base	Yield, 65%; polymerizes on standing	(10, 76; not obtained in pure state)
	Ethylenimine	53–53.5/45 mm.	Cyclic (?)	Yield, 6%	(42)
	N-Methylethanolamine	123/760 mm.	Cyclic		(19, 74)
	2-Hydroxy-3-methylbutylamine	160/760 mm.	Not proven	Yield, 70.4%; picrate, m.p. 106°C.	(113)
	2-Amino-3-methyl-3-butanol	84–85/95 mm.	Cyclic		(18)
	(2-Hydroxy-3-methylbutyl)methylamine	160/760 mm.	Cyclic	Yield, 76.4%; picrate, m.p. 73°C.	(113)
	$\Delta^{5,6}$-3β,17β-Dihydroxy-17α-aminomethylandrostene (A)	189–190 (m.p.)	Cyclic (?)		(62)
	$\Delta^{4,5}$-17β-Hydroxy-17α-aminomethylandrosten-3-one	179–180 (m.p.)	Cyclic (?)	From the preceding compound (A) with aluminum *tert*-butoxide	(62)
	$\Delta^{5,6}$-3β-Acetoxy-17β-hydroxy-17α-acetaminomethylandrostene	162–163 (m.p.)	Cyclic	From compound A with acetic anhydride in pyridine	(62)
	$\Delta^{5,6}$-3β,17β-Dihydroxy-17α-acetaminomethylandrostene	230–232 (m.p.)	Cyclic	From the preceding compound by alkaline hydrolysis	(62)
	$\Delta^{4,5}$-17β-Hydroxy-17α-acetaminomethylandrostan-3-one	212–214 (m.p.)	Cyclic	From the preceding compound with aluminum *tert*-butoxide	(62)
Pyruvic acid	Iso-α-amino-β-hydroxybibenzyl	152 (m.p., with decomposition); *d*- and *l*-forms, 161 (m.p.)	Not proven		(45d)
Ethyl methyl ketone	Ethanolamine	81.5–82/100 mm.	20% Schiff base		(10)
	2-Amino-2-methyl-1-propanol	56–56.5/22 mm.	Cyclic	Yield, 65%; picrate, m.p. 165–167°C. (dec.)	(58)
Methyl propyl ketone	Ethanolamine	77–78/22 mm. 62–62.5/16 mm.	20% Schiff base	Yield, 40%; 85% (35); not quite pure	(10, 35, 38)
Diethyl ketone	2-Amino-1-butanol	62–63/18 mm.	Cyclic	Yield, 93%	(8)
Acetylacetone	Ethanolamine	73 (m.p.)	Not proven		(76)
3-Methyl-3-butanol-2-one	2-Amino-3-methyl-3-butanol	139–140/100 mm.	Cyclic		(18)
	2-Acetamino-3-methyl-3-butanol	135–136 (m.p.)	Cyclic	From the preceding compound by acetylation	(18)
Cyclopentanone	Ethanolamine	66–66.5/2 mm.	Schiff base	Yield, 10%	(7)
	N-Methylethanolamine	91/38 mm.	Cyclic		(19)
	2-Amino-3-methyl-3-butanol	90–92/26 mm.	Cyclic	Yield, 70%	(7, 18)

Cyclopropyl methyl ketone	Ethanolamine	86–87/21 mm.	About 70% Schiff base		(11)
	2-Amino-3-methyl-3-butanol	73/20 mm.	Cyclic (?)		(11)
Isobutyl methyl ketone	Ethanolamine	93–95/17 mm.	70% Schiff base		(10, 18)
	N-Methylethanolamine	108/100 mm.	Cyclic		(19)
	2-Amino-3-methyl-3-butanol	91–94/23 mm. 92–94/27 mm.	Cyclic		(14, 18, 87, 88)
Pinacolone	Ethanolamine	85/28 mm.	25% Schiff base	Yield, 64%	(7, 10)
	2-Amino-3-methyl-3-butanol	83–83.5/26 mm.	Cyclic	Yield, 54%	(7, 10)
Mesityl oxide epoxide	2-Amino-3-methyl-3-butanol	68–69/5 mm.	Cyclic		(18)
Acetonylacetone	2-Amino-3-methyl-3-butanol	88–89/25 mm.	Cyclic		(18)
Ethyl acetoacetate	Ethanolamine	31–32 (m.p.)	Not proven		(76)
	1-Amino-3-chloro-2-propanol	95 (m.p.)	Not proven	From epichlorohydrin, ammonia, and ethyl acetoacetate	(22, 103)
	Iso-α-amino-β-hydroxybibenzyl	145 (m.p.)	Not proven		(45d)
Cyclohexanone	Ethanolamine	89–90/16 mm.	Cyclic	Yield, 94%	(8, 18, 35)
	N-Methylethanolamine	97–97.5/23 mm.	Cyclic		(18, 19)
	1-Amino-2-propanol	95–96/19 mm.	Cyclic	Yield, 86%	(34)
	N-Ethylethanolamine	107–109/80 mm.	Cyclic		(38)
	2-Amino-2-methyl-1-propanol	95–97.5/20 mm.	Cyclic	Yield, 73%; picrate, m.p. 178–180°C. (dec.)	(58)
	Trimethylolmethylamine	118–120 (m.p.)	Not proven	Yield, 63%	(92)
	2-Amino-2-methyl-1,3-propanediol	147–147.5/16 mm.	Cyclic	Yield, 90%	(34)
	Diethanolamine	165–167/24 mm.	Cyclic	Yield, 72%	(19)
	1-Amino-3-methyl-2-butanol	226/760 mm.	Not proven	Yield, 92%; picrate, m.p. 114°C.	(113)
	2-Amino-3-methyl-3-butanol	74–75/5 mm.	Cyclic		(18)
	3-Methyl-1-methylamino-2-butanol	217/760 mm.	Cyclic	Picrate, m.p. 96°C.	(113)
	2-Amino-3-ethyl-3-butanol	82/5 mm.	Cyclic		(18)
	2-Amino-3-isobutyl-3-butanol	146/25 mm.	Cyclic		(18)
	1-(α-Aminoethyl)cyclohexanol	158/25 mm.	Cyclic		(18)
Amyl methyl ketone	Ethanolamine	88–90/7 mm.	Cyclic	Yield, 64%	(35, 38)
	Ethylenimine	88–89/7 mm.	Cyclic	Yield, 5%	(42)
	N-Ethylethanolamine	129–130/65 mm.	Cyclic		(38)
	2-Amino-2-methyl-1-propanol	102–103/19 mm.	Cyclic	Yield, 50%	(58)
Dipropyl ketone	Ethanolamine	102–104/20 mm.	10% Schiff base	Yield, 51%	(10)
	2-Amino-1-butanol	91–91.5/8 mm.	Cyclic	Yield, 92%	(58)
	2-Amino-3-methyl-3-butanol	107/22 mm. 112–113/22 mm.	Cyclic		(14, 18)
Cycloheptanone	Ethanolamine	126/20 mm. 141/43 mm.	Cyclic		(11)
	2-Amino-3-methyl-3-butanol	121/25 mm.	Cyclic		(11)
2-Methylcyclohexanone	2-Amino-3-methyl-3-butanol	115–118/26 mm.	Cyclic		(18)
3-Methylcyclohexanone	2-Amino-3-methyl-3-butanol	112–113/22 mm.	Cyclic		(18, 87)

TABLE 12—*Concluded*

KETONE	AMINOALCOHOL	PRODUCT			REFERENCES
		Boiling or melting point	Structure	Remarks	
		°C.			
4-Methylcyclohexanone	2-Amino-3-methyl-3-butanol	117–118/25 mm. 115/27 mm.	Cyclic		(14, 18)
Diisobutyl ketone	Ethanolamine	96–98/4 mm. 110–111/8 mm.	80% Schiff base	Yield, 56%	(10, 18, 35, 38)
	2-Amino-1-propanol	117–118/15 mm.	Mostly Schiff base	Yield, 53%	(59)
	1-Amino-2-propanol	124–125/20 mm.	Schiff base	Yield, 66%	(34)
	2-Amino-1-butanol	111 5–112/7.5 mm.	Schiff base	Yield, 77%	(58)
	2-Amino-3-methyl-3-butanol	70–71/8 mm.	Cyclic		(18)
Dihydroisophorone	Ethanolamine	132/22 mm.	Mixture of isomers (?)		(18)
	2-Amino-3-methyl-3-butanol	123–125/24 mm.	Cyclic		(18)
Diisoamyl ketone	1-Amino-2-propanol	140–141.5/19 mm.	Cyclic	Yield, 70%	(34)

TABLE 13

Condensation of aromatic aldehydes with β-hydroxy amines

ALDEHYDE	AMINOALCOHOL	PRODUCT			REFERENCES
		Boiling or melting point	Structure	Remarks	
		°C.			
Furfural	2-Amino-2-methyl-1-propanol	73.0 (m.p.)	Not proven	Conversion, 80%	(106)
	Threo-β-*p*-nitrophenylserinol	175 (m.p.)	Not proven		(70)
Benzaldehyde	Ethanolamine	93–94/8 mm. 114–115/1.8 mm. 157/24 mm. 161–162/30 mm. 284/748 mm. 24–25 (m.p.)	Schiff base	Yield, 70% Yield, 76%	(13, 18, 28, 39, 75, 85, 87, 88)
	Ethylenimine	156–157/24 mm.	Mixture of isomers (?)	Yield, 10%	(42)
	N-Methylethanolamine	129/30 mm. 210/746 mm.	Cyclic	Picrate, m.p. 110°C.	(19, 74, 75)
	3-Chloro-2-hydroxypropylamine	82–83 (m.p.)	Not proven		(22, 23)
	1-Amino-2,3-propanediol	75–79 (m.p.) (mixture)	Schiff base		(20, 83)
	N-Ethylethanolamine	73–75/0.1 mm.	Cyclic		(56)
	Diethanolamine	130–133/0.2 mm.	Cyclic		(56)
	2-Amino-2-methyl-1-propanol	66 (m.p.)	Not proven	Conversion, 99%	(106)
	Trimethylolmethylamine	185–189/0.5 mm.	Not proven	Yield, 58%	(92)
	1-Amino-3-methyl-2-butanol	262/760 mm.	Not proven	Yield, 84%; picrate, m.p 152°C.	(113)
	2-Amino-3-methyl-3-butanol	117–118/7 mm.	Mixture of isomers		(13, 18, 87, 88)
	1-(β-Hydroxyethylamino)-2-propanol	96–98/0.05 mm.	Cyclic		(56)
	3-Ethoxy-2-hydroxypropylamine	128/1.1 mm.	Not proven	From the condensation product of benzaldehyde and 3-chloro-2-hydroxypropylamine, with sodium ethoxide	(22)
	N-Isobutylethanolamine	266–268/754 mm.	Cyclic	Yield, 71%; picrate, m.p. *ca.* 110°C.	(75)
	3 Methyl-1-methylamino-2-butanol	238/760 mm.	Cyclic	Yield, 75%; picrate, m.p. 132°C.	(13)
	cis-2-Aminocyclohexanol	90–92 (m.p.)	Schiff base		(83)
	trans-2-Aminocyclohexanol	46–47 (m.p.)	Schiff base		(83)
	(Acetoxymethyl)dimethylolmethylamine	Hydrochloride, m.p. 170–171; nitrate, m.p. 158–160	Not proven (cyclic?)	Hydrolysis of 1-aza-2,8-diphenyl-5-acetoxymethyl-3,7-dioxabicyclo[3.3.0]octane	(91)
	N-Acetyltrimethylolmethylamine	120–122 (m.p.)	Cyclic	From the previous substance with alkali	(91)
	2-Amino-2-methyl-3-hexanol	90–92/0.1 mm.	Cyclic	Conversion, 87%	(106)
	N-Phenylethanolamine	84.5–84.8 (m.p.) 84–85 (m.p.)	Cyclic		(78, 120)
	2-Amino-1-indanol	163–164 (m.p.)	Not proven		(80)
	1-Amino-2-indanol	164.2–165.2 (m.p.)	Not proven		(80)
	2-Amino-1-phenyl-1-propanol	99.5 (m.p.)	Not proven	Conversion, 84%	(106)

TABLE 13—*Continued*

ALDEHYDE	AMINOALCOHOL	PRODUCT			REFERENCES
		Boiling or melting point	Structure	Remarks	
		°C.			
	Threo-*p*-nitrophenylserinol	155–156 (m.p.)	Not proven		(70)
	2-Amino-5-methoxy-1-indanol		Not proven	Hydrochloride, m.p. 154.5°C.	(61)
	2-Amino-6-methoxy-1-indanol	80–82 (m.p.)	Not proven	Hydrochloride, m.p. 137°C. (approx.)	(61)
	2-Amino-7-methoxy-1-indanol	150.5–152 (m.p.)	Not proven	Hydrochloride, m.p. 187.5°C.	(61)
	N-(*p*-Ethoxyphenyl)ethanolamine	72–73 (m.p.)	Cyclic		(23)
	l-Ephedrine	72–73 (m.p.)	Cyclic		(40a, 103a, 116)
	Pseudoephedrine	65 (m.p.)			(103a)
	3-Chloro-1-(*p*-nitrobenzoylamino)-2-propanol	120–122 (m.p.)	Cyclic	From the benzaldehyde derivative of 1-amino-3-chloro-2-propanol by acylation	(22)
	1-Benzamino-3-chloro-2-propanol	(Not isolated)	Cyclic	From the benzaldehyde derivative of 1-amino-3-chloro-2-propanol by benzoylation	(22)
	(Caproyloxymethyl)dimethylolmethylamine	Hydrochloride, m.p. 134–135; nitrate, m.p. 144–145	Not proven (cyclic?)	Hydrolysis of 1-aza-2,8-diphenyl-5-caproyloxymethyl-3,7-dioxabicyclo[3.3.0]octane	(91)
	N-Caproyltrimethylolmethylamine	118–119 (mp..)	Cyclic	From the previous substance with alkali	(91)
	(Benzoxymethyl)dimethylolmethylamine	Hydrochloride, m.p. 188–189	Not proven (cyclic?)	Hydrolysis of 1-aza-2,8-diphenyl-5-benzoxymethyl-3,7-dioxabicyclo[3.3.0]octane	(91)
	2-Amino-4,5-dimethoxy-1-indanol	A, 165.5–166.5 (m.p.) B, 123–124 (m.p.)	Not proven	Hydrochloride of A, m.p. 192°C.	(61)
	2-Amino-5,6-dimethoxy-1-indanol	A, 184.5–185.5 (m.p.) B, 95–96 (m.p.)	Not proven	Hydrochloride of A darkens at about 191°C.	(61)
	Trimethylolmethylamine *O*-mono-*p*-nitrobenzoate	Hydrochloride, m.p. 158–159; nitrate, m.p. 179–181	Cyclic (?)	Hydrolysis of 1-aza-2,8-diphenyl-5-(*p*-nitrobenzoxymethyl)-3,7-dioxabicyclo-[3.3.0]octane	(91)
	N-(*p*-Nitrobenzoyl)trimethylolmethylamine	132–134 (m.p.)	Cyclic	From the previous substance with alkali	(91)
	(Phenoxyacetoxymethyl)-dimethylolmethylamine	Hydrochloride, m.p. 150–152; nitrate, m.p. 166–167	Not proven (cyclic?)	Hydrolysis of 1-aza-2,8-diphenyl-5-phenoxyacetoxymethyl-3,7-dioxabicyclo-[3.3.0]octane	(91)
	(N-Phenoxyacetyl)trimethylolmethylamine	143–145 (m.p.)	Cyclic		(91)
	cis-2-Benzaminocyclohexanol	80–85 (m.p.)	Cyclic	By benzoylation of *cis*-*N*-benzylidene-2-aminocyclohexanol	(83)
	trans-2-Benzaminocyclohexanol	150–151 (m.p.)	Cyclic	By benzoylation of *trans*-*N*-benzylidene-2-aminocyclohexanol	(83)
	α-Amino-β-hydroxybibenzyl	115; 120.5 (m.p.) *d*-form, 109 (m.p.)	Not proven		(23, 45a, 45b)
	Iso-α-amino-β-hydroxybibenzyl	134 (m.p.) *d*-form, 137 (m.p.) *l*-form, 137 (m.p.)	Not proven		(45a) (45d) (95b)

	Iso-α-acetamino-β-hydroxybibenzyl	117 (m.p.) 114 (m.p.)	Considered as *N*-benzylidene-*O*-acetyl-iso-α-amino-β-hydroxybibenzyl	From the foregoing compound with acetic anhydride	(45a) (95a)
	2-Benzylamino-1-phenyl-1-propanol	190–193/0.2 mm.	Cyclic	Conversion, 79%	(106)
	1-Benzamino-2,3-propanediol 3-*O*-benzoate	A, 143 (m.p.) B, 78 (m.p.)	Cyclic Cyclic	By benzoylation of the benzaldehyde derivative of 1-amino-2,3-propanediol	(20)
	Iso-α-benzamino-β-hydroxybibenzyl	177 (m.p.)	Cyclic	By acylation of the benzaldehyde derivative of α-amino-β-hydroxybibenzyl	(23)
	Iso-β-hydroxy-α-(*p*-toluenesulfamino)bibenzyl	179 (m.p.)	Not proven*	From the benzaldehyde derivative of iso-α-amino-β-hydroxybibenzyl by acylation	(95a)
	3-Chloro-2-hydroxy-*N*-stearoylpropylamine	No data	Cyclic	By acylation of the benzaldedehyde derivative of 3-chloro-2-hydroxypropylamine	(23)
Salicylaldehyde	Ethanolamine	137–139/1 mm. 143–144/1.6 mm. 180/13 mm.	Schiff base		(9, 13, 18, 53, 55, 85)
	Iso-α-amino-β-hydroxybibenzyl	113 (m.p.) *l*-form, 132–134 (m.p.)	Not proven		(45d) (95a)
4-Hydroxybenzaldehyde	Ethanolamine	169–170 (m.p.)	Schiff base		(9, 85)
2-Nitrobenzaldehyde	Ethanolamine *Threo*-β-*p*-nitrophenylserinol	58 (m.p.) 144–146 (m.p.)	Not proven Not proven		(85) (70)
3-Nitrobenzaldehyde	Ethanolamine	73 (m.p.)	Not proven		(85)
4-Nitrobenzaldehyde	Ethanolamine γ-(2-Hydroxyisobutylamino)-*N*-(*p*-nitrobenzylidene)propylamine	84.5–85 (m.p.) 124–125 (m.p.)	Schiff base Cyclic	 Made from γ-(2-hydroxyisobutylamino)propylamine	(13, 18) (110a)
	Ethyl *erythro*-*p*-nitrophenylserinate Iso-α-amino-β-hydroxybibenzyl	139 (m.p.) 148 (m.p.) 132 (m.p.)	Schiff base Not proven	From ethyl glycinate and *p*-nitrobenzaldehyde	(6, 8, 40) (45d)
2-Chlorobenzaldehyde	Ethanolamine	132–135/1.6 mm. 178/12 mm. 35–36 (m.p.)	Schiff base		(9, 55, 85)
2-Bromobenzaldehyde	Ethanolamine 2-Amino-3-methyl-3-butanol	50.5 (m.p.) 110/0.05 mm.	Schiff base 60% Schiff base		(13, 15) (13, 18)
3-Bromobenzaldehyde	Ethanolamine 2-Amino-3-methyl-3-butanol	49.5 (m.p.) 108–110/0.01 mm.	Schiff base 70% Schiff base		(9, 13, 18) (13, 18)
4-Bromobenzaldehyde	Ethanolamine 2-Amino-3-methyl-3-butanol	84.5 (m.p.) 125–132/1 mm.	Schiff base 60% Schiff base		(13, 14, 18) (13, 18)

TABLE 13—*Concluded*

ALDEHYDE	AMINOALCOHOL	PRODUCT			REFERENCES
		Boiling or melting point	Structure	Remarks	
		C°			
m-Tolualdehyde	Ethanolamine	159/14 mm.	Not proven		(85)
p-Tolualdehyde	Ethanolamine	153/15 mm.	Not proven		(85)
	N-Ethylethanolamine	68–70/0.03 mm.	Cyclic		(56)
	Diethanolamine	123–124/0.2 mm.	Cyclic		(56)
Phenylacetaldehyde	Trimethylolmethylamine	188–189/1 mm.	Not proven	Yield, 20%	(91)
2-Methoxybenzaldehyde	Ethanolamine	137–142/1 mm. 195/27 mm. 44.5–45 (m.p.)	Schiff base		(18, 85)
Anisaldehyde	Ethanolamine	106–109/0.03 mm. 147–148/1.6 mm. 180/12 mm. 35–36 (m.p.)	Schiff base		(9, 39, 57, 85)
	N-Methylethanolamine	133–136/3 mm.	Cyclic		(14, 19, 53)
	1-Amino-3-chloro-2-propanol	129/1.1 mm.	Not proven		(22)
	2-Amino-1-indanol	174–175.8 (m.p.)	Not proven		(80)
	1-Amino-2-indanol	193–194 (m.p.)	Not proven		(80)
	Threo-β-*p*-nitrophenylserinol	145–146 (m.p.)	Not proven		(70)
	Iso-α-amino-β-hydroxybibenzyl	145 (m.p.) *l*-form, 152 (m.p.)	Not proven		(45d)
4-Hydroxy-3-methoxybenzaldehyde	*Threo*-β-*p*-nitrophenylserinol	121 (m.p.)	Not proven		(70, 32a)
	Iso-α-amino-β-hydroxybibenzyl	148 (m.p.) *l*-form, 155 (m.p.)	Not proven		(45d)
Piperonal	Diethanolamine	148–150/0.02 mm.	Cyclic		(56)
	2-Amino-1-indanol	171.8–173.0 (m.p.)	Not proven		(80)
Dimethylaminobenzaldehyde	Ethanolamine	102 (m.p.)	Schiff base		(11)
4-Isopropylbenzaldehyde	Diethanolamine	128–130/0.2 mm.	Cyclic		(56)
α-Naphthaldehyde	Ethanolamine	49–49.5 (m.p.)	Schiff base		(9, 13, 14, 18)
	2-Amino-3-methyl-3-butanol	150–154/0.05 mm.	Mixture of isomers		(13, 18)
β-Naphthaldehyde	Ethanolamine	103–103.5 (m.p.)	Schiff base		(9, 13, 18)

* An isomer melting at 173–174°C. was also obtained, which was tentatively assumed to be *O*-(*p*-toluenesulfonyl)-*N*-benzylidene-iso-α-amino-β-hydroxybibenzyl.

TABLE 14

Condensation of aromatic ketones with β-hydroxy amines

KETONE	AMINOALCOHOL	PRODUCT			REFERENCES
		Boiling or melting point	Structure	Remarks	
		°C.			
Acetophenone	Ethanolamine	Not pure			(76)
	N-Methylethanolamine	99/3 mm.	Cyclic		(19)
	2-Amino-3-methyl-3-butanol	107–108/7 mm.	Mixture of isomers		(18)
	1-Amino-3-methyl-2-butanol	246/760 mm.	Not proven	Picrate, m.p. 104°C.	(113)
	3-Methyl-1-methylamino-2-butanol	205/760 mm.	Cyclic	Picrate, m.p. 116°C.	(113)
3-Nitroacetophenone	Ethanolamine	82–83 (m.p.)	Mixture, mostly cyclic		(13, 18)
	2-Amino-3-methyl-3-butanol	90.8–91 (m.p.)	Cyclic		(18)
4-Fluoroacetophonone	Ethanolamine	88–90/1 mm.	Mixture of isomers	See page 331	(13, 18)
	2-Amino-3-methyl-3-butanol	83–87/2.5 mm.	Cyclic		(18)
4-Methyl-4-phenyl-2-pentanone	Ethanolamine	178–184/24 mm.	35% Schiff base	Yield, 83%	(7, 10)
	2-Amino-3-methyl-3-butanol	136–138/2 mm.	50% Schiff base	Yield, 60%	(7, 10)
Benzophenone	Ethanolamine	73–73.5 (m.p.)	Schiff base		(9, 13, 18)
Desoxybenzoin	Ethanolamine	No data	Not proven		(57)

TABLE 15

Condensation of α,β-unsaturated aldehydes and ketones with β-hydroxy amines

CARBONYL COMPOUND	AMINOALCOHOL	PRODUCT			REFERENCES
		Boiling or melting point	Structure	Remarks	
		°C.			
2-Ethyl-2-hexenal	Ethanolamine	119–121/8 mm.	Not proven	Obtained in reaction with butyraldehyde	(89)
	N-Methylethanolamine	62.5–64/2.5 mm.	Cyclic		(19)
	2-Amino-3-methyl-3-butanol	102–104/5 mm.	Mostly Schiff base		(13, 18, 70, 87, 88)
Cinnamaldehyde	Iso-α-amino-β-hydroxybibenzyl	185 (m.p.) (dec.) *d*-form, and *l*-form in two isomers, m. p. 190 and 137	Not proven		(45c, 45d)
Isophorone	Ethanolamine	97–100/0.5 mm.	Mostly Schiff base		(18)
	2-Amino-3-methyl-3-butanol	91–93/0.5 mm. 129–130/8 mm.	Mostly Schiff base		(13, 18)
2,4,6-Triethyl-2,4,6-decatrienal	Ethanolamine	133–135/8 mm.	Not proven	Obtained in reaction with butyraldehyde	(89)

TABLE 16

Condensation of carbonyl compounds with α,γ-dihydroxy-β-amines (1-aza-3,7-dioxabicyclo[3.3.0]octanes)

CARBONYL COMPOUND	AMINOALCOHOL	PRODUCT		REFERENCES
		Boiling or melting point	Remarks	
		°C.		
Formaldehyde	2-Amino-1,3-propanediol	66.5/10 mm.	Conversion, 77%	(106)
	2-Amino-2-methyl-1,3-propanediol	66/10 mm. 170–180/760 mm. −5 (m.p.)	Conversion, 97%	(1, 106)
	Trimethylolmethylamine*	59–60 (m.p.) 62–63 (m.p.) 65 (m.p.)	Conversion, 90% Yield, 77%	(1, 92, 106)
	2-Amino-2-ethyl-1,3-propanediol	74.5/10 mm. 75–77/1–2 mm.	Conversion, 94%	(1, 106)
	3-Amino-2-propyl-1,3-propanediol	90–91/10 mm.	Conversion, 95%	(106)
	2-Amino-2-isopropyl-1,3-propanediol	84–85/10 mm.	Conversion, 90%	(106)
Butyraldehyde	2-Amino-2-methyl-1,3-propanediol	94–95/10 mm.	Conversion, 94%	(106)
	2-Amino-2-ethyl-1,3-propanediol	104.5/10 mm.	Conversion, 81%	(106)
	Trimethylolmethylamine	112.5–113.5/0.3 mm.	Yield, 75%	(92)
Hexanal	Trimethylolmethylamine	151–153/0.3 mm. 216–217/32 mm.	Yield, 89%	(92)
Benzaldehyde	2-Amino-2-methyl-1,3-propanediol	123 (m.p.)	Conversion, 95%	(106)
	Trimethylolmethylamine	93–95 (m.p.)	Yield, 85%; hydrochloride, m.p. 130–131°C.	(92)
	Trimethylolmethylamine mono-*O*-*p*-nitrobenzoate	Hydrochloride, hygroscopic	From the preceding compound with *p*-nitrobenzoyl chloride	(91)
2-Ethylhexanal	2-Amino-2-methyl-1,3-propanediol	114–118/10 mm.	Conversion, 70%	(106)
Phenylacetaldehyde	Trimethylolmethylamine	238–240/1 mm.	Yield, 50%	(92)

* 1-Phenylcyclohexane-1-carboxylic acid ester (49).

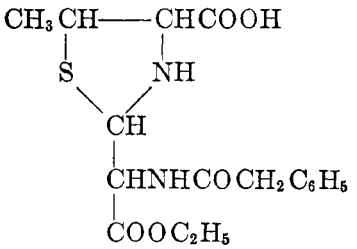
manner as the oxazolidines, though only under much more stringent conditions (36).

Some interesting information can be gleaned from the investigations on the thiazolidine system which have been carried out in connection with the elucidation of the structure of penicillin (33). In this series, it has been possible to prepare the hydrogenated system by reduction (with aluminum amalgam in moist ether) of the corresponding Δ^2-thiazolines, although under more stringent conditions the thiazolidines suffer reductive cleavage to *N*-alkylated β-mercaptoethylamines. Substitution of the hydrogen atom in the 3-position is possible both by acyl residues and by alkyl radicals (alkyl halides in liquid ammonia). Ethylene oxide reacts in the presence of boron trifluoride to introduce the β-hydroxyethyl group (see page 321).

The infrared spectra of the "thiazolidines" have shown the absence of a carbon–nitrogen double bond, so that no Schiff bases appear to be formed (no systematic study, however, has been carried out). Analogous conclusions can be drawn from the ultraviolet spectra. Nevertheless, the thiazolidine system is, under certain conditions, much more mobile than that of the oxazolidine. As indicated by the appearance of the blue color reaction, free mercapto groups appear easily when the thiazolidines are heated with ferric chloride solution. The rate of the isomerization, however, depends on the substituents. This is indicated by table 10.

Similar observations have been made when thiazolidines are heated with iodine solution (25, 119; see also 95, 104, 105); here, too, *N*-acyl derivatives are not attacked. The stabilization by *N*-acylation is so pronounced that the *N*-acylthiazolidines are converted into the corresponding sulfones by hydrogen peroxide in glacial acetic acid (95).

In this connection, it is worthy of note that the two thiothreonines (31) give with ethyl benzylpenaldate two different thiazolidines, melting at 134–137°C. and 182°C., respectively.



As to the molecular refraction of the thiazolidine system, the only figure available is that for thiazolidine itself (95). The calculated value is 25.58 and the experimental 24.92, so that also here a specific depression appears to be characteristic for the heterocyclic ring.

VIII. TABLES OF PRODUCTS FORMED BY THE CONDENSATION OF AMINOALCOHOLS WITH CARBONYL COMPOUNDS

In tables 11 to 16, the material is organized according to the molecular formulas of the carbonyl compounds used in the condensations; also, under each carbonyl

compound the aminoalcohols are arranged according to the number of carbon atoms contained in them. For the sake of simplicity, those "oxazolidines" which have not been prepared by condensation of a carbonyl compound with an aminoalcohol (the products from carbonyl compounds and ethylenimine; acyl derivatives of the primary condensation products) have been listed under the compounds from which they are derived *formally* (e.g., in the latter case, under the carbonyl compound and the *N*-acyl derivative of the aminoalcohol); in these cases, an explanatory statement has been added in the column headed "Remarks."

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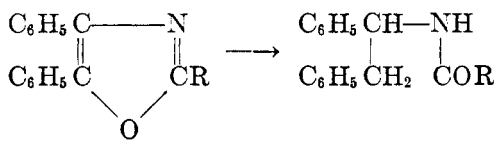
Addendum[3]

SECTION II

Cantarel and Charles (122) have shown that the condensation of benzophenone-imine with ethanolamine gives the same product as does benzophenone itself.

The formation of oxazolidines as intermediates in rearrangement reactions has been postulated in the case of aminoborneol (131) and recently in the hydrolytic transformation of α-(benzoylamino)cinnamyl alcohol to α-phenyl-α′-benzoyloxyacetone (121).

The reduction of oxazoles has been studied systematically by Dornow and Eichholtz (124). The observation of E. Fischer (47) that 2,5-diphenyloxazole is transformed by sodium and alcohol into 2-benzylamino-1-phenyl-1-propanol has been confirmed; 2,4,5-triphenyloxazole shows an analogous behavior. If, however, the $C_{(2)}$ atom is substituted by an *aliphatic* radical, fission takes place between the oxygen and $C_{(5)}$ and (not $C_{(2)}$), and an acid amide is formed:

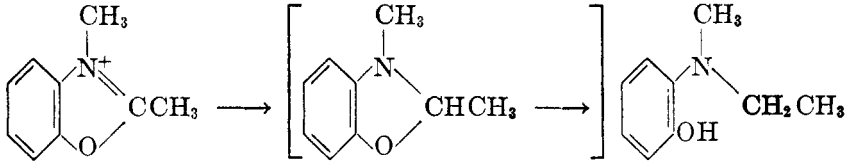


R represents an aliphatic radical.

The authors also quote some prior investigations (123, 128, 129, 133) in which no fission of the oxazole system by reducing agents, especially of a catalytic nature, could be achieved.

SECTION III, C

In connection with the reductive fission of oxazolidines by lithium aluminum hydride, the observation of Torrosian and Sannié (130) is of interest that the reaction of alkylbenzoxazolium salts with potassium borohydride leads to an *o*-hydroxy-*N*,*N*-dialkylaniline, according to the following scheme:



[3] This addendum covers the literature approximately up to September 1, 1953.

For the preparation of secondary from primary aminoalcohols by condensation with ketones, see reference 127.

SECTION VII

In continuation of his previous studies (98), Riebsomer and coworkers (125) have investigated the condensation of mono-*N*-alkylethylenediamines with aldehydes. On the basis of the ultraviolet spectra, the products could be identified in several cases as imidazolidines.

The formation of a 1,3-oxazine derivative from nortropanol and *p*-nitrobenzaldehyde has been used by Hardegger and Ott (126) as a means of assigning to the cyclic aminoalcohol the *N*,*O cis*-configuration in the boat form.

SECTION VIII

In table 11 the following items should be added.

ALDEHYDE	AMINOALCOHOL	PRODUCT			REFERENCE
		Boiling point	Structure	Remarks	
		°C.			
3,4-Dihydro-2*H*-pyran-2-carboxaldehyde	Ethanolamine	86–88°/2 mm.	Not proven	Yield, 69%	(132)
	2-Amino-2-methyl-1-propanol	81–82°/2 mm.	Not proven	Yield, 89%	(132)

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