Master's Theses   Student Research

1951

Cyclic derivatives of Tris (hydroxymethyl) aminomethane : monourethans and ureas

Julian Lee Rush Jr.

Recommended Citation

Rush, Julian Lee Jr., "Cyclic derivatives of Tris (hydroxymethyl) aminomethane : monourethans and ureas" (1951). *Master's Theses.* Paper 919.

CYCLIC DERIVATIVES OF TRIS(HYDROXYMETHYL)AMINOMETHANE:

MONOURETHANS AND UREAS

BY

JULIAN LEE RUSH JR.

THESIS

SUBMITTED TO THE GRADUATE FACULTY

OF THE UNIVERSITY OF RICHMOND

IN CANDIDACY

FOR THE DEGREE OF

MASTER OF SCIENCE IN CHEMISTRY

JANUARY, 1951

APPROVED BY:

_____

ACKNOWLEDGEMENT

TABLE OF CONTENTS

INTRODUCTION

The purpose of the work reported in this thesis was
to study the chemistry of tris(hydroxymethyl)aminomethane (A),
$H_2NC(CH_2OH)_3$, a beta-hydroxy amine.

Tris(hydroxymethyl)aminomethane may best be prepared by
the exhaustive hydroxymethylation of nitromethane with the
subsequent reduction of the nitro group. (A) is structurally
related to pentaerythritol (1), $(HOCH_2)_4C$, which has been
studied extensively because of its four functional groups.
The plurality of reactive units in (A) make it a potential
rival of pentaerythritol for popularity of study. By joining
specific functional groups in a chemical bond, it is possible
to carry out controlled reactions with a desired group.

This work involves the preparation of monourethans and
ureas through cyclic intermediates of (A), which may be
hydrolyzed to yield the corresponding simple ureas and mono-
urethan hydrochlorides of (A).

(1) Marrian, Chem. Rev. 43, 149 (1948).

A general discussion of reactions involving organic
isocyanates is given in the historical section, together
with a discussion of reactions of tris(hydroxymethyl)amino-
methane. In conclusion, some recent work on the migration of
the acyl group between nitrogen and oxygen has been discussed.

HISTORICAL

REACTIONS OF ISOCYANATES AND THE BEHAVIOR OF COMPOUNDS
FORMED AS A RESULT OF THESE REACTIONS.

In general, isocyanates are extremely hygroscopic and
it is this affinity for water, together with subsequent urea
formation, which makes storage and handling very difficult.
Extreme care must be used in drying all equipment used in
handling the isocyanates.

Isocyanates are hydrolyzed by water with varying degrees
of rapidity yielding:

$$RNCO + H_2O \longrightarrow RNHCOOH \longrightarrow RNH_2 + CO_2$$
$$RNH_2 + RNCO \longrightarrow RNHCONHR$$
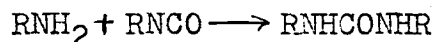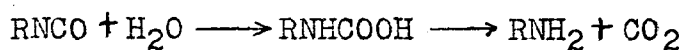
The most characteristic reactions of isocyanates are
those which involve compounds containing an active hydrogen
as shown below:

$$RNCO + HX \longrightarrow (RN=C-OH-X) \longrightarrow RNHCOX$$
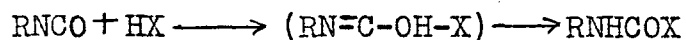
Practically all compounds containing a hydrogen atom

attached to a nitrogen atom will react with isocyanates as follows:

$$RNCO + HN< \longleftrightarrow RNHCON<$$

Amines react to give substituted ureas, while amides give acyl ureas and ureas give biurets.

A consideration of the relative reactivity of active hydrogen compounds toward isocyanates indicates that amines react much faster than alcohols, which in turn react faster than water (2). An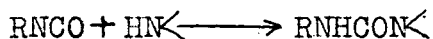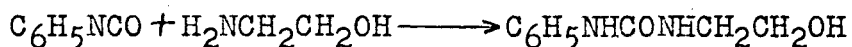 example of such a sequence is found in the reaction of equimolar amounts of ethanolamine and phenyl isocyanate in which a urea is formed rather than a carbamate. This fact has also been brought out by Charlton and Day (3). They stated that when an isocyanate was reacted with ethanolamine that a urea was formed.

$$C_6H_5NCO + H_2NCH_2CH_2OH \longrightarrow C_6H_5NHCONHCH_2CH_2OH$$

If, however, excess isocyanate is used a urea-urethan will be formed. The fact that the isocyanate reacted with the amino group rather than the hydroxyl group was readily established. The reaction with the amine hydrogen was quite vigorous, and considerable heat was evolved. When alpha-naphthyl isocyanate was added to a primary alcohol there was no vigorous reaction. With a primary amine, however, a rapid and fairly vigorous reaction resulted.

(2). Saunders and Slocombe - Chem. Rev. 43, 203-218 (1948).
(3). Charlton and Day, J. Org. Chem. Vol. I, 552-8.

Many of the normal reactions of isocyanates with active hydrogen compounds may be reversed by heating (2). For example, carbamates may be decomposed to give the isocyanate and the alcohol.

Rider was one of the first to point out the anesthetic value of phenyl urethans (4). He showed that dialkyl aminoalkanols react under anhydrous conditions to yield the phenyl urethans.

$$R_2NCH_2CH_2CH_2OH + C_6H_5NCO \longrightarrow R_2NCH_2CH_2CH_2OCONHC_6H_5$$

Cope and Hancock prepared 2-alkylaminoethyl phenylurethan hydrochlorides by reacting a hydrochloride of the alkylamino-alkanol with phenyl isocyanate (5).

$$HOCH_2CH_2NHR \cdot HCl + C_6H_5NCO \longrightarrow C_6H_5NHCOOCH_2CH_2NHR \cdot HCl$$
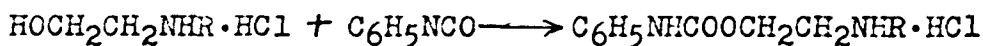
In an attempt to rearrange N-phenyl-N'-(2-hydroxy-2-methylpropyl)-N'-phenyl urea to the corresponding urethan, the urea underwent hydrolysis under conditions for rearrangement of other amides. The conditions for the amide-ester rearrangement was the boiling of the amide in alcohol with the addition of a 50 percent excess of concentrated hydrochloric acid. This reaction with the urea was carried out without hydrolysis by heating the urea in a chloroform solution saturated with dry hydrogen chloride for seventy hours at a

(4). Cook and Rider, J. Am. Chem. Soc. 58, 1079-81 (1936).
(5). Cope & Hancock, J. Am. Chem. Soc. 66, 1448-52 (1944).

temperature of 55° (6).

$$\text{C}_6\text{H}_5\text{—NHCONCH}_2\text{COH(CH}_3)_2 \xrightarrow[\text{in CHCl}_3]{\text{HCl}} \text{C}_6\text{H}_5\text{—NHCOOC(CH}_3)_2\text{CH}_2\text{NH·HCl}$$
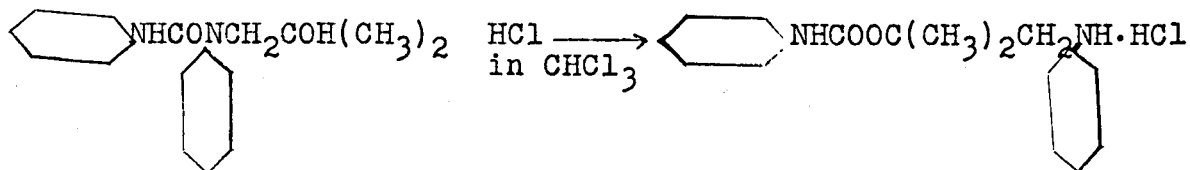
When beta-chlorethyl chlorocarbonate is condensed with aniline the corresponding urethan is produced, and then by treatment of the latter substance with alkali 3-phenyl-2-oxazolidone is formed (7).

$$\text{ClCOOCH}_2\text{CH}_2\text{Cl} + \text{C}_6\text{H}_5\text{NH}_2 \longrightarrow \text{C}_6\text{H}_5\text{NHCOOCH}_2\text{CH}_2\text{Cl} + \text{HCl}$$
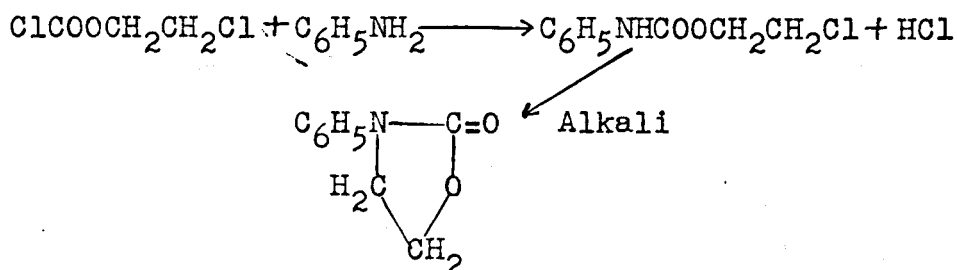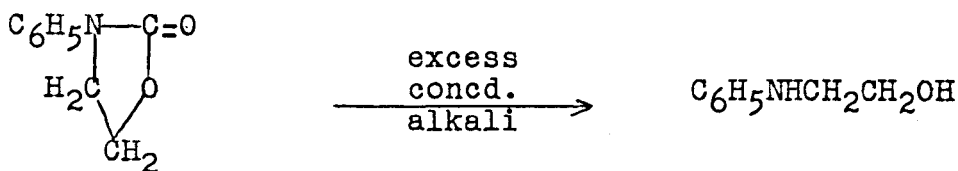
$$\begin{array}{c} \text{C}_6\text{H}_5\text{N——C=O} \\ | \quad\quad | \\ \text{H}_2\text{C} \quad\quad \text{O} \\ \backslash \quad / \\ \text{CH}_2 \end{array} \xleftarrow{\text{Alkali}}$$

If the oxazolidone is treated with an excess of concentrated alkali or if the urethan derivative is treated directly with excess concentrated alkali, very good yields of N-aryl amino alcohols are produced.

$$\begin{array}{c} \text{C}_6\text{H}_5\text{N——C=O} \\ | \quad\quad | \\ \text{H}_2\text{C} \quad\quad \text{O} \\ \backslash \quad / \\ \text{CH}_2 \end{array} \xrightarrow[\text{alkali}]{\substack{\text{excess} \\ \text{concd.}}} \text{C}_6\text{H}_5\text{NHCH}_2\text{CH}_2\text{OH}$$

Adams and Pierce carried out a similar series of reactions using gamma chloropropyl chloroformate (8).

(6). Hancock and Cope, J. Am. Chem. Soc. 66, 1738-47 (1944).
(7). Adams and Segur, Science 52, 185 (1920).
(8). Adams and Pierce, J. Am. Chem. 45, 790-5 (1923).

The oxazolidones may also be prepared as follows: the amino
alcohol is condensed with dialkyl carbonate giving the cyclic
compound according to the equation (9):

$$RNHC(R')_2C(R')_2OH + (R''O)_2CO \longrightarrow 2R''OH + RNC(R')_2C(R')_2O$$

$$\underset{\underset{O}{\overset{\parallel}{C}}}{}$$
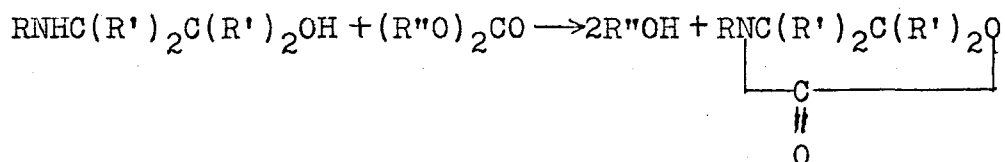
Amines of the type $C_6H_5CH(NH_2)R$ were found to be active
local anesthetics by Ogata (10) and Fourneau and his collabor-
ators (11). Certain compounds analogous to the above structure
were studied and found to be quite active although rather
irritating. Experience has shown that in some cases, mixed
or aliphatic-aromatic types, are often more active than the
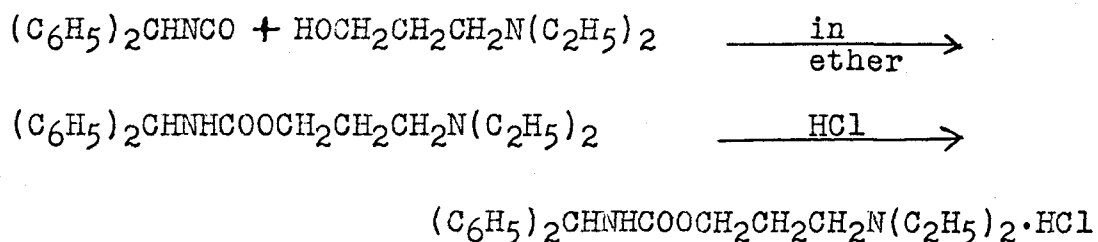diaryl derivatives.

It was thought possible that the introduction of groups
on the nitrogen atom in compounds of this type might act to
decrease the irritation produced in test animals. Among the
groups considered for this purpose was the COOR group.

The compounds prepared were of the type $R_1R_2CHNHCOO(CH_2)_nNR_2$
where R_1 and R_2 are either aromatic or aliphatic radicals,
where n was equal to one, two and three.

A typical reaction of this series is the preparation of

(9). Homeyer, U. S. 2,399,118 Apr. 23, 1946.
(10). Ogata, J. Pham. Soc. Japan 456, 81 (1920).
(11). Valette, Bull. Soc. Chem. (4) 47, 289 (1930); Torres,
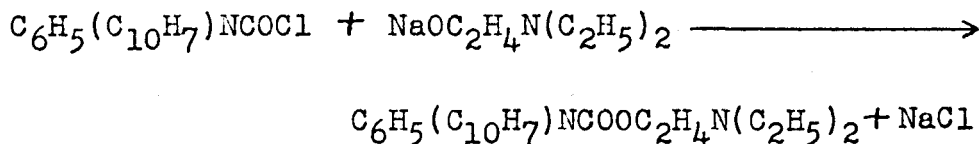ibid, (4) 37, 1591 (1925); Bonnard and Bulif, ibid (4)
(49, 1303 (1931).

gamma-diethylaminopropyl-diphenylmethyl carbamate hydrochloride
by dissolving the dipenylmethyl isocyanate in dry ether,
adding an equivalent amount of the amino alcohol and refluxing
for three hours. On passing in dry hydrogen chloride the basic
urethan hydrochloride precipitated in a fairly pure state.
These salts, which are soluble in water and somewhat hygroscopic,
may be prepared as follows (12):

$$(C_6H_5)_2CHNCO + HOCH_2CH_2CH_2N(C_2H_5)_2 \xrightarrow[\text{ether}]{\text{in}}$$

$$(C_6H_5)_2CHNHCOOCH_2CH_2CH_2N(C_2H_5)_2 \xrightarrow{\text{HCl}}$$

$$(C_6H_5)_2CHNHCOOCH_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$$

Rider reported that a number of N-aryl urethans seemed
to be promising local anesthetics. Fromherz (13) reported in
1914 that diethylaminoethyl diphenylamine N-carboxylate had a
strong local anesthetic action.

When phenyl-alpha-naphthylcarbamyl chloride was treated
with a suspension of the sodium derivative of diethyl amino-
ethyl alcohol in an inert high boiling solvent such as xylene,
an immediate reaction took place. Sodium chloride was formed
and a good yield of diethylaminoethyl phenyl-alpha-naphthylamine-
N-carboxylate was obtained, according to the following equa-
tions (14):

(12). Donleavy and English, J. Am. Chem. Soc. 62, 218-19 (1949).
(13). Fromherz, Arch. Exptl. Path. Phamacol 76, 257 (1914).
(14). Boese and Major, J. Am. Chem. Soc. 57, 175-76 (1935).

$$C_6H_5(C_{10}H_7)NCOCl + NaOC_2H_4N(C_2H_5)_2 \longrightarrow$$

$$C_6H_5(C_{10}H_7)NCOOC_2H_4N(C_2H_5)_2 + NaCl$$

Rider describes in one of his papers the preparation of mono and diphenylurethans, prepared by the action of phenyl isocyanate on the dialkylamino propanediols. The diurethans are formed with comparative ease, when the
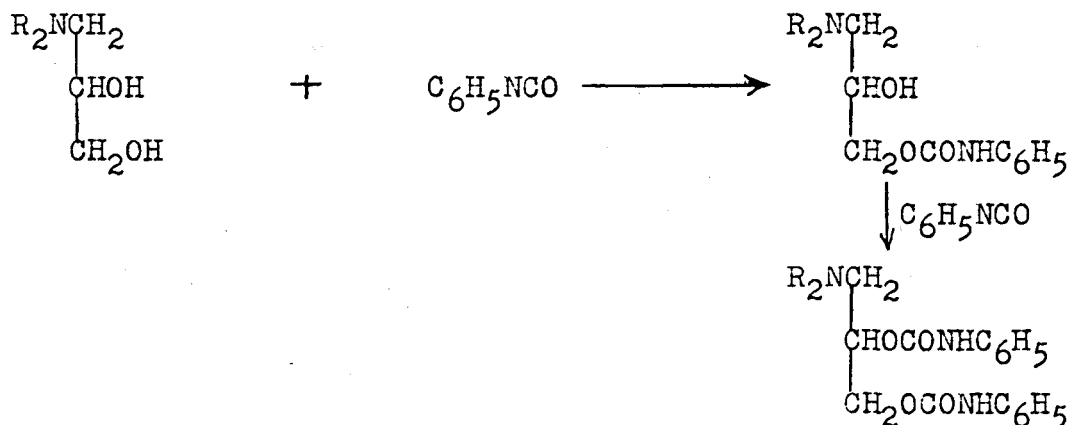
alcohols are reacted with two molecular proportions of phenyl isocyanate. The mono-urethans, however, are more difficult to obtain, since there is a decided tendency of the β-hydroxyl group to react, even in the presence of an excess of the alcohol, yielding the diurethans where the mono-urethans might be expected (15). In isolating the product from the reaction mixture, the obvious procedure would be to extract with dilute acid and liberate the free base by the addition of alkali. While it is possible to isolate the diurethans in this manner, the mono-

(15). Rider, J. Am. Chem. Soc. 52, 2115 (1930).

urethans are decomposed by alkali before they can be isolated (15). In view of this fact, in most cases the hydrochlorides of the urethans were prepared without isolating the free bases. The yields in these cases ran from 25 percent to 60 percent.

When Rosenmund heated $H_2NCH_2CH_2NH_2$ and diethyl carbonate on a water bath for five hours the product obtained was $H_2NCH_2CH_2NHCOOC_2H_5$. This product is useful as a drug intermediate (16).

If the compound studied in this paper, tris(hydroxymethyl) aminomethane, is named as a diol then it is 2-amino-2-hydroxy-methyl-1,3-propanediol. When a very similar compound 2-amino-2-methyl-1,3-propanediol is reacted with diethyl carbonate a urethan is formed. Continuation of the reaction yields a cyclic urethan by the elimination of ethanol as shown below (17).
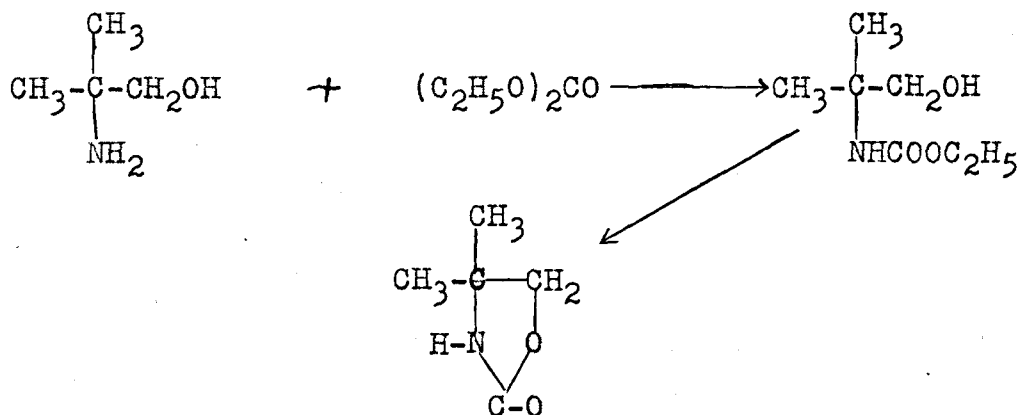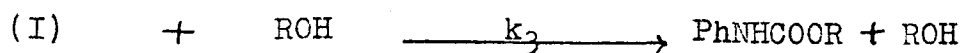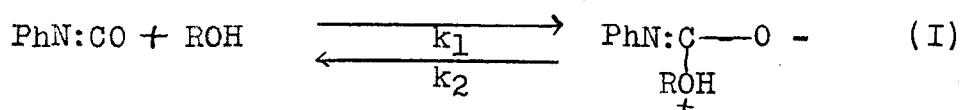

Various urethans and urethan hydrochloride salts were

(16). Rosenmund, Ger. 676,049, May 25, 1939; C. A. 33, 6529.
(17). Hodgins and Hovey, U. S. 2,215038 Sept. 17, 1941; C. A. 35, 830 (1941).

prepared from aryl isocyanates and amino alcohols of the type $RNHCMe_2CH_2OH$ by several different methods (18).

The spontaneous reaction between phenyl-isocyanate and methanol, ethanol, iso-propanol; tert-butanol and phenol in butyl ether has been studied kinetically at 20° and 30°. The reaction is catalyzed by the reactant alcohol itself acting as a base, the mechanism being of the types (19):

$$PhN:CO + ROH \underset{k_2}{\overset{k_1}{\rightleftarrows}} PhN:\overset{|}{\underset{\underset{+}{ROH}}{C}}—O- \qquad (I)$$

$$(I) + ROH \xrightarrow{k_3} PhNHCOOR + ROH$$

Stationary-state conditions being used, the 2nd order velocity coefficient for the reaction is $k_o = k_1k_3(ROH)/(k_2+k_3 [ROH])$, whence $ROH/k_o = k_2/k_1k_3 + ROH/k_1$; this straight line relationship has been verified experimentally when $R = Me$, Et, and iso-Pr. The significance of the values of k_1k_2/k_3, E_o, E_1, and E_3-E_2 (arrhenius activation energies for the various stages) thus determined is discussed on the basis of the combined operation of polar and steric effects of the group R: It is shown that the exptl. velocity, order $R = Me < Et (max) > iso-Pr \gg$ tert-Bu, is in harmony with the theoretical deductions.

(18). Pierce, Murphey and Shaia, J. Am. Chem. Soc. 71, 1765 (1949).
(19). Baker and Gaunt, J. Chem. Soc. (1949) 9-18; C. A. 43, 7440-42 (1949).

REACTIONS OF TRIS(HYDROXYMETHYL)AMINOMETHANE AND CLOSELY
RELATED COMPOUNDS.

Previous studies of tris(hydroxymethyl)aminomethane (A)
in this laboratory led to the preparation of polyhydroxyamines
(20) of the type $(HOCH_2)_3CNH(CH_2)_nNHC(CH_2OH)_3$. At the same
time various alkylation products of tris(hydroxymethyl)amino-
methane (A) were prepared (21). More recent studies involved
the reaction of (A) with ethyl oxalate, N-substituted ethyl-
oxamates, arylisocyanates, and aldehydes (22). This work has
been accepted for publication by the Journal of the American
Chemical Society.

Three new buffers (23) have been proposed for biochemical
experts to study; these are 2,4,6-trimethylpyridine, tris
(hydroxymethyl)aminomethane, and its closely related compound
2-amino-2-methyl-1,3-propanediol.

The following pK_b values for aqueous solutions at 25°C
were calculated from pH measurements made with a glass
electrode (24): $H_2N(CH_2)_2OH$ 4.55, $CH_3CH(NH_2)CH_2OH$ 4.57,
$CH_3CH_2CH(NH_2)CH_2OH$ 4.48, $(CH_3)_2C(NH_2)CH_2OH$ 4.28,
$HOCH_2C(CH_3)(NH_2)CH_2OH$ 5.24, $HOCH_2C(C_2H_5)(NH_2)CH_2OH$ 5.20,
$(HOCH_2)_3CNH_2$ 5.97. For comparison, $C_2H_5NH_2$ has a pK_b value

(20). Pierce and Wotiz, J. Am. Chem. Soc. 66, 879-881 (1944).
(21). Pierce and Wotiz, unpublished work.
(22). Pierce, Lunsford, Raiford, Rush and Wiley-unpublished
      work.
(23). Gomori, C. A. 40, 5078 (1946).
(24). Glasstone and Scharm, J. Am. Chem. Soc. 69, 1213-14
      (1947).

of 3.25; thus the introduction of an OH group into an aliphatic

amine decreased its basic strength, while the effect of the

methyl group is almost negligible.

The p-acetamidobenzenesulfonyl chloride was reacted with

tris(hydroxymethyl)aminomethane forming the sulfonamide by

the Schotten-Baumann reaction (25).

$$CH_3CONHC_6H_4SO_2Cl + (HOCH_2)_3CNH_2 \longrightarrow CH_3CONHC_6H_4SO_2NHC(CH_2OH)_3$$
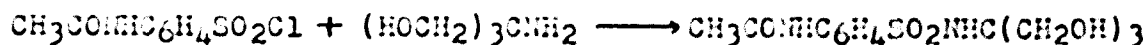
Billman and Parker (26) prepared 4,4-bis(hydroxymethyl)-

2-phenyl oxazoline by refluxing tris(hydroxymethyl)aminomethane

with benzoic acid by the following equation using xylene as

a solvent:
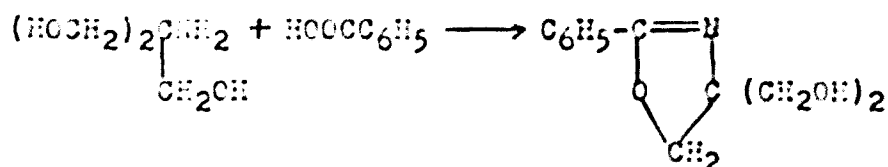
Valco claims in his patent (27) that oxazolines are

formed from beta-aminoalcohols through cyclization of the amides

of the amino alcohols. He states that the gradual heating

of 120 parts of tris(hydroxymethyl)aminomethane with 50 parts

of acetic anhydride to 230°C in the absence of condensing

agents, until approximately 27 parts of water are collected

(25). Adams, Long, and Johanson, J. Am. Chem. Soc. 61, 2342
      (1939).
(26). Billman and Parker, J. Am. Chem. Soc. 67, 1069-70
      (1945).
(27). Valco, U. S. 2,416,552, Feb. 25, 1947; C. A. 41, 3823.

in a water separator, gives 2-methyl-4,4-bis(hydroxymethyl) oxazoline.

$(HOCH_2)_2$ C——NH_2 $\quad + \quad$ $(CH_3CO)_2O \longrightarrow$ $(HOCH_2)_2$ C——NH
$\quad\quad\quad\quad\quad$ CH_2OH $\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad$ $CH_2OH \quad COCH_3$

$(HOCH_2)_2$ C——N $\quad\quad\quad \longleftarrow \quad\quad\quad$ $(HOCH_2)_2$ C——N
$\quad\quad\quad\quad$ $H_2C \quad\quad C-CH_3$ $\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad$ $CH_2OH \quad CCH_3$
$\quad\quad\quad\quad\quad\quad O$ $\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad$ OH
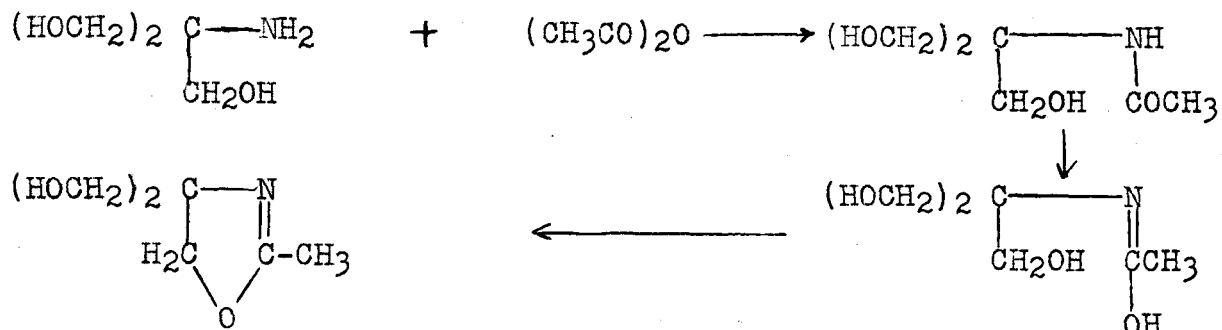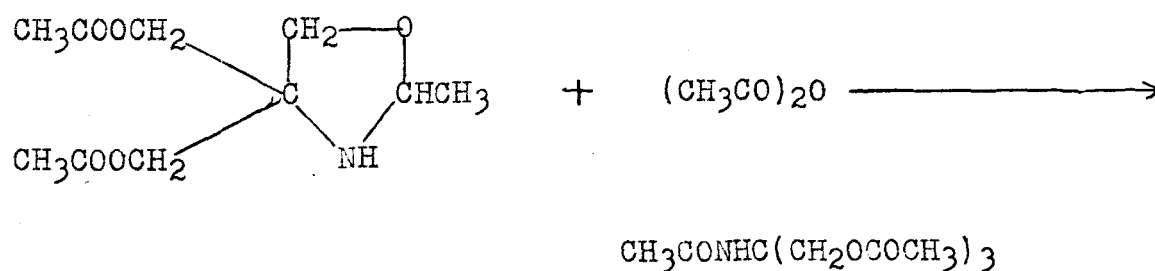
Tyron reports that when one equivalent of 2-methyl-4,4-bis(acetoxymethyl)-2-oxazolidine is refluxed for fifteen minutes with 2 equivalents of acetic anhydride the compound formed is tris(acetoxymethyl)acetamidomethane (28). The oxazolidine ring opens to yield the triester amide. No physical constants were given other than the melting point

CH_3COOCH_2 $\quad\quad$ CH_2——O
$\quad\quad\quad\quad\quad\quad$ C $\quad\quad\quad\quad$ CHCH_3 $\quad + \quad$ $(CH_3CO)_2O \longrightarrow$
CH_3COOCH_2 $\quad\quad\quad\quad$ NH

$CH_3CONHC(CH_2OCOCH_3)_3$

(28). Tyron, U. S. 2,410,318, Oct. 29, 1946; C. A. 41, 2076 (1947).

113-115°C. The same compound as the one given above was prepared by Piloty and Ruff (29) using a slightly different procedure. The 2-amino-2-hydroxymethyl-1,3-propanediol-hydrochloride (A)·HCl, was converted into the triester by reaction with acetic anhydride as shown below. The triester monoamide was isolated as a side reaction from the reaction mixture.

$$HCl \cdot H_2NC(CH_2OH)_3 + (CH_3CO)_2O \longrightarrow$$

$$HCl \cdot H_2NC(CH_2OCOCH_3)_3 + CH_3CONHC(CH_2OCOCH_3)_3$$
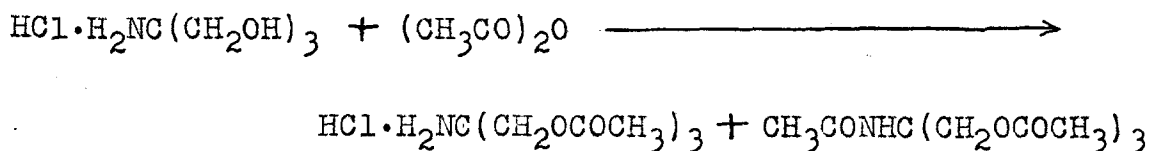
Cason and Prout recently prepared tetraacetyl tris (hydroxymethyl)aminomethane by the following procedure. (A) was reacted with an excess of acetic anhydride which was used as a solvent. A trace of sodium acetate was employed as a catalyst (30). The amine went into solution immediately, with the evolution of heat and the mixture refluxed so violently that external cooling was necessary. The product was re-crystallized from mixtures of acetic acid and ether.

N-acetyl tris(hydroxymethyl)aminomethane was prepared by treating 72.3g of the tetraacetyl-tris(hydroxymethyl)amino-methane with 800 ml. of 0.9844 N sodium hydroxide at room temperature and allowing to stand for three hours. Then an amount of hydrochloric acid equivalent to the alkali used

(29). Piloty and Ruff, Berichte 30, 2062 (1897).
(30). Cason and Prout, J. Am. Chem. Soc. 71, 1218-21 (1949).

was added to the solution. When the water was removed and
the residue extracted with alcohol, the product was precipitat-
ed from the alcohol solution by addition of nitromethane which
may be employed for recrystallization. Various attempts to
prepare the N-acetyl tris(hydroxymethyl)aminomethane by other
methods proved unsuccessful (30). When an aqueous solution
of tris(hydroxymethyl)aminomethane was treated at room tem-
perature with one mole equivalent of acetic anhydride, prac-
tically no crystalline monoacetyl derivative could be isolated
from the reaction mixture. When a sample of tetraacetyl
tris(hydroxymethyl)aminomethane was boiled with absolute
ethanol containing a trace of anhydrous hydrogen chloride,
the starting material was essentially unaffected. When the
amount of hydrogen chloride was increased the material re-
covered was the hydrochloride of tris(hydroxymethyl)aminomethane.

Senkus (31) prepared 1-aza-5-hydroxymethyl-3,7-dioxabicyclo
(3.3.0) octane by refluxing 2 moles of formaldehyde and one
mole of tris(hydroxymethyl)aminomethane in benzene until the
water ceased to separate and be collected by the Dean and
Stark moisture trap (32). If only one mole aldehyde is
used the intermediate oxazolidine was obtained as shown by
the following reactions:

(31). Senkus, J. Am. Chem. Soc. 67, 1515 (1945).
(32). Dean and Stark, Ind. Eng. Chem. 12, 486 (1920).

$$CH_2O + H_2N-\overset{\overset{\displaystyle CH_2OH}{|}}{\underset{\underset{\displaystyle CH_2OH}{|}}{C}}-CH_2OH \longrightarrow HOCH_2-\overset{\overset{\displaystyle CH_2O}{|}}{\underset{\underset{\displaystyle CH_2OH}{|}}{C}}-\overset{CH_2}{\underset{}{N-H}}$$

$$\downarrow CH_2O$$

$$HOCH_2-\overset{\overset{\displaystyle CH_2O}{|}}{\underset{\underset{\displaystyle CH_2O}{|}}{C}}-N\overset{CH_2}{\underset{CH_2}{<}}$$

When 1-aza-5-hydroxymethyl-3,7-dioxabicyclo(3.3.0) octane is reduced with butyl magnesium chloride the product produced is tris(hydroxymethyl)diamylaminomethane. Oxazolidines are split in the same manner. This same octane was prepared by the American Cyanamid Co., about the same time, without the

$$HOCH_2-\overset{\overset{\displaystyle CH_2O}{|}}{\underset{\underset{\displaystyle CH_2O}{|}}{C}}-N\overset{CH_2}{\underset{CH_2}{<}} + 2C_4H_9MgCl \longrightarrow HOCH_2-\overset{\overset{\displaystyle CH_2OH}{|}}{\underset{\underset{\displaystyle CH_2OH}{|}}{C}}-N(C_5H_{11})_2$$

use of a condensing agent (33). A similar compound was formed from the reaction of formaldehyde and 2-amino-2-methyl-1,3-propanediol in the following manner:

$$2CH_2O + CH_3-\overset{\overset{\displaystyle CH_2OH}{|}}{\underset{\underset{\displaystyle CH_2OH}{|}}{C}}-NH_2 \longrightarrow CH_3-\overset{\overset{\displaystyle CH_2O}{|}}{\underset{\underset{\displaystyle CH_2O}{|}}{C}}-N\overset{CH_2}{\underset{CH_2}{<}}$$

(33). Brit. 564,506, Oct. 2, 1944; C. A. 4084 (1946).

Attempts to nitrate 8-hydroxymethyl-2,6-dioxapyrrolizidine,
which is 1-aza-5-hydroxymethyl-3,7-dioxabicyelo(3.3.0) octane
(31),failed to yield the desired product but gave instead
3-nitro-4,4-bisnitroxymethyl oxazolidine which resulted from
the fission of one ring (34).
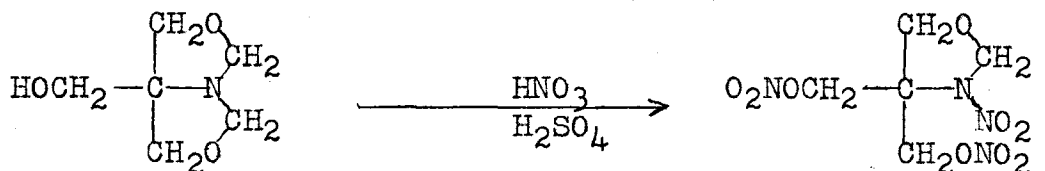
The preparation of 2-amino-3-hydroxy-2-hydroxymethyl-
propyl-1-phenylcyclohexanecarboxylate hydrochloride by trans-
esterification was reported by Tilford, Van Campen, and
Shelton (35), by reacting 1-aza-5-hydroxymethyl-3,7-dioxabicyclo
(3.3.0)-octane and ethyl-1-phenylcyclohexanecarboxylate. The
product was isolated as the hydrochloride.
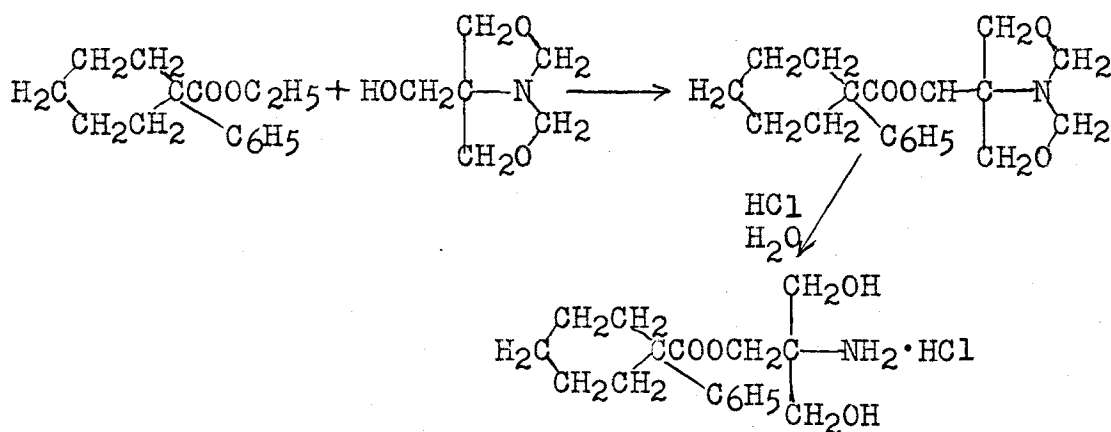
_____
(34). Godfrey and McLean, J. Chem. Soc. 1902 (1948).
(35). Tilford Van Campen, and Shelton, J. Amer. Chem. Soc.
      69, 2902-6 (1947).

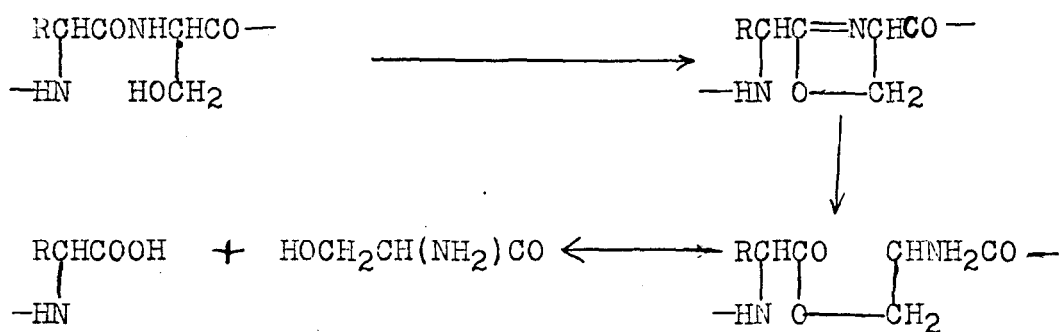MIGRATION OF THE ACYL GROUP BETWEEN OXYGEN AND NITROGEN

Ransom (36) described the rearrangement of ethyl-o-amino-phenyl carbonate to the urethan as follows:
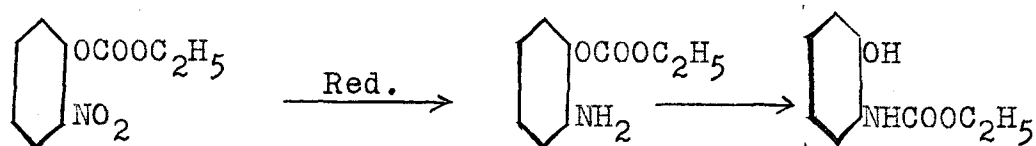

It has been shown that the stability of the peptide linkage to acid hydrolysis is diminished when a beta-hydroxy acid group is adjacent to the amide linkage, as compared to the ordinary peptide linkage. This is especially true when the concentration of hydrolyzing acid is increased to 10 $\underline{N}$ hydrochloric acid and the temperature of the hydrolysis is reduced from 37° to 30° (37). Of the possible free groups present in proteins only the hydroxyl groups had any appreciable effect on the peptide linkage adjacent thereto. The instability of the amide linkage is said to be due to the intermediate formation of an oxazoline ring, with subsequent rupture of the ring double bond formed and migration of the acyl group from N to O.

(36). Ransom, Ber. $\underline{31}$, 1055 (1898).
(37). Desnuelle and Casal, Biochim, et Biophys. Acta $\underline{2}$, 64-75 (1948); C. A. $\underline{43}$ p. 2944, (1949).

RCHCONHCHCO—   ⟶   RCHC=NCHCO—

—HN   HOCH₂   —HN O——CH₂

RCHCOOH + HOCH₂CH(NH₂)CO ⟷ RCHCO   CHNH₂CO—

—HN   —HN O——CH₂

Fodor and Kiss made a thorough study of cis-and trans-2-benzamido-cyclohexanol and found the following to be true (38).


Ia ⟶(HCl)⟵(NaOH) Ib

IIa ⟶(HCl)⟵(NaOH) IIb
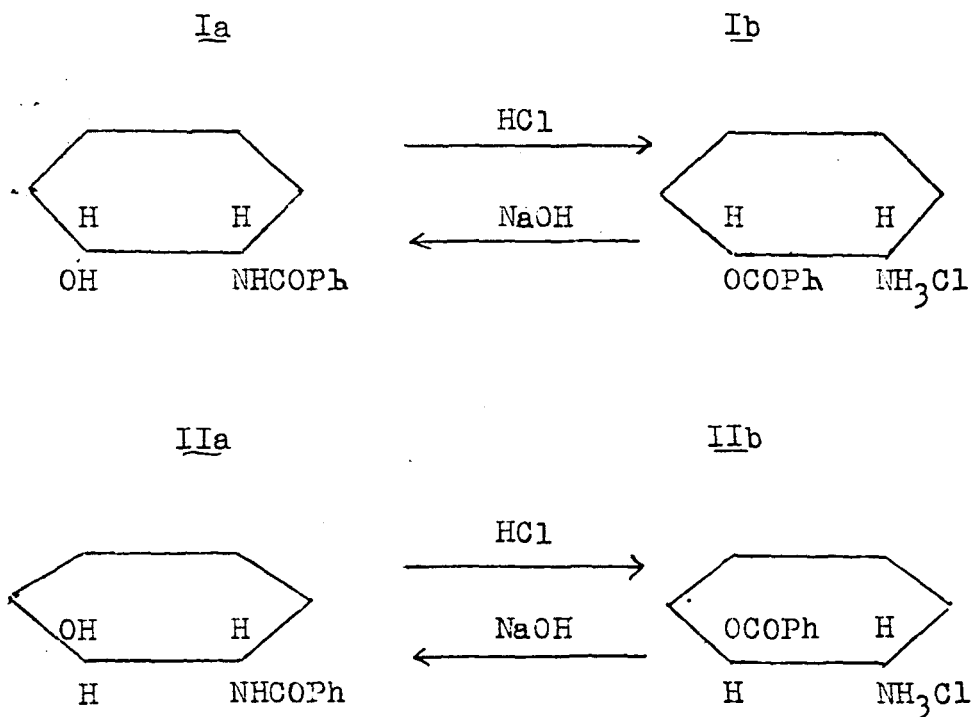
(38). Fodor and Kiss, Nature 164, 917 (1949).

The amide (Ia) gave, on reaction with 2 moles of hydrochloric acid, O-benzoyl-2-amino-cyclohexanol hydrochloride. Under identical conditions 2-benzamido-cyclohexanol (IIa) furnished the corresponding O-benzoyl-2-amino cyclohexanol hydrochloride. Each amino-ester salt was rearranged by alkalinization into the amide from which it was prepared; as an acyl shift O $\longrightarrow$ N never occurs with inversion (39); consequently the benzoyl shift O $\longrightarrow$ N took place in both cases with retention of configuration. The results obtained here are in accord with those of McCasland (40).

In the rearrangement of acyl from N $\longrightarrow$ O there is an intermediate oxazolidine formation which involves two mechanisms, one leading to inversion, the other to retention of configuration (41). A mechanism for retention is shown below (42). Such a process would lead to retention of configuration
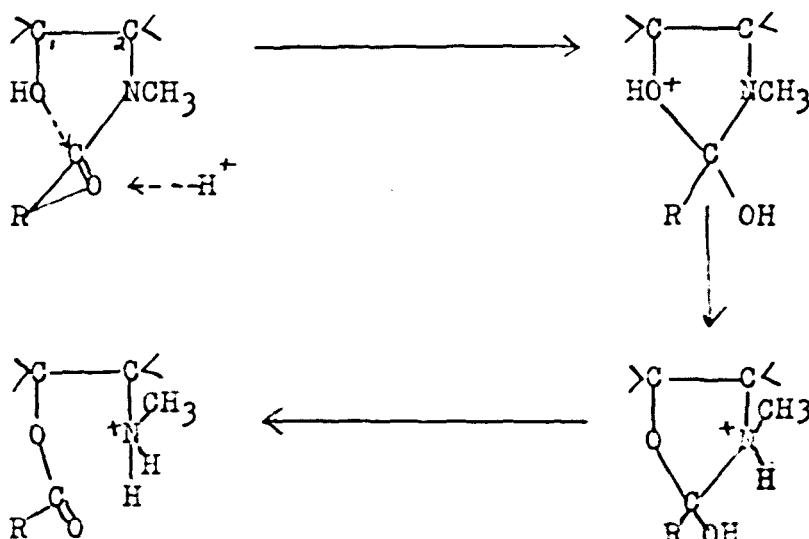
(39). Welsh, J. Am. Chem. Soc. 69, 128 (1947).
(40). McCasland, J. Am. Chem. Soc. 71, 638 (1949).
(41). Welsh, J. Am. Chem. Soc. 71, 3500 (1949).
(42). Phillips and Baltzly, J. Am. Chem. Soc. 69, 200 (1947).

since no bond of the asymetric center is involved. In

the rearrangement, the alcoholic hydroxyl, rather than a

water molecule, acts as an electron donor to the carbonyl

carbon.

A suitable mechanism for inversion, given below, assumes

that complete inversion at carbon one would occur as a result

of a backside approach of carbonyl oxygen while a proton

attacks the hydroxyl oxygen (43).
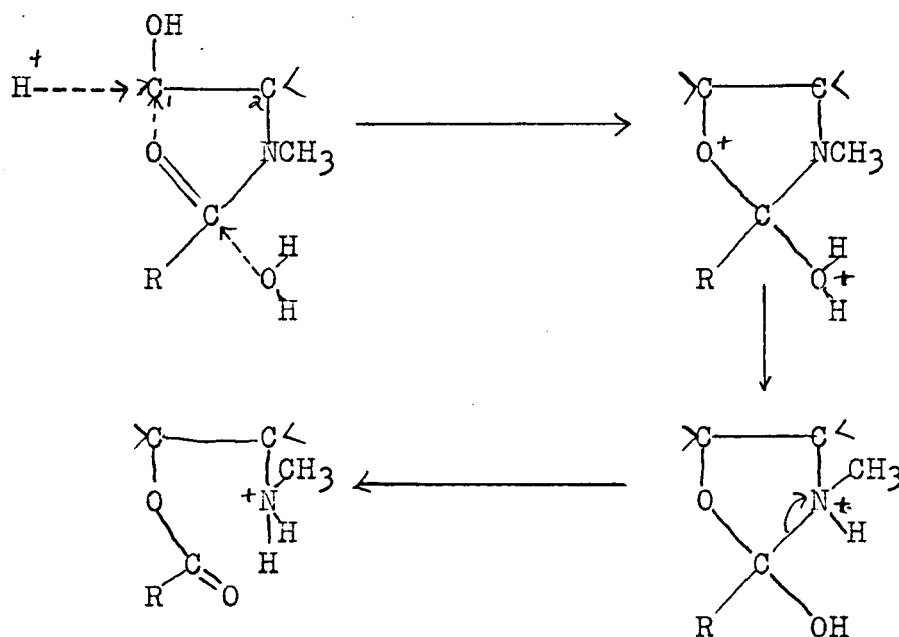
Winstein and Boschan give a very interesting contribu-

tion to the mechanism of the acyl migration which is as

follows (44):

(43). Frush and Isbell, Bur. Standards J. Research 27, 413
       (1941); Welsh,J. Am. Chem. Soc. 71, 3500 (1949).
(44). Winstein and Boschan, J. Am. Chem. Soc. 72, 4669 (1950).

$$C_6H_5$$

XXI

XXII

XXIII

$+H_2O$

$-H^+$

$+H^+$

XXIV

NaOH
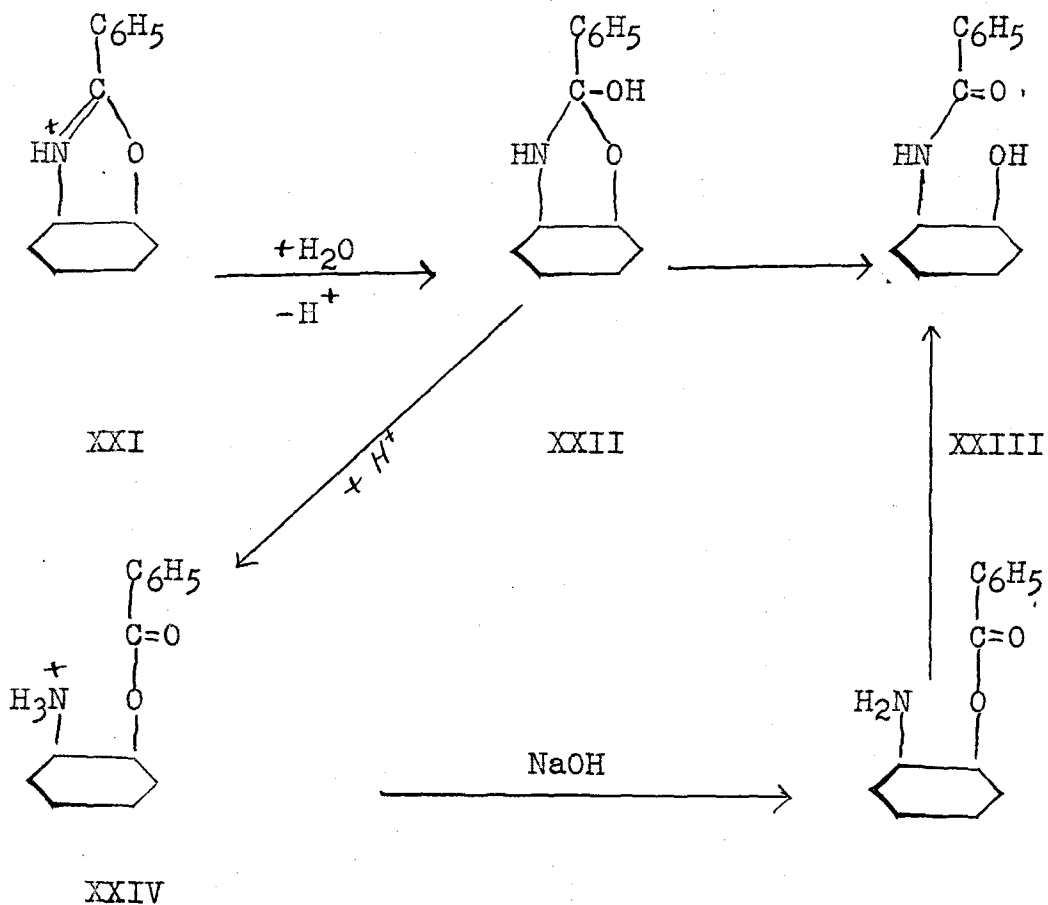
Here we have the reaction of the oxazolinium ion XXI
with water to yield the intermediate XXII, which gives rise
to the ordinary amide XXIII. A structure of the type XXII
is an intermediate, as suggested by Bergmann, for acyl
migration $O \longrightarrow N$ or $N \longrightarrow O$.

The hydrolysis of oxazolinium ion XXI is very smooth in
water and a high yield of cis-2-benzamidocyclohexanol XXIII
is obtained on making alkaline the clear solution of the
salt XXIV.
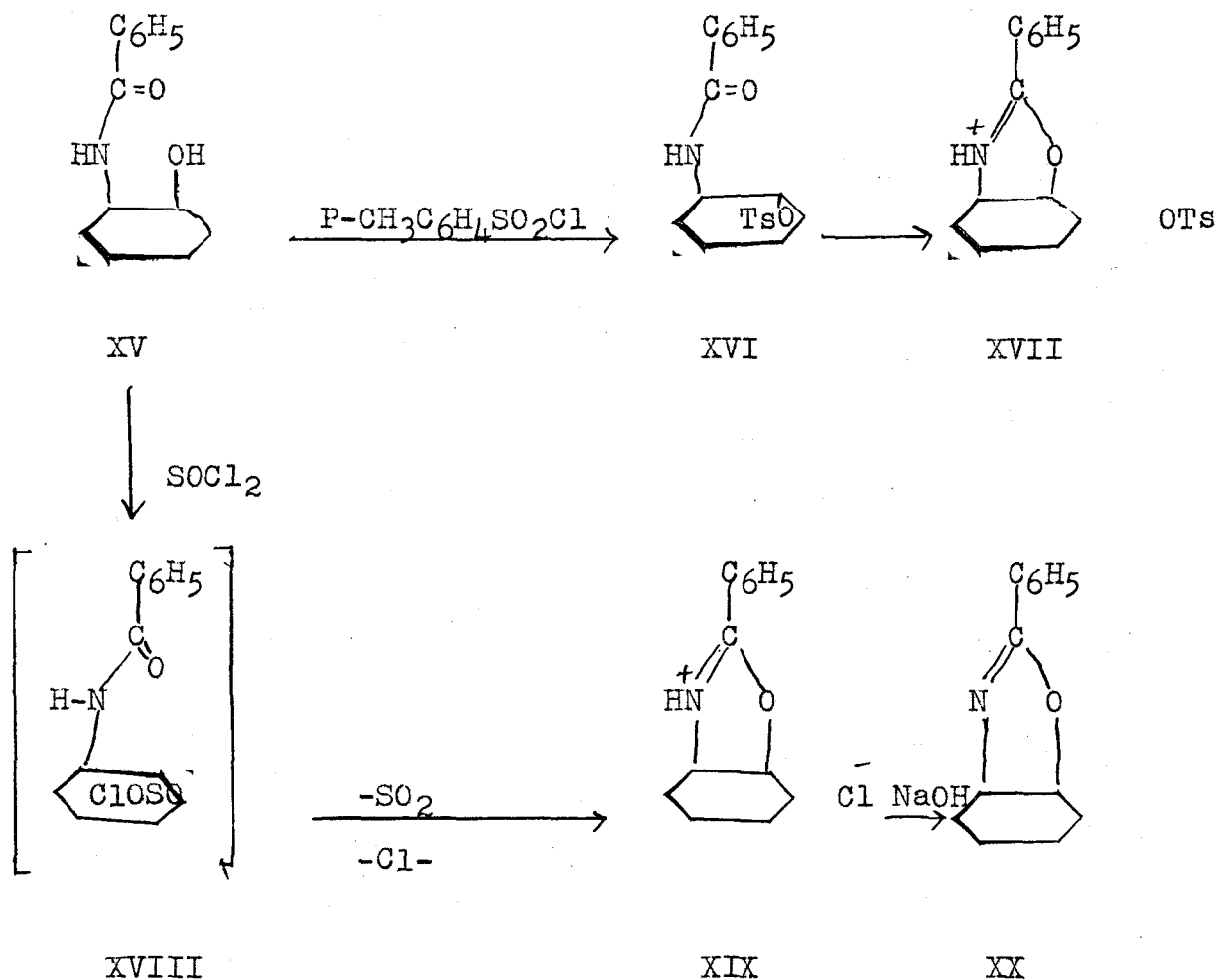
The oxazolinium ion which is produced by ionization of
XVI is relatively stable and is insufficiently acidic to be
titrated with sodium acetate in glacial acetic acid. The
solvolysis in absolute ethanol containing potassium acetate
was, however, easily followed by titration with aqueous base
to phenolphtlaein endpoint, this titration liberating free
oxazoline from oxazolinium salt.

Treatment of the benzamido alcohol with thionyl chloride
at room temperature gave a deliquescent oxazoline hydrochloride

XIX, which was not easily handled as such but which could be converted to the oxazoline XX and then to the picrate which proved identical with the picrate from solvolysis of XVI. Evidently the benzamido alcohol XV is converted to the chlorosulfinate XVIII and it is the OSOCl group which is the departing group.

The oxazolinium tosylate XVII is very stable in hot dry acetic acid, but addition of potassium acetate very markedly increases the rate of destruction of oxazolinium ion and therefore liberation of acid. From heating oxazolinium tosylate XVII with potassium acetate in dry acetic acid, trans-2-benzamidocyclohexyl acetate XXVI may be isolated in 40 percent yield, again not much higher than the yield reported by McCasland, Clark and Carter (40) for the over all treatment of XVI. There are also possibilities for complications, and this reaction is being examined further. While the study of this reaction by Winstein and Boschen is not yet complete, they suggest that the simplest reaction would be the attack of the oxazolinium ion by the acetate ion as indicated below in XXV.
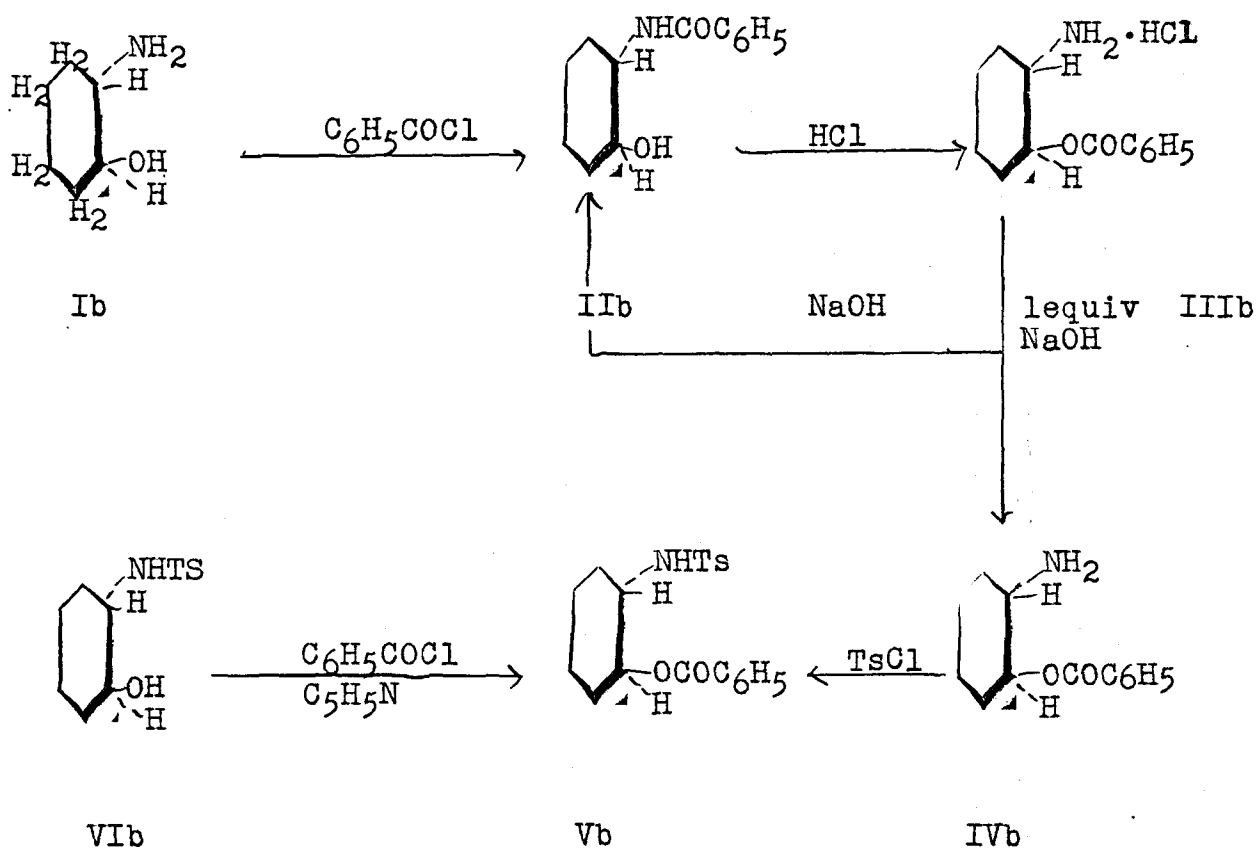

XXV   XXVI
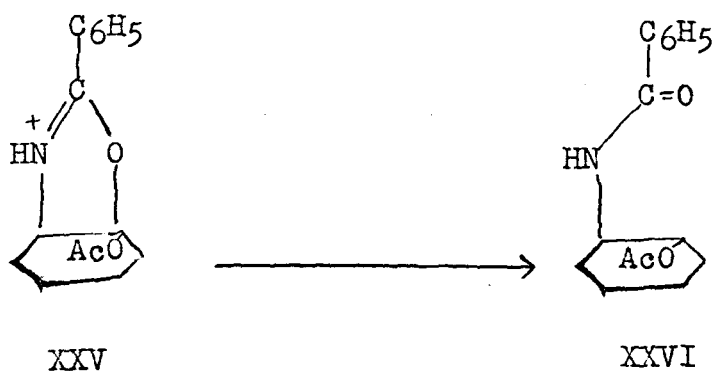
The most recent work on acyl migration from O $\longrightarrow$ N is by Fodor & Kiss (45). This acyl migration occurs when the diastereomeric 2-aminocyclohexylbenzoate hydrochlorides are treated with alkali.
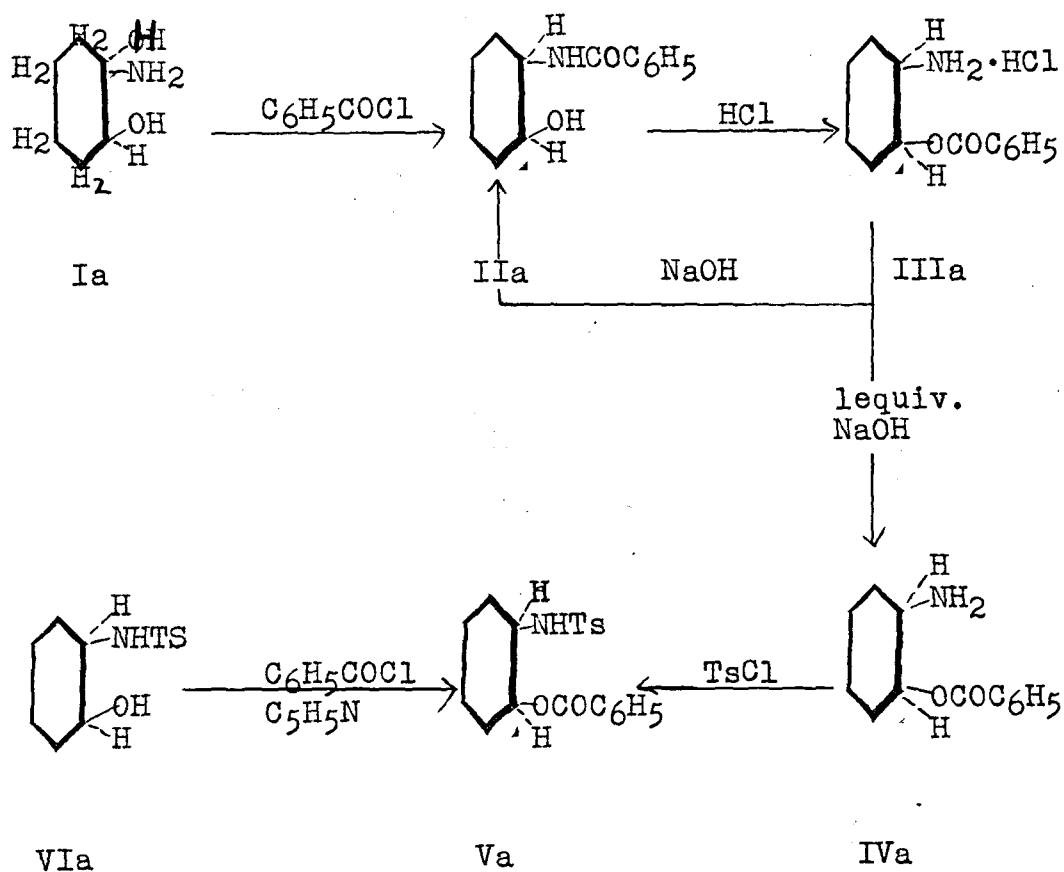
Cis-Series

(45). Fodor and Kiss, J. Am. Chem. Soc. <u>72</u>, 3495 (1950).

Ib

IIb   NaOH   lequiv IIIb
                NaOH

VIb   Vb   IVb

Trans-Series

Aqueous solutions of cis- and trans-2-~~benzamide~~*amino*cyclohexyl
benzoate hydrochloride, (IIIa), and its transisomer, (IIIb),
showed a pH of 5.5-6.0. The combined hydrogen chloride of
a 1% solution of (IIIa) could be titrated with 0.1 N
sodium hydroxide to a sharp end-point in the presence

of phenolphthalein. During the addition of one equivalent of alkali an oil gradually separated; it was identified as cis-2-aminocyclohexyl benzoate, (IVa), since, when immediately tosylated at pH 8, it yielded a product identical with cis-2-tosylamidocyclohexyl benzoate (Va) prepared by benzoylating cis-2-tosylamidocyclohexanol (VIa) in pyridine.

On adding one equivalent of alkali to an aqueous solution of (IIIa) and stirring the mixture for five minutes at pH 8, a portion of the precipitated (IVa) underwent the $O \rightarrow N$ acyl shift to yield cis-2-benzamidocyclohexanol (IIa). However, when an excess of 0.3 - 0.4 equivalent of alkali was added to the system containing the oily ester base, (IVa) a complete solution of the oil took place and was followed in one-half minute by precipitation of (IIa). This is in agreement with the observation of Phillips and Baltzly (46) who stated that a rise in pH increases the speed of $O \rightarrow N$ shift in esters of 2-aminoalcohols.

The combined hydrogen chloride of trans-2-aminocyclohexyl benzoate hydrochloride (IIIb) like that of its cisisomer could be titrated with alkali. Titration was accompanied by the deposition of oily trans-2-aminocyclohexyl benzoate (IVb) identifiable by virtue of its yielding on tosylation trans-2-tosylamidocyclohexyl benzoate (Vb) identical with the product obtained by treating trans-2-tosylamido-cyclohexanol (VIb) with benzoyl chloride in pyridine. The

(46). Phillips and Baltzly, J. Am. Chem. Soc. 69, 200 (1947).

ester base (IVb) yielded no hydroxyamide, (.IIb), when shaken

thirty minutes with the aqueous phase at pH 8. However,

dropwise addition of an excess of 0.6-1.0 mole of alkali

caused (IVb) to dissolve and after about five minutes dep-

osition of (IIb) began.

The tendency of the oily aminoesters to dissolve· in

alkali is considered as experimental evidence indicating the

formation of a cyclic ortho-acid derivative (47) as an inter-

mediate in the rearrangement, which may conceivably occur

by the following mechanism (44) and (38).
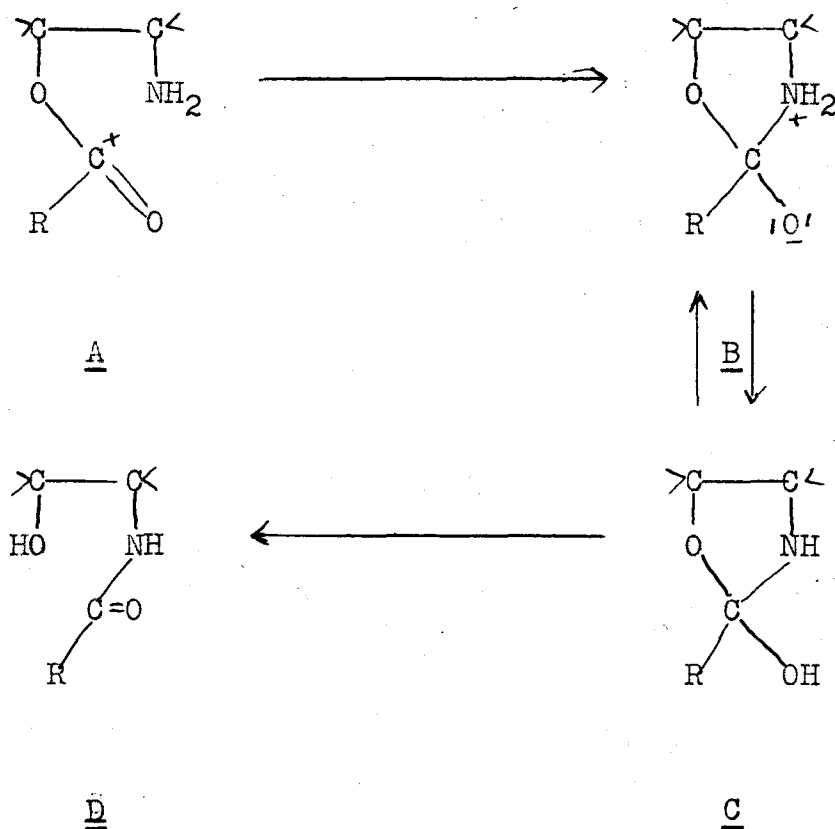
(47). The formation of a cyclic intermediate of similar
structure has been assumed previously by Bell, J.
Chem. Soc., 2966 (1931) in rearrangements of
acylated aminophenols.

In the aminoester, A, which formed as a result of
adding alkali to the ammonium salt, polarization of the
carbonyl group results in the attraction of the unshared
electrons of the nitrogen atom to carbonyl carbon. In the
cis-compound space relationships should be more favorable
than in the trans for the mutual approach of these two atoms
and the formation of a cyclic dipolar ion, B, the greater
speed of rearrangement of the cis- derivative may be attribut-
ed to this circumstance. Shift of a proton from nitrogen to
carbonyl oxygen gives unstable, cyclic alkali soluble ortho-
acid derivative, C. Rupture of the ester bond, perhaps by
hydrolysis, yields the alkali-insoluble hydroxyamide D.

In the preceeding pages I have attempted to cover, the
properties and reactions of the isocyanates, the reactions of
tris(hydroxymethyl)aminomethane and closely related compounds,
and some of the problems involved in acyl migration. For
a more thorough treatment of acyl migration or ester-amide
interchange see the thesis submitted to the graduate faculty
of the University of Richmond by Carl D. Lunsford, August 1950
entitled "TRIS(HYDROXYMETHYL)AMINOMETHANE: SUBSTITUTED 4-
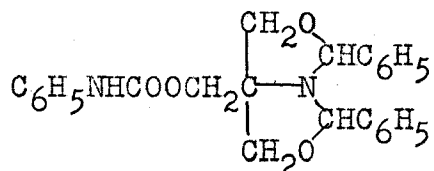HYDROXYMETHYL OXAZOLIDINES; ESTER-AMIDE INTERCHANGE".

EXPERIMENTAL

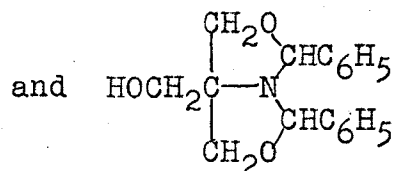1-Aza-2,8-diphenyl-5-hydroxymethyl-3,7-dioxabicyclo(3.3.0)octane(22)

$$HOCH_2C \begin{matrix} CH_2O \\ | \\ \\ | \\ CH_2O \end{matrix} N \begin{matrix} CHC_6H_5 \\ \\ CHC_6H_5 \end{matrix}$$
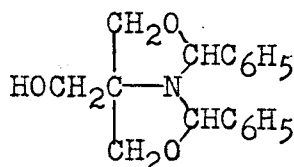
Reactants: C_6H_5CHO and $H_2N(CH_2OH)_3$

Procedure: To a mixture of 242 g. (2.0 mole) of tris—
(hydroxymethyl)aminomethane and 1000 ml. of benzene was added
424 g. (4.0 mole) of benzaldehyde. The resulting mixture was
refluxed overnight while 72 ml. of water was collected in a water
trap. The benzene was removed by distillation, under vacuum,
from a water bath and the residue was dissolved in ethyl alcohol.
Addition of water to the alcoholic solution threw out an oil
which crystallized on stirring with ice. This crude product
was recrystallized from cyclohexane and butyl ether. Yield:
535 g., 90%. Recrystallized from (a) cyclohexane, M.p. 93-95,
(b) butyl ether, M.p. 93-95°.

1-Aza-2,8-diphenyl-5-(N-phenylcarbamyloxymethyl)-3,7-dioxabicyclo (3.3.0)octane.
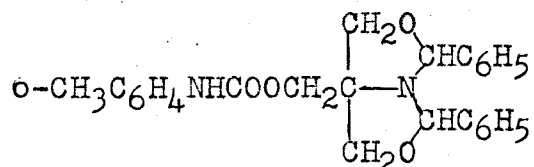
$$C_6H_5NHCOOCH_2C-N \begin{matrix} CH_2O \\ | \\ CH_2O \end{matrix} \begin{matrix} CHC_6H_5 \\ CHC_6H_5 \end{matrix}$$

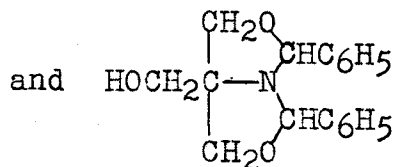Reactants: C_6H_5NCO and $HOCH_2C-N \begin{matrix} CH_2O \\ CH_2O \end{matrix} \begin{matrix} CHC_6H_5 \\ CHC_6H_5 \end{matrix}$

Procedure: Dissolved 14.85 g. (.05 mole) of 1-aza-2, 8-diphenyl-5-hydroxymethyl-3,7-dioxabicyclo(3.3.0)octane in 100 ml. of benzene, added 5.95 g. (.05 mole) of phenyl isocyanate and refluxed for fifteen hours. After cooling the solution was evaporated to low volume. To this solution 250 ml. of cyclohexane was added, and it was then heated to boiling. On cooling a heavy white precipitate was formed. Yield: 18.9 g., 91%. The product was recrystallized to a constant melting point from 95% ethanol.

1-Aza-2,8-diphenyl-5-(o-tolylcarbamyloxymethyl)-3,7-dioxabicyclo (3.3.0)octane.
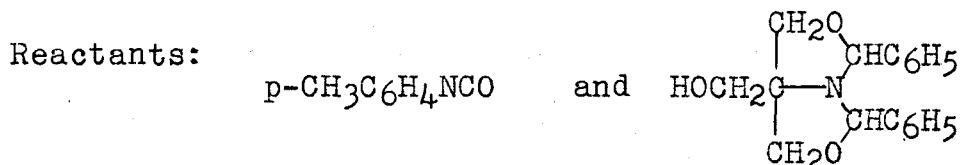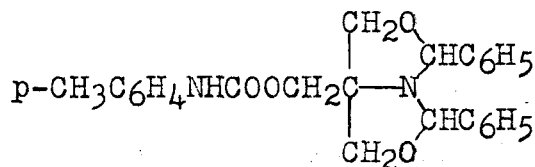
$$o-CH_3C_6H_4NHCOOCH_2C-N \begin{matrix} CH_2O \\ | \\ CH_2O \end{matrix} \begin{matrix} CHC_6H_5 \\ CHC_6H_5 \end{matrix}$$

Reactants: $o-CH_3C_6H_4NCO$ and $HOCH_2C-N \begin{matrix} CH_2O \\ CH_2O \end{matrix} \begin{matrix} CHC_6H_5 \\ CHC_6H_5 \end{matrix}$

Procedure: Dissolved 14.85 g. (.05 mole) of 1-aza-2,8-diphenyl-5-hydroxymethyl-3,7-dioxabicyclo(3.3.0)octane in 100 ml. of benzene, added 6.15 g. (.05 mole) of o-tolyl isocyanate and refluxed overnight. After cooling the solution was evaporated to low volume. Added 250 ml of cyclohexane, boiled until there was complete solution and allowed to cool. A flaky white precipitate formed. Yield: 14.9 g., 71%. The product was recrystallized to constant melting point from 95% ethanol.
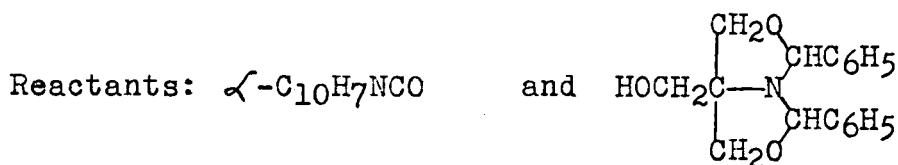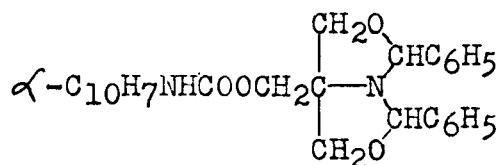
1-Aza-2,8-diphenyl-5-(N-p-tolylcarbamyloxymethyl)-3,7-dioxabicyclo(3.3.0)octane.

$$\text{p-CH}_3\text{C}_6\text{H}_4\text{NHCOOCH}_2\text{C} \overset{\overset{\displaystyle \text{CH}_2\text{O}}{|}}{\underset{\underset{\displaystyle \text{CH}_2\text{O}}{|}}{\text{—N}}} \overset{\displaystyle \text{CHC}_6\text{H}_5}{\underset{\displaystyle \text{CHC}_6\text{H}_5}{}}$$

Reactants: p-CH$_3$C$_6$H$_4$NCO   and $$\text{HOCH}_2\text{C} \overset{\overset{\displaystyle \text{CH}_2\text{O}}{|}}{\underset{\underset{\displaystyle \text{CH}_2\text{O}}{|}}{\text{—N}}} \overset{\displaystyle \text{CHC}_6\text{H}_5}{\underset{\displaystyle \text{CHC}_6\text{H}_5}{}}$$

Procedure: Dissolved 14.85 g. (.05 mole) of 1-aza-2,8-diphenyl-5-hydroxymethyl-3,7-dioxabicyclo(3.3.0)octane in 100 ml. of benzene, added 6.15 g. (.05 mole) of p-tolyl isocyanate and refluxed overnight. After cooling the solution was evaporated to low volume. Then 250 ml. of cyclohexane was added and the solution was heated until everything was dissolved. On cooling a white precipitate was formed. Yield: 14.5 g., 69%.
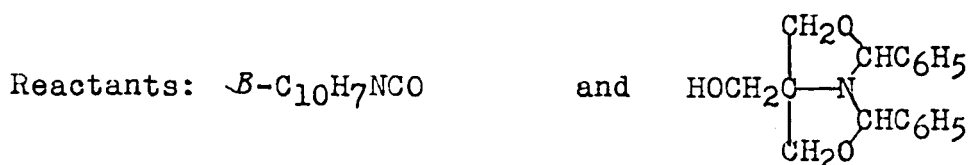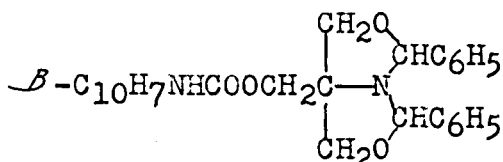
The product was recrystallized to a constant melting point
from 95% ethanol.

1-Aza-2,8-diphenyl-5-(N-αnaphthylcarbamyloxymethyl)-3,7-
dioxabicyclo(3.3.0)octane.

$$\alpha\text{-}C_{10}H_7NHCOOCH_2C \overset{\overset{\displaystyle CH_2O}{|}}{\underset{\underset{\displaystyle CH_2O}{|}}{-N}} \begin{matrix} CHC_6H_5 \\ \\ CHC_6H_5 \end{matrix}$$

Reactants: α-$C_{10}H_7NCO$ and $HOCH_2C \overset{\overset{\displaystyle CH_2O}{|}}{\underset{\underset{\displaystyle CH_2O}{|}}{-N}} \begin{matrix} CHC_6H_5 \\ \\ CHC_6H_5 \end{matrix}$

Procedure: Dissolved 14.85 g. (.05 mole) of 1-aza-
2,8-diphenyl-5-hydroxymethyl-3,7-dioxabicyclo(3.3.0)octane
in 100 ml. of benzene, added 8.45 g. (.05 mole) of α-naphthyl
isocyanate and refluxed overnight. On cooling a precipitate
formed. This precipitate was filtered and dried and its
weight was 8.4 g. M.p. 164-68. On several recrystallizations
from 95% alcohol the M.p. was 169-70°. The benzene solution
was evaporated to low volume, 250 ml. cyclohexane was added
and the solution was heated to boiling. On cooling a white
precipitate formed weighing 5.9 g.,m.p. 165-68°. Recrystalliza-
tion to constant melting point from 95% ethanol gave a compound
melting at 169-70° which proved to be identical to the one
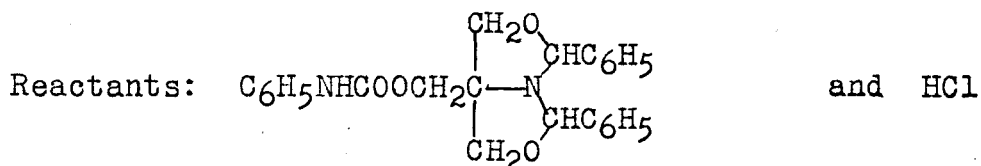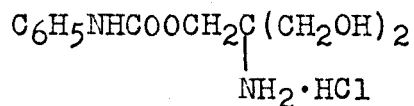obtained from the first step. Yield: 14.3g., 62%.

1-Aza-2,8-diphenyl-5-(N-β-naphthylcarbamyloxymethyl)-3,7-dioxabicyclo(3.3.0)octane.

$$\beta\text{-}C_{10}H_7NHCOOCH_2C\text{---}N \begin{array}{c} CH_2O \\[2pt] \\[2pt] CH_2O \end{array} \begin{array}{c} CHC_6H_5 \\[6pt] CHC_6H_5 \end{array}$$

Reactants: $\beta\text{-}C_{10}H_7NCO$ and $HOCH_2C\text{---}N \begin{array}{c} CH_2O \\ \\ CH_2O \end{array} \begin{array}{c} CHC_6H_5 \\ CHC_6H_5 \end{array}$

Procedure: Dissolved 14.85 g., (.05 mole) of 1-aza-2,8-diphenyl-5-hydroxymethyl-3,7-dioxybicyclo(3.3.0)octane in 100 ml. of benzene, added 8.45 g., (.05 mole) of β-naphthyl isocyanate, and refluxed for 10 hours. A precipitate formed during the reaction. When this precipitate was filtered and dried it weighed 1.1 g., and melted considerably above 250°C. This compound was identified as the symmetrical urea, formed from (β)-$C_{10}H_7NCO$.
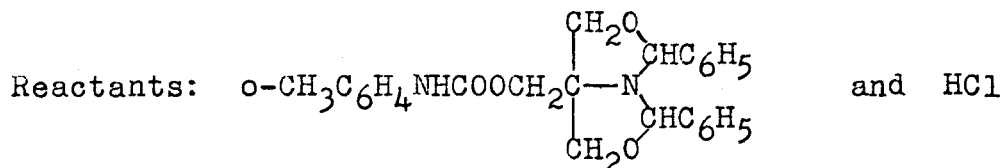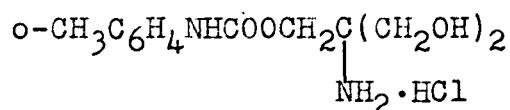
The benzene solution was evaporated to near dryness, 250 ml. of cyclohexane was added and the solution was heated to boiling. On cooling a white precipitate was formed. Yield: 8.8 g., 40%. The product was recrystallized to a constant melting point from 95% ethanol.
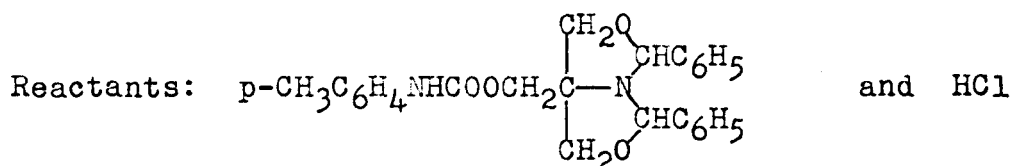
2-Amino-3-hydroxy-2-hydroxymethylpropyl-N-phenyl carbamate hydrochloride.

$$C_6H_5NHCOOCH_2C(CH_2OH)_2$$
$$NH_2 \cdot HCl$$

Reactants:
$$C_6H_5NHCOOCH_2C \overset{CH_2O}{\underset{CH_2O}{\begin{array}{c}\\ \end{array}}} N \overset{CHC_6H_5}{\underset{CHC_6H_5}{\begin{array}{c}\\ \end{array}}}$$
and HCl

Procedure: To a solution of 3.0 g., (.0072 mole) of 1-aza-2,8-diphenyl-5-(N-phenylcarbamyloxymethyl)-3,7-dioxabicyclo (3.3.0)octane in 25 ml. of absolute ethanol was added 1.5 ml. of concentrated hydrochloric acid. The solution was evaporated to near dryness on a hot plate. Then 20 ml. of cyclohexane was added and the solution again evaporated to low volume. On cooling a gummy mass formed which became crystalline on being stirred with dry ethyl ether. Yield: 1.7 g., 85%. The product was recrystallized from n-butanol.
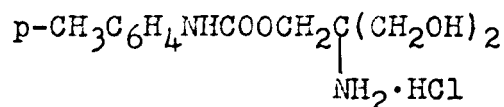
2-Amino-3-hydroxy-2-hydroxymethylpropyl-N-o-tolyl carbamate hydrochloride.
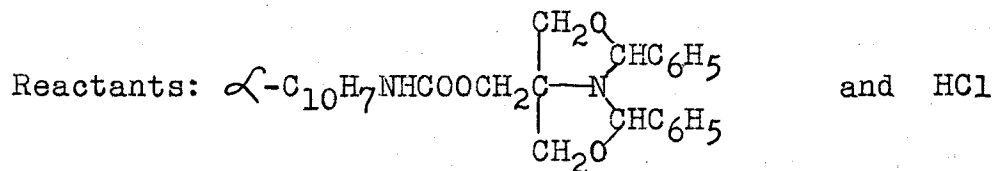
$$o\text{-}CH_3C_6H_4NHCOOCH_2C(CH_2OH)_2$$
$$NH_2 \cdot HCl$$

Reactants:
$$o\text{-}CH_3C_6H_4NHCOOCH_2C \overset{CH_2O}{\underset{CH_2O}{\begin{array}{c}\\ \end{array}}} N \overset{CHC_6H_5}{\underset{CHC_6H_5}{\begin{array}{c}\\ \end{array}}}$$
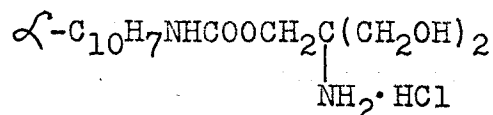and HCl

Procedure: To a solution of 2.8 g., (.0065 mole) of 1-aza-2,8-diphenyl-5-(N-o-tolylcarbamyloxymethyl)-3,7-dioxabicyclo (3.3.0)octane in 50 ml. of absolute ethanol was added 1.5 ml. of concentrated hydrochloric acid. The solution was evaporated to near dryness on the hot plate, 20 ml. of cyclohexane was added and the solution was again evaporated to low volume. On cooling a white crystalline precipitate formed. Yield: 1.85 g., 98%. The product was recrystallized from n-butanol.

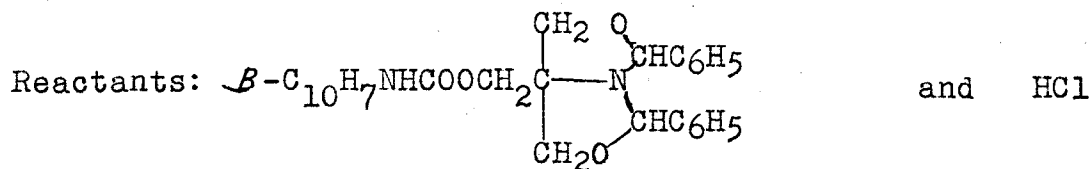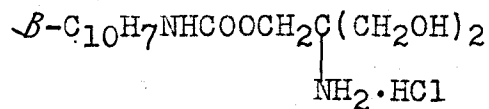2-Amino-3-hydroxy-2-hydroxymethylpropyl-N-p-tolyl carbamate hydrochloride.

$$p\text{-}CH_3C_6H_4NHCOOCH_2\underset{\underset{NH_2\cdot HCl}{|}}{C}(CH_2OH)_2$$

Reactants:
$$p\text{-}CH_3C_6H_4NHCOOCH_2C\overset{\overset{\displaystyle CH_2O}{|}}{\underset{\underset{\displaystyle CH_2O}{|}}{}}\!\!-\!\!N\overset{CHC_6H_5}{\underset{CHC_6H_5}{<}}$$
and HCl

Procedure: To a solution of 3.0 g., (.007 mole) of 1-aza-2,8-diphenyl-5-(N-p-tolylcarbamyloxymethyl)-3,7-dioxabicyclo (3.3.0)octane in 50 ml. of absolute ethanol was added 1.5 ml. of concentrated hydrochloric acid. The solution was evaporated to low volume on a hot plate, 20 ml. of cyclohexane was added and the solution was again evaporated to low volume. On cooling a yellowish white precipitate formed. Yield: 2.0 g., 99%. This product was recrystallized from n-butanol.

2-Amino-3-hydroxy-2-hydroxymethylpropyl-N-α-naphthyl carbamate hydrochloride.

$$\alpha\text{-C}_{10}\text{H}_7\text{NHCOOCH}_2\text{C(CH}_2\text{OH)}_2$$
$$\overset{|}{\text{NH}_2}\cdot\text{HCl}$$

Reactants: α-C$_{10}$H$_7$NHCOOCH$_2$C—N (with CH$_2$O–CHC$_6$H$_5$ and CH$_2$O–CHC$_6$H$_5$ ring) and HCl

Procedure: To a solution of 5.0 g., (.017 mole) of 1-aza-2,8-diphenyl-5-(N-α-naphthylcarbamyloxymethyl)-3,7-dioxabicyclo (3.3.0)octane in 75 ml. of absolute ethanol was added 2ml. of concentrated hydrochloric acid. The solution was evaporated to near dryness, 20 ml. of cyclohexane was added and the solution again evaporated to low volume. On cooling a gummy precipitate was formed which crystallized on stirring with dry ethyl ether. Yield: 3.0 g., 86%. The product was recrystallized from absolute ethanol-cyclohexane.

2-Amino-3-hydroxy-2-hydroxymethylpropyl-N-β-naphthyl carbamate hydrochloride.

$$\beta\text{-C}_{10}\text{H}_7\text{NHCOOCH}_2\text{C(CH}_2\text{OH)}_2$$
$$\overset{|}{\text{NH}_2}\cdot\text{HCl}$$

Reactants: β-C$_{10}$H$_7$NHCOOCH$_2$C—N (with CH$_2$O–CHC$_6$H$_5$ and CH$_2$O–CHC$_6$H$_5$ ring) and HCl

Procedure: To a solution of 3.0 g., (.0064 mole) of 1-aza-2,8-diphenyl-5-(N-β-naphthylcarbamyloxymethyl)-3,7-dioxabicyclo (3.3.0)octane in 50 ml. of absolute ethanol was added 2 ml. of concentrated hydrochloric acid. The solution was evaporated to low volume, 20 ml. of cyclohexane was added and the solution again was evaporated to low volume. On cooling a gummy precipitate was formed which crystallized on stirring with dry ethyl ether. Yield: 1.8 g., 84%. The compound was recrystallized from absolute ethanol-acetone.

8,8-Bis(hydroxymethyl)-7-aza-10-oxaspiro(5.4)decane (48).

Reactants:

and $H_2NC(CH_2OH)_3$
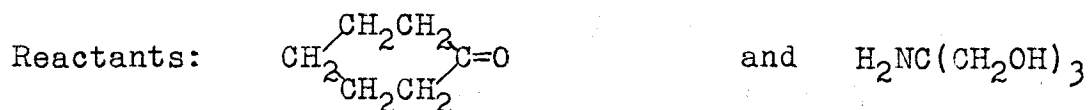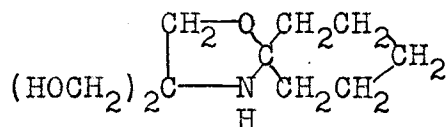
Procedure: To a mixture of 12.1 g., (0.1 mole) of tris(hydroxymethyl)aminomethane and 75 ml. of xylene was added 20 g., (0.2 mole) of cyclohexanone. The resulting mixture was refluxed 22 hours with a water separator. To the solution 150 ml. of acetone was added and then heated boiling

(48). Also prepared by R. W. Raiford, Jr., thesis submitted to the graduate faculty of the University of Richmond, September 1949 entitled "Some Reactions of Tris (hydroxymethyl)aminomethane."
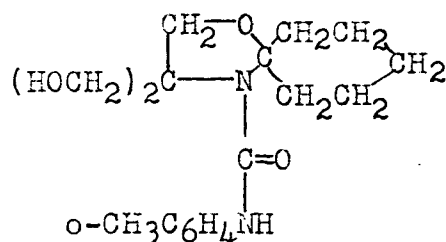
and filtered while hot. On cooling the filtrate, crystals
separated. These were filtered off and recrystallized from
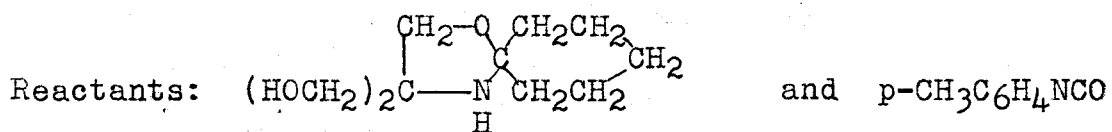anhydrous acetone. Yield: 12.6 g., 62.7%.

8,8-Bis(hydroxymethyl)-7-(phenylcarbamyl)-7-aza-10-oxaspiro
(5.4)decane.
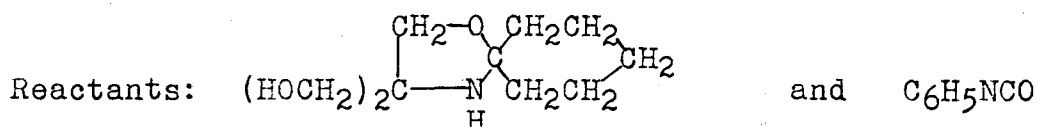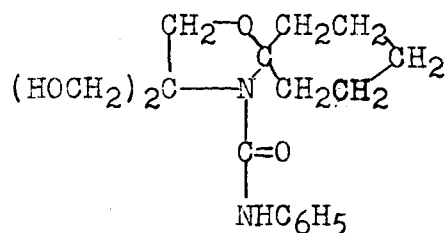
$$(HOCH_2)_2C \underset{\underset{\underset{\underset{NHC_6H_5}{C=0}}{|}}{|}}{---N}$$

Reactants: $(HOCH_2)_2C---N-H$ and C_6H_5NCO

Procedure: To a mixture of 10.15 g., (.05 mole) of
8,8-bis(hydroxymethyl)-7-aza-10-oxaspiro(5.4)decane and 200
ml. of benzene was added 5.9 g., (0.5 mole) of phenyl isocyanate.
This mixture was refluxed overnight and complete solution occured.
On cooling a fine white crystalline precipitate formed. Yield:
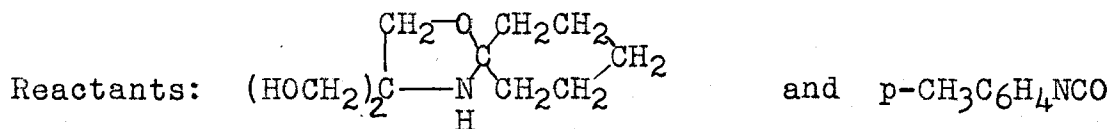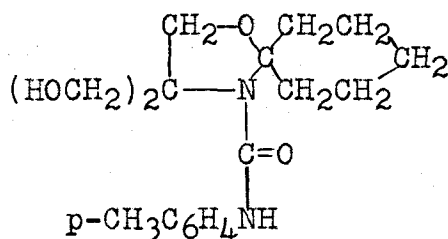11.6 g., 72%. This compound was recrystallized from benzene.

8,8-Bis(hydroxymethyl)-7-(o-tolylcarbamyl)-7-aza-10-oxaspiro
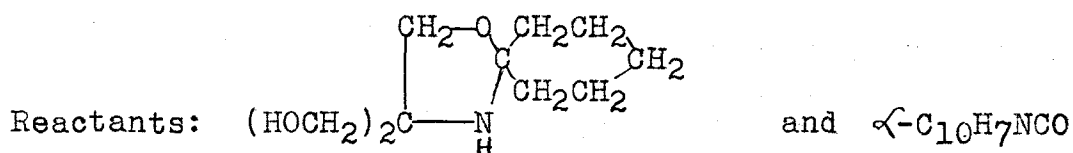(5.4)decane.

$$(HOCH_2)_2C---N \underset{\underset{\underset{o-CH_3C_6H_4NH}{C=0}}{|}}{}$$

Reactants: $(HOCH_2)_2C$——N (8,8-bis(hydroxymethyl)-7-aza-10-oxaspiro(5.4)decane structure) and p-CH$_3$C$_6$H$_4$NCO
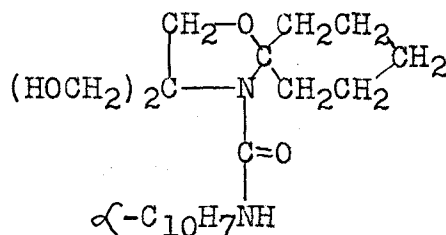
Procedure: To a mixture of 10.15 g., (.05 mole) of 8,8-bis(hydroxymethyl)-7-aza-10-oxaspiro (5.4)decane and 200 ml. of benzene was added 6.67 g., (.05 mole) of o-tolyl isocyanate. This mixture was refluxed overnight. On cooling a fine white precipitate was formed. Yield: 9.3 g., 55%. The product was recrystallized from butyl ether.

8,8-Bis(hydroxymethyl)-7-(p-tolylcarbamyl)-7-aza-10-oxaspiro (5.4)decane.

$(HOCH_2)_2C$——N (structure with C=O and p-CH$_3$C$_6$H$_4$NH)

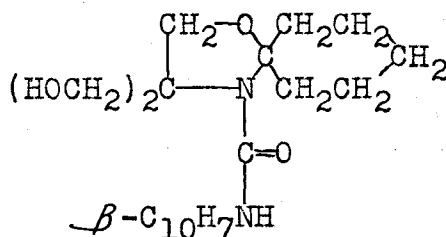Reactants: $(HOCH_2)_2C$——N (structure) and p-CH$_3$C$_6$H$_4$NCO

Procedure: To a mixture of 10.15 g., (.05 mole) of 8,8-bis(hydroxymethyl)-7-aza-10-oxaspiro(5.4)decane and 200 ml. of benzene was added 6.15 g., (.05 mole) of p-tolyl isocyanate. This mixture was refluxed for 5½ hours with a considerable amount of bumping being involved. On cooling and standing for several hours a white precipitate formed. Yield: 12.6 g., 77%. The product was recrystallized from butyl ether.
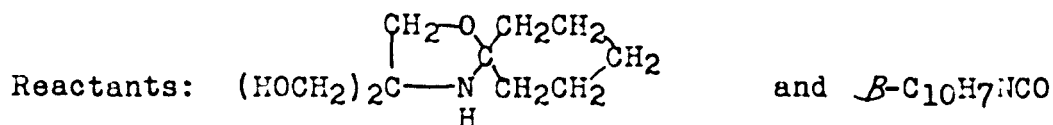

Reactants: $(HOCH_2)_2C$——N ... and $\beta\text{-}C_{10}H_7NCO$
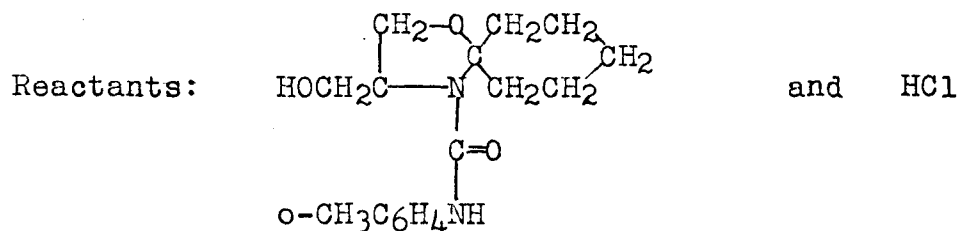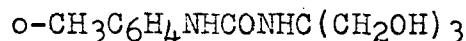
Procedure: To a mixture of 10.15 g., (.05 mole) of 8,8-bis(hydroxymethyl)-7-aza-10-oxaspiro(5.4)decane and 200 ml. of benzene was added 8.45 g., (.05 mole) of β-naphthyl isocyanate. This mixture was refluxed for 8 hours. On cooling a white precipitate formed. Yield: 17.0 g., 91%. This product was recrystallized from butyl ether.

N-Phenyl-N'-tris(hydroxymethyl)methylurea.

$$C_6H_5NHCONHC(CH_2OH)_3$$

Reactants: HOCH₂C——N ... and HCl
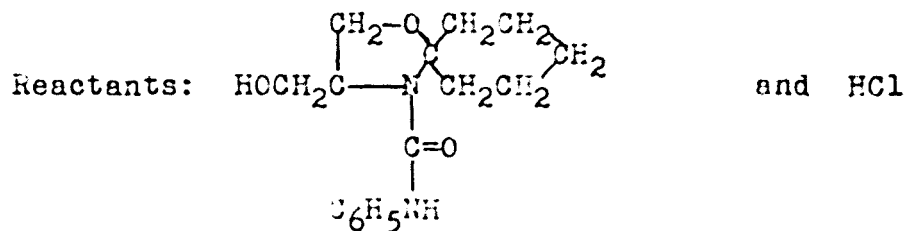
Procedure: To a solution of 3.0 g., (0.1 mole) of 8,8-bis(hydroxymethyl)-7-(phenylcarbamyl)-7-aza-10-oxaspiro(5.4) decane in 50 ml. of absolute alcohol was added 2 ml. of concentrated hydrochloric acid. The solution was evaporated to low volume, 25 ml. of cyclohexane was added and the solution again was evaporated to a low volume, and a precipitate formed immediately. Yield: 2.0 g., 85%. The product was recrystallized from 95% ethanol.

N-o-Tolyl-N'-tris(hydroxymethyl)methlurea.

$$o-CH_3C_6H_4NHCONHC(CH_2OH)_3$$

Reactants:

$$HOCH_2C \underset{\underset{o-CH_3C_6H_4NH}{\overset{|}{\underset{C=O}{|}}}}{-N} \overset{CH_2-O}{\underset{CH_2CH_2}{\overset{|}{C}}} \overset{CH_2CH_2}{\underset{CH_2CH_2}{}}CH_2$$
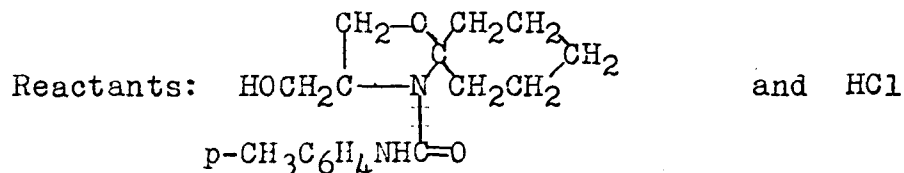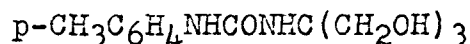
and   HCl

Procedure: To a solution of 2.0 g., (.006 mole) of 8,8-bis(hydroxymethyl)-7-(o-tolylcarbamyl)-7-aza-10-oxaspiro(5.4) decane in 50 ml. of absolute ethanol was added 2 ml. of concentrated hydrochloric acid. The solution was evaporated to low volume, 20 ml. of cyclohexane was added and it was again evaporated to low volume. On cooling a gum formed which crystallized on stirring with dry ethyl ether. Yield: 1.4 g., 93%. The product was recrystallized from n-butanol.

N-p-Tolyl-N'-tris(hydroxymethyl)methylurea.

$$p-CH_3C_6H_4NHCONHC(CH_2OH)_3$$

Reactants:

$$HOCH_2C \underset{\underset{p-CH_3C_6H_4NHC=O}{|}}{-N} \overset{CH_2-O}{\underset{CH_2CH_2}{\overset{|}{C}}} \overset{CH_2CH_2}{\underset{CH_2CH_2}{}}CH_2$$
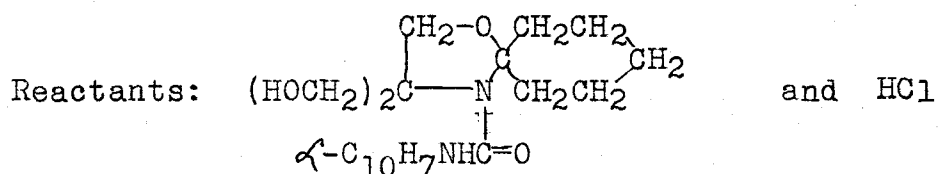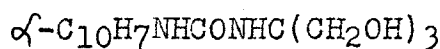
and   HCl

Procedure: To a solution of 2.0 g., (.006 mole) of 8,8-bis(hydroxymethyl)-7-(p-tolylcarbamyl)-7-aza-10-oxaspiro(5.4)
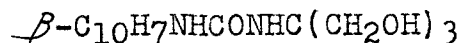
decane in 50 ml. of absolute ethanol was added 2 ml. of concentrated hydrochloric acid. The solution was evaporated to low volume and 20 ml. of cyclohexane was added and it was again evaporated to low volume. On cooling a gum formed which crystallized on stirring with dry ethyl ether. Yield: 1.3 g., 86%. The precipitate was recrystallized from n-butanol.

N-α-Naphthyl-N'-tris(hydroxymethyl)methylurea.

$$\alpha\text{-}C_{10}H_7NHCONHC(CH_2OH)_3$$

Reactants:
$$(HOCH_2)_2C\begin{matrix} CH_2-O \\ | \\ \text{---N} \end{matrix}\begin{matrix} CH_2CH_2 \\ C \\ CH_2CH_2 \end{matrix}CH_2$$
$$\alpha\text{-}C_{10}H_7NHC{=}O$$
and   HCl

Procedure: To a solution of 5.0 g., (.013 mole) of 8,8-bis(hydroxymethyl)-7-(α-naphthylcarbamyl)-7-aza-10-oxaspiro (5.4)octane in 50 ml. of absolute ethanol was added 2 ml. of concentrated hydrochloric acid and it was evaporated to low volume. Added 20 ml. of cyclohexane and again evaporated to low volume. On cooling a white crystalline precipitate formed. Yield: 3.6 g., 92%. This product was recrystallized from n-butanol.

N-β-Naphthyl-N'-tris(hydroxymethyl)methylurea.

$$\beta\text{-}C_{10}H_7NHCONHC(CH_2OH)_3$$

Reactants: (HOCH$_2$)$_2$C——N CH$_2$CH$_2$ CH$_2$ ... and HCl

$$CH_2-O \quad CH_2CH_2$$

with β-C$_{10}$H$_7$NHC=O
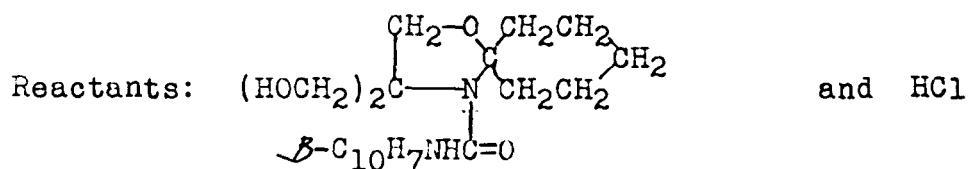
Procedure; To a solution of 2.0 g., (.006 mole) of 8,8-bis(hydroxymethyl)-7-(β-naphthylcarbamyl)-7-aza-10-oxaspiro (5.4)octane in 50 ml. of absolute ethanol was added 1 ml. of concentrated hydrochloric acid and it was evaporated to low volume. Added 20 ml. of cyclohexane and again evaporated to low volume. On cooling a white crystalline precipitate formed. Yield: 1.3 g., 91%. This compound was recrystallized from n-butanol.
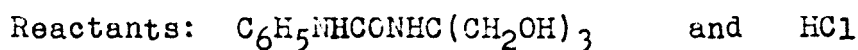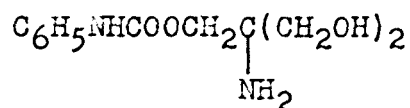
2-Amino-3-hydroxy-2-hydroxymethylpropyl-N-phenyl.carbamate.

$$C_6H_5NHCOOCH_2C(CH_2OH)_2$$
$$NH_2$$

Reactants: C$_6$H$_5$NHCONHC(CH$_2$OH)$_3$ and HCl

Procedure: Dissolved 5.0 g., (.021 mole) of N-phenyl-N'-tris(hydroxymethyl)methylurea in 75 ml. of concentrated hydrochloric acid and evaporated the solution to low volume. Added 25 ml. of water to above solution and neutralized with concentrated sodium hydroxide. On cooling in an ice bath a shiny tan precipitate formed. The product was recrystallized from water m.p. 166-67°. Yield: 3.3 g., 66%. Analysis: Nitrogen %, calcd. 11.67, found 11.84.

TABULATED RESULTS

1-Aza-2,8-diphenyl-5-(N-arylcarbamloxymethyl)-3,7-dioxabicyclo (3.3.0)octanes.

$$\text{ArNHCOOCH}_2\text{C} \overset{\overset{\displaystyle CH_2-O}{|}}{\underset{\underset{\displaystyle CH_2-O}{|}}{}} \text{N} \overset{\displaystyle CHC_6H_5}{\underset{\displaystyle CHC_6H_5}{}}$$
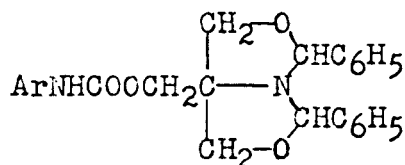
Ar	M.p. °C (uncor.)	Yield %	Nitrogen, % Calcd.	Found
C_6H_5	132-33°	91	6.75	6.65
$o\text{-}CH_3C_6H_4$	166-67	71	6.52	6.71
$p\text{-}CH_3C_6H_4$	137-38	69	6.52	6.49
$\alpha\text{-}C_{10}H_7$	169-70	62	6.01	5.91
$\beta\text{-}C_{10}H_7$	198-99	39	6.01	6.26

2-Amino-3-hydroxy-2-hydroxymethylpropyl-N-aryl carbamate hydrochlorides.

$$ArNHCOOCH_2C(CH_2OH)_2$$
$$NH_2 \cdot HCl$$
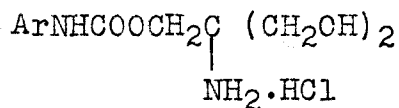
Ar	M.p. °C (uncor.)	Yield %	Chloride, % Calcd.	Found
C_6H_5	207-08	85	12.68	12.69
$o\text{-}CH_3C_6H_4$	190-92	98	12.41	12.20
$p\text{-}CH_3C_6H_4$	200-01	99	12.41	12.35
$\alpha\text{-}C_{10}H_7$	128-30	86	10.74	10.90
$\beta\text{-}C_{10}H_7$	159-61	84	10.74	10.56

8,8-Bis(hydroxymethyl)-7(arylcarbamyl)-7-aza-10-oxaspiro (5.4)decanes.
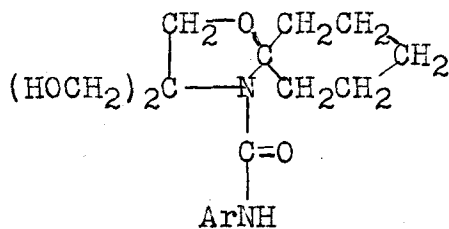
Ar	M.p. °C (uncor.)	Yield %	Nitrogen, % Calcd.	Found
C_6H_5	180–81	72	8.73	8.83
o-$CH_3C_6H_4$	178–79	55	8.33	8.37
p-$CH_3C_6H_4$	179–80	77	8.33	8.44
α-$C_{10}H_7$	190–92	84	7.53	7.68
β-$C_{10}H_7$	203–05	91	7.53	7.66

N-Aryl-N'-tris(hydroxymethyl)methylureas.

$$ArNHCONHC(CH_2OH)_3$$
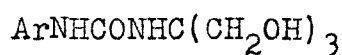
Ar	M.p. °C (uncor.)	Yield %	Mixed M.p. [*]
C_6H_5	193–94	86	192–95
o-$CH_3C_6H_4$	193–95	93	190–93
p-$CH_3C_6H_5$	191–93	86	191–94
α-$C_{10}H_7$	212–14	92	210–13
β-$C_{10}H_7$	200–01	91	200–02

[*] Also prepared by R. W. Raiford Jr., (48).

DISCUSSION OF RESULTS

The insolubility of tris(hydroxymethyl)aminomethane
(A) in inert solvents makes controlled reactions with it
difficult to perform. Monourethans and monoureas are made
by locking up two or three of its functional groups in ring
formation with aldehydes or ketones, reacting the unbound
alcohol or amino groups with aryl isocyanates and hydrolyzing
the products formed.

Generally, the 1-aza-2,8-diphenyl-5-(N-aryl-carbamyloxy-
methyl)-3,7-dioxybicyclo(3.3.0)octanes were prepared when a
solution of 1-aza-2,8-diphenyl-5-hydroxymethyl-3,7-dioxybicyclo
(3.3.0)octanes were mixed with an aryl isocyanate in a 1:1
ratio and refluxed overnight in benzene solution.

The hydrolysis of the above octanes yielded the 2-
amino-3-hydroxy-2-hydroxymethylpropyl-N-arylcarbamate hydro-
chloride. To date only one of these hydrochlorides has been
converted to the urethan free base. The N-phenyl urethan
hydrochloride was dissolved in absolute ethanol and sodium
ethoxide was added until the solution was basic. A precipitate

formed which proved to be almost entirely sodium chloride.
The product was thrown out of the absolute ethanol solution
with cyclohexane. The precipitate formed was analyzed un-
purified and the nitrogen analysis was about one percent,
below the calculated value. Subsequent attempts to repeat
this experiment were unsuccessful. Failure to isolate these
urethan free bases may be partially explained by Rider's
statement (15) that mono-urethans are decomposed by alkali
before they can be isolated. Because of this fact most mono-
urethans are isolated only as the hydrochlorides.

In an attempt to form the hydrochlorides of the bicyclic
urethans the products isolated proved to be urethan hydro-
chlorides of (A).

The cyclic ureas were formed by refluxing a mixture
of one equivalent of 8,8-bis(hydroxymethyl)-7-aza-10-oxaspiro
(5.4)decane and one equivalent of an aryl isocyanate in
benzene. On hydrolysis these cyclic ureas gave the N-sub-
stituted-N'-tris(hydroxymethyl)methylureas which were also
prepared by R. W. Raiford Jr., (48).

The attempts to convert the ureas to urethans were un-
successful except in the case of the N-phenyl-N'-tris(hydroxy-
methyl)methylurea. Other members of this series decomposed
to give the corresponding aryl amines. Attempts to rearrange
the ureas according to the method of Hancock and Cope (6) yield-
ed the unchanged urea. This method involved the heating of the

urea in a chloroform solution saturated with dry hydrogen
chloride for seventy hours at a temperature of 55°C. It
is probable that most of the hydrogen chloride escaped from
the solution before the seventy hours passed.

In an attempt to prepare the acetal of (A) the product
isolated gave a nitrogen analysis and several derivatives
corresponding to the bicyclic compound described in the ex-
perimental section. The former compound was prepared as
follows: A mixture of 242 g., (2 moles) of (A) and 212 g.,
(2 moles) of benzaldehyde were dissolved in 600 ml. of glacial
acetic acid and the mixture was allowed to stand for forty
hours. The acetic acid was removed on a water bath under
vacuum. The residue was made alkaline with concentrated
potassium hydroxide, forming an oil. The aqueous layer was
extracted with ethyl ether, combined with the oil and dried
for ten hours over potassium carbonate. The ether was re-
moved on a water bath and then the benzaldehyde was removed
under a pressure of 3 mm. The product distilled at 210-12°C
under a pressure of 2 mm. The distillate was a thick oil which
became semi-solid on standing for several days. Yield: 140 g.,
30%. When the above compound was reacted with an equivalent
quantity of β-naphthyl isocyanate two products, were isolated.
One product which melted at 198-99° corresponded to the
bicyclic urethan prepared from the crystalline bicyclic octane,
m.p. 77-78°. The other product melted at 129-30°. The high

melting product was isolated from the benzene solution, after

cooling the reaction mixture. The low melting compound was

thrown out of the benzene solution, by cyclohexane, after

being evaporated to low volume. When the two products are

hydrolyzed they both give chloride analyses corresponding to

2-amino-3-hydroxy-2-hydroxymethyl-N-β-naphthylcarbamate *propyl*

hydrochloride. This along with other evidence leads us to

believe that the two compounds are stereoisomers.

Analyses of the products described in the preceding

section were made by the Dumas method for nitrogen. Some of

the chloride analyses were made by the Volhard method, others

by the Fajans.

SUMMARY

The preparation of some derivatives of tris(hydroxymethyl) aminomethane is described. The compounds reported are: five 1-aza-2,8-diphenyl-5-(N-arylcarbamyloxymethyl)-3,7-dioxybicyclo (3.3.0)octanes, five 2-amino-3-hydroxy-2-hydroxymethyl-propyl-N-arylcarbamate hydrochlorides, five 8,8-bis(hydroxy-methyl)-7-(arylcarbamyl)-7-aza-10-oxaspiro(5.4)decanes, five N-aryl-N'-tris(hydroxymethyl)omethylureas (48) and 2-amino-3-hydroxy-2-hydroxymethylpropyl-N-phenyl-carbamate.

BIBLIOGRAPHY

Adams, Long, Johanson, J. Am. Chem. Soc. $\underline{61}$, 2342 (1939).

Adams and Segur, Science $\underline{52}$, 185 (1920).

Adams and Pierce, J. Am. Chem. Soc. $\underline{45}$, 790-95 (1923).

Baker and Gaunt, J. Chem. Soc. (1949) 9-18.

Billman and Parker, J. Am. Chem. Soc. $\underline{67}$, 1067-70 (1945).

Boese and Major, J. Am. Chem. Soc. $\underline{57}$, 175-76 (1935).

Charlton and Day, J. Org. Chem. Vol I, 552-8.

Cooke and Rider, J. Am. Chem. Soc. $\underline{58}$, 1079-81 (1936).

Cope, U. S. 2,456,555, Dec. 14, 1948; C. A. $\underline{43}$, 2639 (1949).

Cope and Hancock, J. Am. Chem. Soc. 66, 1448-1452 (1944).

Dean and Stark, Ind. Eng. Chem. 12, 486 (1920).

Desnuelle and Casal, Biochim et Biophys. Acta 2, 64-75
    (1948); C. A. 43, 2944 (1949).

Donleavy and English, J. Am. Chem. Soc. 62, 218-19 (1940).

Fodor and Kiss, Nature 164, 917 (1949).

Fodor and Kiss, J. Am. Chem. 72, 3495 (1950).

Fort and McLean, J. Chem. Soc. (1948) 1902.

Frush and Isbell, Bur. Standards J. Research 27, 413 (1941).

Glasstone and Scharmn, J. Am. Chem. Soc. 69, 1213-14 (1947).

Hancock and Cope, J. Am. Chem. Soc. 66, 1738-47 (1944).

Hodgins and Hovey, U. S. 2,215,038, Sept. 17, 1940; C. A. 35,
    830 (1941).

Homeyer, U. S. 2,399,118, April 23, 1946.

McCasland, Clark and Carter, J. Am. Chem. Soc. 71, 637 (1949).

Ogata, J. Pharm. Soc. Japan 456, 81 (1920).

Phillips and Baltzly, J. Am. Chem. 69, 200 (1947).

Pierce, Lunsford, Raiford, Rush and Wiley - unpublished work.

Pierce, Murphy and Shaia, J. Am. Chem. Soc. 71, 1765 (1949).

Pierce and Wotiz, J. Am. Chem. Soc. 66, 879-881 (1944).

Piloty and Ruff, Berichte 30, 2062 (1897).

Ransom, Ber. 31, 1055 (1898).

Rider, Can. 353,743, October 29, 1935; C. A. 30, 2325.

Rider, J. Am. Chem. Soc. 52, 2115 (1930).

Rosenmund, Ger. 676,049, May 25, 1939; C. A. 33, 6529.

Saunders and Slocombe, Chem. Rev. 43, 203-18 (1948).

Senkus, J. Am. Chem. Soc. 67, 1515 - 1519 (1945).

Tilford, Van Campen and Shelton, J. Am. Chem. Soc. 69,
    2902-6 (1947).

Tyron, U. S. 2,410,318, October 29, 1946; C. A. 41, 2076
     (1947).

Valco, U. S. 2,416,552, Feb. 25, 1947; C. A. 41, 3823.

Wiese and Jones, J. Am. Pharm. Soc. Sci. Ed. 37, 380-81.

Winstein and Boschan, J. Am. Chem. Soc. 72, 4669 (1950).

AUTOBIOGRAPHY

I, Julian Lee Rush Jr., was born on December 2, 1922, in Richmond, Virginia. My early education was received in the public schools of that city and I graduated from Thomas Jefferson High School in February, 1940. I went to work as a freight rate clerk for the R. F. & P. railroad and remained there for sixteen months. I left this job to accept a position as a chemical technician in the Research Laboratory of The American Tobacco Company. I left the employment of the American Tobacco Company after two years to enter the United States Army Air Force.

I entered the University of Richmond in February, 1946. I completed my requirements for a B.S. degree in chemistry at this institution in August, 1948. I was employed as an instructor in chemistry at the University of Richmond for the academic year 1948-49.

I remained at the University to work for the M.S. degree for which this thesis is submitted as a partial requirement.