CHAPTER I

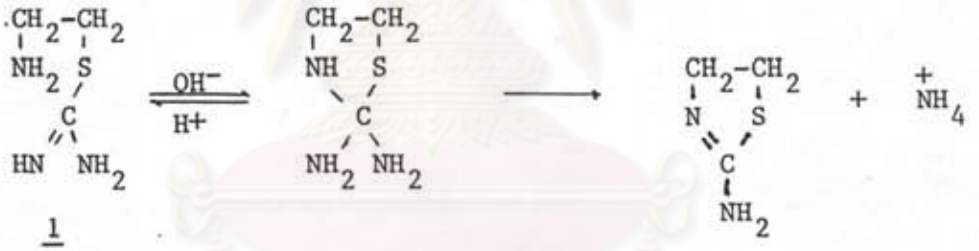
INTRODUCTION

1. A Review on 2-Amino-2-thiazoline

1.1 Chemical Synthesis of 2-Amino-2-thiazoline

There have been numerous reports concerning the synthesis of 2-amino-2-thiazoline as follows:

1.1.1 The conversion of S-(2-aminoethyl) isothiourea 1 which was dependent on pH and time[8-14].



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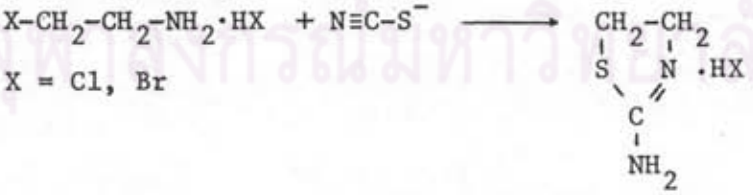
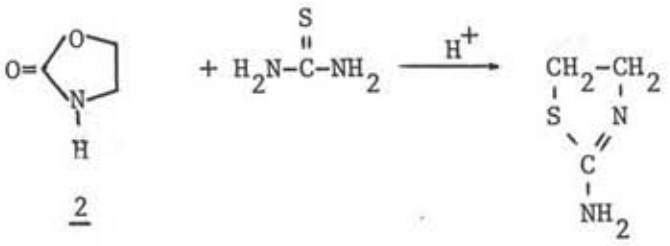
1.1.2 The reaction of either 2-chloroethylamine hydrochloride or 2-bromoethylamine hydrobromide with a thiocyanate[15-19].



X = Cl, Br

1.1.3 The reaction of thiourea with oxazolid-2-one 2 in the presence of acid e.g. HCl, p-$MeC_6H_4SO_3H$ and HBr[20].



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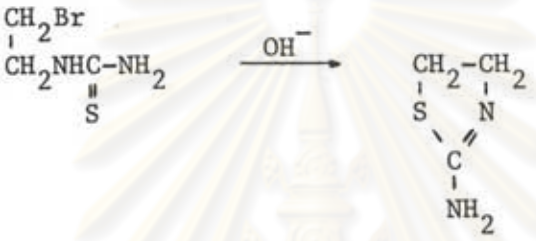
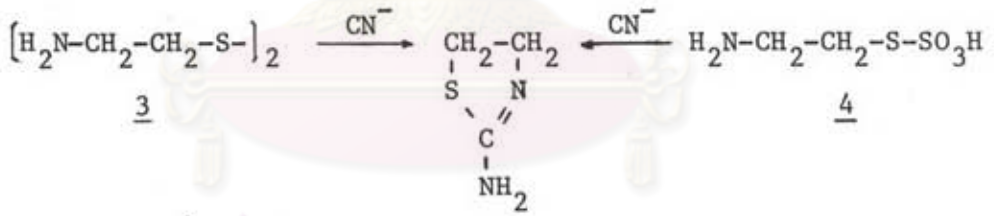
1.1.4 The reaction of 2-bromoethylthiourea with caustic soda solution[19,21].



1.1.5 The action of cyanide ion on cystamine 3[22] or 2-aminoethanethiosulfuric acid 4[23-25].



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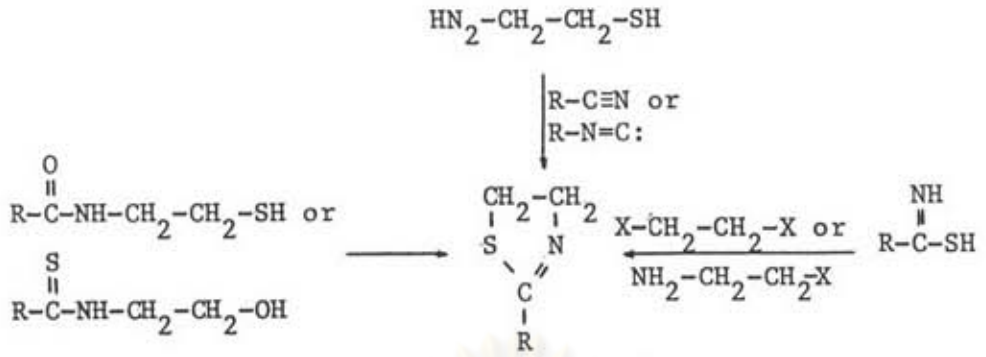
In addition, the synthesis of 2-acyl- and 2-alkyl-2-thiazolines has been classified into three categories[26]:

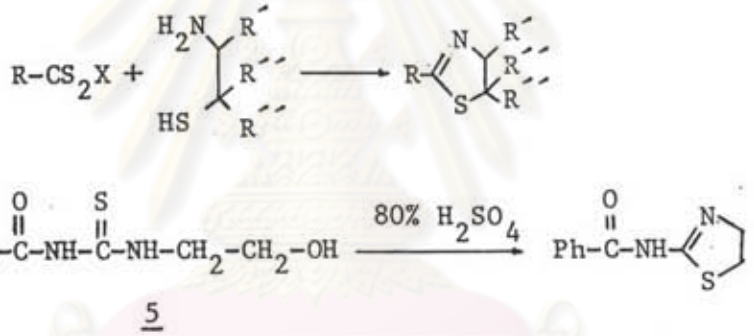
A) condensation of nitriles (R-C≡N) or isonitriles (R´-N=C:) with 2-aminoethane thiol ($H_2N-CH_2-CH_2-SH$).

B) dehydration of N-acyl-2-aminoethane thiols ($R-\overset{O}{\overset{\|}{C}}-NH-CH_2-CH_2-SH$) or N-thioacyl-2-aminoethanols ($R-\overset{S}{\overset{\|}{C}}-NH-CH_2-CH_2-OH$).

C) condensation of thioamides or iminothiazoles [R-(C=NH)SH] with 1, 2-dihalides ($X-CH_2-CH_2-X$) or 2-haloethylamines ($H_2N-CH_2-CH_2-X$) where R and R´ = alkyl, aryl or H and X = Br or Cl.



The single-step syntheses of 2-substituted-2-thiazolines were also reported by the condensation of dithioates with the corresponding 2-aminoethane thiols under slightly alkaline media[26] and also by cyclization of 1-benzoyl-3-(2-hydroxyethyl)-2-thiourea 5 with 80% H_2SO_4[27].



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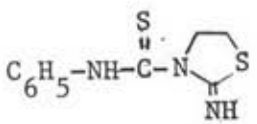
1.2 Chemical Reactions of 2-Amino-2-thiazoline

2-Amino-2-thiazoline and its derivative undergoes a number of reactions depending on the reactants and conditions:

1.2.1 with phenylisothiocyanate in ethanol "under strong cooling" gave 2-imino-3-phenylthiocarbamoylthiazolidine 6 according to Fromm and Kapeller-Adler[28].



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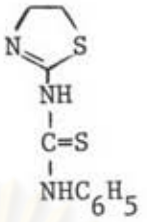
However, the careful repetition of this reaction either at 0-4°C or at reflux temperature, gave 2-phenylthiureido-2-thiazoline 7[28-30].



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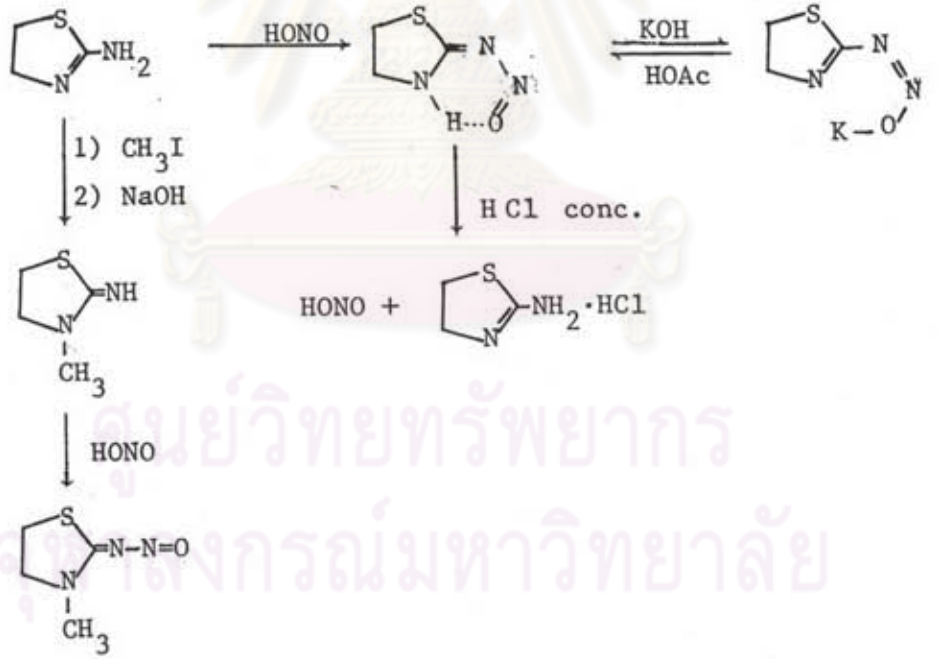
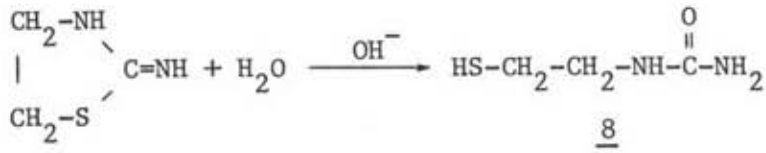
1.2.2 with nitrous acid produced several products as shown in the Scheme I[29,31].

Scheme I The reaction of 2-amino-2-thiazoline with nitrous acid.



1.2.3 under hydrolysis resulted in the formation of 2-mercaptoethylurea 8 [23,32].



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1.2.4 with metal ions. It was found that 2-amino-2-thiazoline was not a powerful coupling ligand with Ca, Mg, Mn, Ni, Cu and Zn metal ions. The amino group is the role electron donor involving in the complexation [33].

1.3 Pharmacological Uses of 2-Amino-2-thiazoline

1.3.1 As an antitumour agent. 2-Amino-2-thiazoline as well as its salts, in injection or tablet form, have been used for the treatment of neoplastic disease [34]. Clinical experiments on humans showed complete remission in certain tumor systems [35]. The metal complexing proporties of 2-amino-2-thiazoline hydrochloride with Mg^{2+}, Ca^{2+}, Ni^{2+}, Mn^{2+}, Cu^{2+} and Zn^{2+} have also been investigated and reported to be a new type of anticancer agent [36].

1.3.2 As a potential radioprotective agent. The organic and inorganic salts of 2-aminothiazoline were synthesized as potential protective agents against radiation injury. Some of organic salts tested, such as 2-aminothiazoline adipate, succinate, cinnamate, nicotinate, were less toxic than inorganic salts [37]. 2-Aminothiazoline was found to be a metabolite of S-(2-aminoethyl) isothiouronium bromide hydrobromide [38,39], and a precursor for the preparation of mercaptoethylguanidine. It is interesting to note that mercaptoethylguanidine which was the starting material for the preparation of 2-amino-2-thiazoline in our investigation, has also been reported to be protective against ionizing radiation [3-7].

It was believed that those mercaptoalkylguanidines which were capable of forming five and six membered cyclic intermediates will be the most active protective agents[11]. However, a more recent report argued that the radioprotective activity was not necessarily related to the formation of mercaptoalkylguanidines[38]. No significant transfomation into mercapto-alkylureas was found in the metabolism of 2-amino-2-thiazoline in mice[40].

Other biological activities of its derivatives and analogues have been reported in numerous literatures as antiradiation agents[41,42], antituberculosis[43], antiparasitic agents[44,45], antitumor agents[46], and antibody reducer[47,48]. Generally speaking the thiazole, isothiazole, thiazoline and thiazolidine ring condensed on several positions of the steroidal skeleton, has shown great interest due to the physiological properties[18].

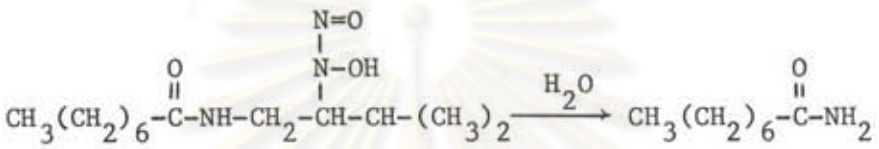
1.3.3 As an antiinflammatory, analgesic and antipyretic agents. Thiazolinobutazone was tested and found to be the only one, among the six substituted ammonium salts of phenylbutazone, more active as an antiinflammatory, analgesic and antipyretic but less toxic and less ulcerogenic than phenylbutazone[49]. Other derivatives and analogues on such activities were also reported[50-52].

2. A Review on Aliphatic primary amides

2.1 Chemical Synthesis of Aliphatic primary amides

There are several ways to make aliphatic primary amides.

2.1.1 The hydrolysis of N-(2-N-nitrosohydroxylamino-3-methylbutyl) octanamide 9, produced one of the aliphatic primary amides made in their investigation namely n-octanoylamide[53].



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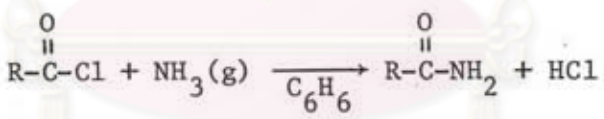
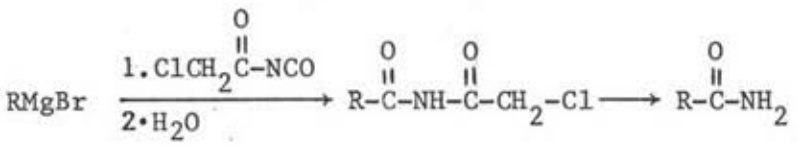
2.1.2 The reaction of acid chlorides with dry gaseous ammonia in anhydrous benzene[54], which is a general way to make the B-series compounds.



2.1.3 The reaction of a Grignard reagent with chloroacetylisocyanate. The initially isolated product is the imide 10. Hydrolytic or reductive removal of the chloroacetyl group affords the unsubstituted amides. Experimental procedures for each of these transformations are as follows[55]:



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2.1.4 The hydration of nitriles with Ni as a catalyst. It is notably important that the hydration of nitriles is effected in water without any acid, alkali or hydrogen peroxide and that it is generally stopped at the amide stage[56].

$$RC{\equiv}N \xrightarrow{H_2O,\ Ni} R{-}\overset{O}{\overset{\|}{C}}{-}NH_2$$

2.1.5 The transformation of normal aliphatic ketone by the reaction mixture of sulfur, ketone, dioxane, ammonium polysulfide at 165-170°C which is called Willgerodt reaction[57-61].

$$R{-}\overset{O}{\overset{\|}{C}}{-}CH_3 \xrightarrow{NH_4SS_x} R{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}NH_2$$

2.1.6 The dehydration of the ammonium salt of the corresponding acids, which is called Hofmann reaction[62].

$$R{-}\overset{O}{\overset{\|}{C}}{-}O^{-}\overset{+}{N}H_4 \xrightarrow{\Delta} R{-}\overset{O}{\overset{\|}{C}}{-}NH_2$$

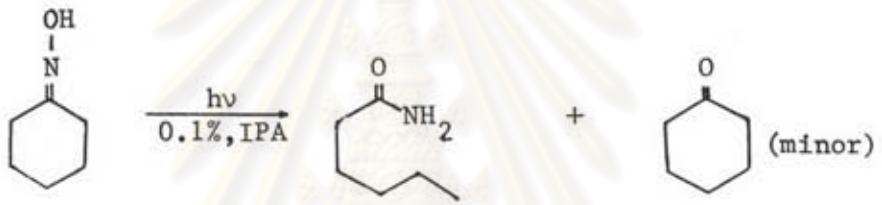
2.1.7 The hydrolysis of aldoximes. The reaction appears to be a base-catalyzed dehydration of the aldoximes to the corresponding nitriles followed by hydrolysis of the nitriles, through amides, to their acids. This sequence is borne out by the detection of both the nitrile and the amide as intermediates in those cases where the reaction was incomplete[63].

$$R{-}\overset{H}{\overset{|}{C}}{=}N{-}OH \xrightarrow[-H_2O]{OH^-} R{-}C{\equiv}N \xrightarrow{OH^-} R{-}\overset{O}{\overset{\|}{C}}{-}NH_2 \xrightarrow{OH^-} R{-}COOH$$

2.1.8 The reaction of nitriles and formic acid. Aliphatic primary amides and CO were obtained from nitriles by treating with an equivalent amount of HCO_2H[64-66].

$$R\text{-}C{\equiv}N + HCOOH \longrightarrow R\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH_2 + CO$$

2.1.9 The irradiation of either cyclic oximes in iso-propanol[67] or a mixture of formamide, 1-decene, tert-butanol and acetone[68] gave, among other products, the desired aliphatic primary amides.



$$HC(=O)\text{-}NH_2 + CH_2{=}CH(CH_2)_7CH_3 \xrightarrow[1\ hr]{h\nu} H_2N\text{-}\overset{\overset{O}{\|}}{C}\text{-}(CH_2)_9\text{-}CH_3$$

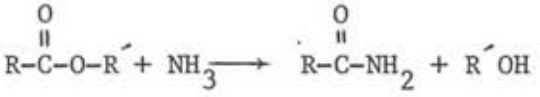
2.1.10 The oxidation of amines with benzyltriethylammonium permanganate. The oxidation was less selective in the case of secondary and primary amines[69].

$$RCH_2NH_2 \xrightarrow[CH_2Cl_2]{PhCH_2N^+Et_3MnO_4^-} \underset{\text{major}}{R\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH_2} + RC{\equiv}N$$

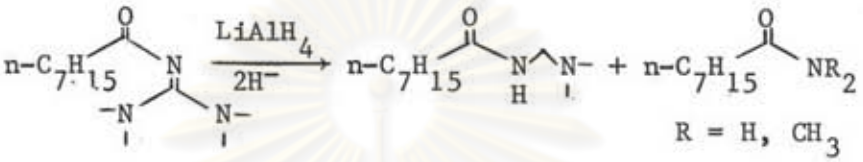
2.1.11 The formation of aliphatic primary amides from hydrazides by using copper (II) chloride[70] or activated Raney nickel[71].

$$R\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}NH_2 \xrightarrow[\text{or Raney nickel } -NH_3\uparrow]{THF:CuCl_2:\text{pyridine}(1:5:5)-N_2\uparrow} R\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH_2$$

2.1.12 The ammonolysis of esters[72,73].



2.1.13 The reduction of acylguanidine 11[74].



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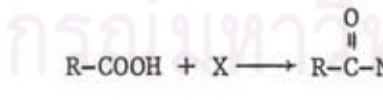
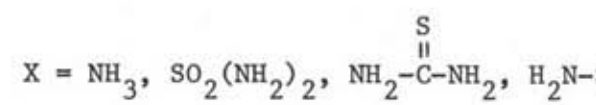
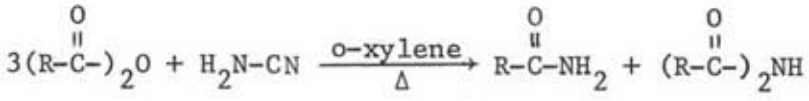
2.1.14 The conversion of carboxylic acids. Carboxylic acids can be converted to amides, in laboratory through their acid chlorides or acid anhydrides reacting with ammonia[75,76]. However, in industry amides are often made by heating the ammonium salts of carboxylic acids[73]. Other conversions of carboxylic acids into their corresponding amides have been reported by direct reaction with ammonia in the presence of transition metal compounds[77], $SO_2(NH_2)_2$ in pyridine[78], thiourea[79], H_2N-SO_3H[80]. In addition formation of amides from the reaction of cyanamide with anhydrides of aliphatic acids have also been reported[81].







2.1.15 The catalytic carbonylation of aliphatic amines in the presence of nickel and cobalt halides. The catalytic carbonylation of Et_2NH, Et_3N, $BuNH_2$, iso-Bu_2NH, amylamine, and hexylamine was studied. The main product at 220-260°C was the formyl derivative of the corresponding amine. NiI_2 was found to be a more effective catalyst than $NiCl_2$ and iodine. During this process, olefins were formed which gave amides of carboxylic acid with NH_3 and CO[82].

$$(RCH_2\text{-}CH_2)_3\text{-}N + CO \xrightarrow{220\text{-}260^{\circ}C} RCH_2\text{-}CH_2\text{-}COOH \xrightarrow{NiI_2} \overset{O}{\overset{\|}{HC}}\text{-}NH_2$$

$$+ NH_3 + RCH{=}CH_2 \xrightarrow{CO} R\text{-}CH_2\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2$$

2.1.16 Other reactions to make aliphatic amides have been described such as elimination of CO_2 from nitroketones by heating with HCO_2H (1)[83], reaction of vicinal nitroketone with NH_3, and either a primary or secondary amine at 60-130°C (2)[84], reaction of aldehydes and alcohols with NH_3 and $MeNH_2$ in the presence of $Ni_2O_3.3H_2O$ (3)[85].

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}NO_2 + \overset{O}{\overset{\|}{HC}}\text{-}OH \xrightarrow[\Delta]{} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 \qquad \text{.....(1)}$$

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}NO_2 + NH_3(1^{\circ},2^{\circ}\text{ amine}) \xrightarrow[\Delta]{} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 \qquad \text{.....(2)}$$

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}H,\ R\text{-}CH_2\text{-}OH \xrightarrow[Ni_2O_3.3H_2O]{NH_3,\ MeNH_2} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2, R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}Me \qquad \text{.....(3)}$$

2.2 Chemical reactions of aliphatic primary amides

2.2.1 Ureas formations. Reaction of aliphatic primary amides with aromatic isocyanates in refluxing xylene, generally with in 1 hr. forms crystalline acylaryl ureas 12[86].

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 + R'\text{-}N{=}C{=}O \underset{<150^oC}{\overset{\geq 160^oC}{\rightleftharpoons}} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}NHR'$$

12

2.2.2 Rearrangements. Generally speaking an amide can undergo rearrangements such as aliphatic primary amides when treated with lead tetraacetate in acetic acid or benzene-acetic acid mixture in the presence of pyridine, produced a mixture of N-alkylacetamides 13 and N,N'-dialkylureas 14, with one carbon less in the alkyl chains[87].

$$CH_3\text{-}(CH_2\text{-})_n\overset{O}{\overset{\|}{C}}\text{-}NH_2 \xrightarrow{Pb(OAc)_4} CH_3\text{-}(CH_2)_n\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 +$$

13

$$CH_3\text{-}(CH_2)_n\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH\text{-}(CH_2)_n\text{-}CH_3$$

14

The reaction of aliphatic primary amides to cabamates 15 is easily accomplished under mild conditions[88-90].

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 \xrightarrow[KBr/CH_3OH]{-2e} R\text{-}N{=}C{=}O \xrightarrow{CH_3OH} R\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}CH_3$$

15

These reactions were carried out by means of a Hofmann rearrangement on each amide.

In addition, aliphatic and cycloaliphatic amides can be converted to isocyanates by phase transfer catalysis with alkali hypobromites and quaternary salts[91].

$$Me\text{-}(CH_2)_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 + Br,\ NaOH,\ CH_2Cl_2,\ Bu_4N^+HSO_4^- \xrightarrow[\text{Stirred}]{RT} Me(CH_2)_5N{=}C{=}O$$

2.2.3 Hydrolysis to acid in both acidic and basic conditions. It is well known that a primary amide can be hydrolyzed to its corresponding acids[72,73,92].

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 + H_2O \begin{cases} \xrightarrow{H^+} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH + \overset{+}{N}H_4 \\ \xrightarrow{OH^-} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}O^- + NH_3 \end{cases}$$

2.2.4 Reductions. An amide can be reduced to form an amine and other products by either catalytic or electrolytic reductions.

Under the catalytic reductions several procedures have been reported such as:

- converting amides to their corresponding nitriles followed by reduction[93].

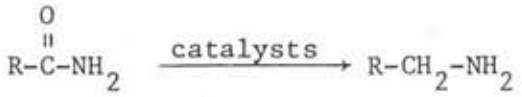
$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 \longrightarrow R\text{-}CN + H_2O$$

$$R\text{-}CN + 2H_2 \longrightarrow R\text{-}CH_2\text{-}NH_2$$

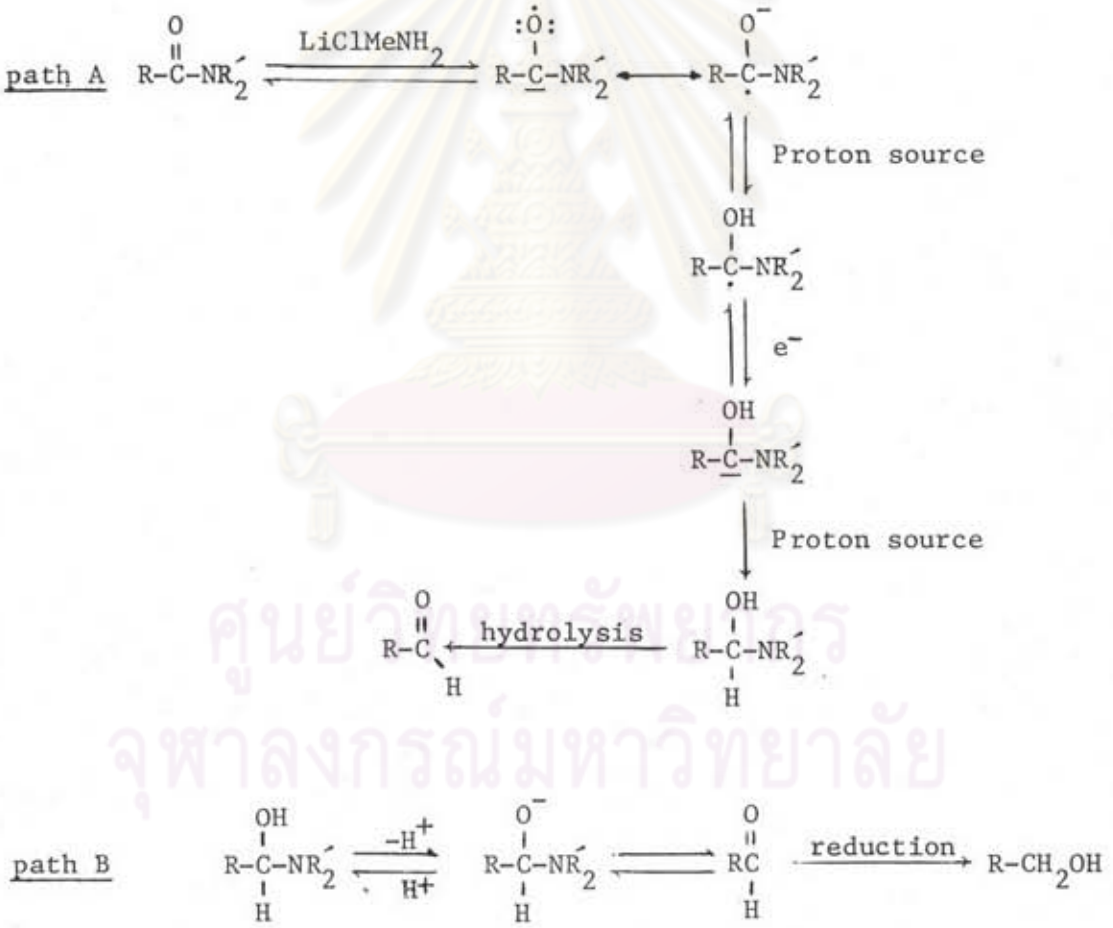
- treating N-chloroamides with alkali and akali earth hydroxides[94,95].

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 \xrightarrow[pH\leq 7]{Cl} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NHCl \xrightarrow{NaOH} R\text{-}CH_2\text{-}NH_2$$

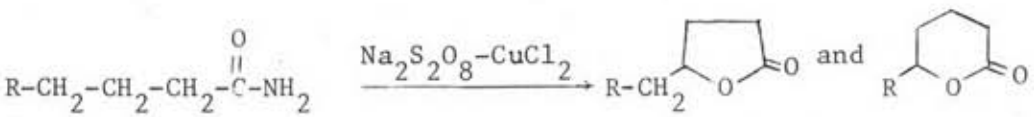
- and reduction of amides with titanium (IV) chloride, sodium bromide[96].



Under the electrolytic reduction, a new eletrochemical method for the selective reduction of aliphatic amides to aldehydes or alcohols have been demonstrated and the following mechanism was proposed[97,98]

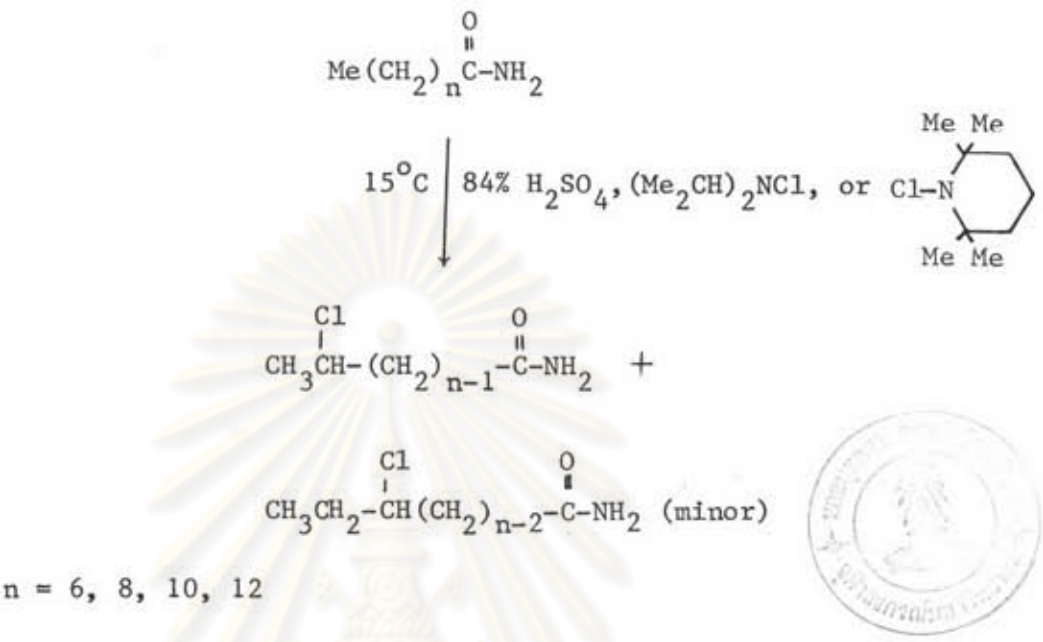


2.2.5 Oxidations. Direct oxidation of amides to lactones have been described[99].



(R = Me, Et)

2.2.6 Photochemical reactions. Photochlorination of certain amides have been reported as follows:



The reaction gave selective chlorination of amides and minor amounts of products monochlorinated at other positions[100].

A photochemistry of a series of amides were also carried out by the examination of the gaseous products from the reaction in dioxane and hexane. The following equations were suggested with equation (4) as a major reaction[101].

$$R\ CH_2CH_2CH_2CONH_2 \xrightarrow{h\nu} RCH{=}CH_2 + CH_3CONH_2 \qquad (4)$$

$$R\ CONH_2 \xrightarrow{h\nu} \cdot CONH_2 + R\cdot \xrightarrow[solvent]{\sim H} RH \qquad (5)$$

$$R\ CONH_2 \xrightarrow{h\nu} \cdot NH_2 + RCO\cdot \xrightarrow[solvent]{\sim H} RCHO \qquad (6)$$

$$R\ CONH_2 \xrightarrow{h\nu} RNH_2 + CO \qquad (7)$$

2.2.7 Conversion to nitriles. Aliphatic primary amides undergo transformation into their corresponding nitriles by reacting with H_2NSO_3H at 180-220°C[102], and also by chromatography on phosphoric acid

treated prolyester columns. They were quantitatively converted to nitriles[103].

2.3 The Activities and Applications of Amides and Their Derivatives

2.3.1 As enzyme substrates. Hexanamide and heptanamide have been reported as the best substrates for a chick embryo liver amidase. The enzyme activity was decreased with shorter or longer chain lengths of the alkyl group. Amides branched at the 2-carbon atom were poor substrates and those branched at the 2 and 3-carbon atoms were not hydrolyzed. Hydrolysis of both straight-and branched-chain amides was inhibited to varying extents by bis-[p-nitrophenyl] phosphate (BNPP). Branched-chain amides, while poor substrates of the amidase, were hydrolyzed solely by a BNPP-sensitive enzyme. However, the straight-chain amides were hydrolyzed by a BNPP-sensitive and a BNPP-resistant enzyme[104].

2.3.2 As enzyme inhibitors. A series of amides were tested as inhibitors of liver alcohol dehydrogenase and ethanol metabolism in rat and horse. It was found that with ethanol as substrate, fatty acid amides inhibited the enzymes competitively[105] and that increasing the hydrophobicity resulted in better inhibition, but introduction of polar groups reduced inhibition[106].

2.3.3 As effective foam stabilizers. The polar aliphatic amides and N-polar substituted amides with straight hydrocarbon chains of 8-14 carbon atoms were among the more effective foam-stabilizers[84,107,108] These effectiveness increased in the order 1) primary alcohols, 2) glyceral ethers, 3) sulfolanyl ethers, 4) amides and 5) N-polar substituted amides. This order is in general, the order of increasing surface activity and critical micelle concentration depressing activity[109].

2.3.4 As antimicrobial agents. Several derivatives of amide have been tested as antimicrobial agents[110], including 10-hendecenoic acid and its amide were tested on antimicrobial activities and found that they were weakly bacteriostatic but had a strong fungistatic action on various fungi pathogenic to plants and man[111]. Other aliphatic and aromatic amides were found to be active in both fungicides[112], and bactericides[113] including those chlorinated amides were also active against Candida albicans[114]. Methyl pyridinium chloride derivative of long chain fatty acid amides were found to be active in the emulsifying, dispersion, and antimicrobial activities[110] and that they were similar to those of the usual cationic surfactants[115], some nitropyridinecarboxamide derivatives have been reported to be effective for the treatment of coccidiosis in fowl[116].

2.3.5 As antistatic agents. A large number of antistatic amides, among other comounds, were tested in polyethylene and found to be effective in antistatics[117]. Other polyolefins made from the condensation of ethylene oxide and long chain aliphalic amides were also found to improve antistatic properties[118].

2.3.6 As antiparasitic agents. Long chain aliphatic amides with C_{10-15} was found to be strong nematocides[119].

2.3.7 As pharmaceutically useful compounds. A total of 168 amides most of them aliphatic diamides were prepared and studied for their lipid lowering activities[120].

2.3.8 As surface coating agents. Some of the aliphatic amides were used as surface coating agents in order to improve the properties of glass fibers[121,128], coefficient of friction[129], corrosion and rust on metal surface[84,130].

2.3.9 As catalysts for olefin polymerization. Certain amides such as $HCONMe_2$, $AcNMe_2$, N-tert-butylbenzamide, N-benzylacetamide, or n-heptanamide were used as one of the three-component alkyl aluminium halide catalysts for olefin polymerization[131-135].

2.3.10 As thermosensitive substances. Certain long chain aliphatic amides were used in temperature indicator as the thermosensitive substance such as capramide, lauramide, myristamide, and caprylamide were used for indicating 94, 97, 103 and 107°C respectively[136].

2.3.11 Miscellaneous applications. Further to the applications already mentioned, a variety of aliphatic amides have been used for other purposes such as lowering blood serum triglycerides in rats[137], waterproofing agents and fuel oil additives[84], antidandruff agents[138], and improving the method for the preparation of acylureas[139].

3. A Review on N,N´-Diacyl-cystamines

To the best of my knowledge there is no such compounds as N,N´-diacyl-cystamines, with the acyl group as big as heptanoyl have been reported, with their properties, in the literatures[140,141]. Only a few smaller ones have been made by Kuhn and Quadbeck[140], and also by Endo and his coworkers[141]. A-series of N-acyl-2-mercaptoethylamines was reported by Foye and his coworkers[142,143], but they did not undergo further the process ot get the disulfides. Nevertheless, a review on general disulfides has been done in the following aspects:

3.1 Chemical Synthesis of Disulfides

3.1.1 Oxidation of mercaptans. Mercaptans are easily oxidized to disulfides by using hydrogen peroxide as the most common reagent[144].

$$2R\text{-}SH \xrightarrow{H_2O_2} R\text{-}S\text{-}S\text{-}R$$

Many oxidizing agents also give the disulfides such as sulfinic acid[145],

$$R\text{-}SH + R\text{-}S\text{-}OH \xrightarrow{\hat{O}} R\text{-}S\text{-}S\text{-}R + H_2O$$

sulfuryl chloride[146],

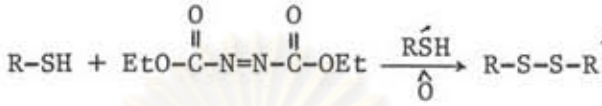
$$2R\text{-}SH + SO_2Cl_2 \xrightarrow{\hat{O}} R\text{-}S\text{-}S\text{-}R + 2HCl + SO_2$$

even the oxygen in the air oxidizes mercaptans on standing, if a small amount of base is present[144].

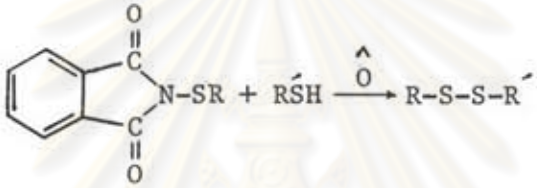
3.1.2 Autoxidation of N-acetyl-cysteamine. N-Acetyl-cysteamine undergoes autoxidation to form the corresponding disulfide[140].

$$CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}SH \xrightarrow{\hat{O}} CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3$$

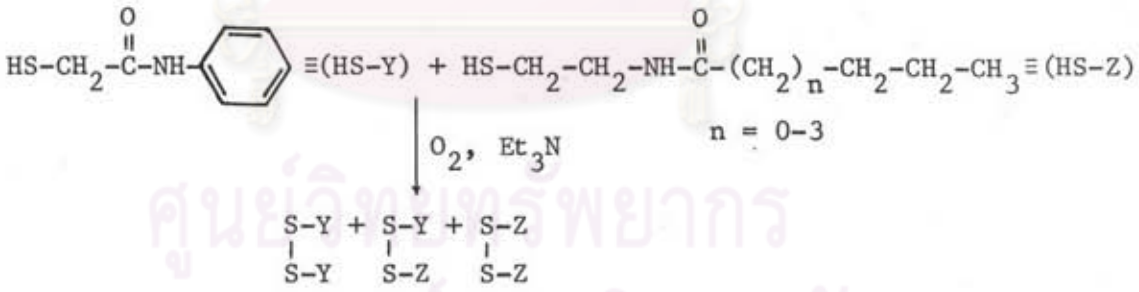
3.1.3 Unsymmetrical disulfides. Unsymmetrical disulfides can be prepared by treatment of a mercaptan with diethylazodicarboxylate to give an adduct, to which another mercaptan is then added, producing the disulfides[144].



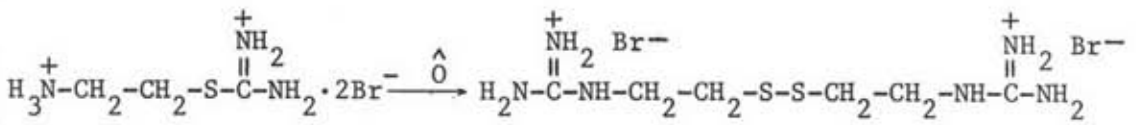
Another method involves treatment of R´SH with a thiophthalimide[144].



In addition a mixture of symmetrical and unsymmetrical disulfides has been made from the reaction of two different mercaptans as shown in the following equation[141].



3.1.4 Oxidation of S-(2-aminoethyl) isothiouronium bromide hydrobromide. S-(2-Aminoethyl) isothiuronium bromide hydrobromide was oxidized by hydrogen peroxide in concentrated ammonia water to afford 2-guanidinoethyl disulfide dihydrobromide[1].



3.1.5 Treatment of alkyl halides with disulfides ions. Disulfides can be prepared by treatment of alkyl halides with disulfide ions[144].

$$2R\text{-}X + S_2^{2-} \longrightarrow R\text{-}S\text{-}S\text{-}R + 2X^-$$

3.1.6 Reaction of Bunte salts. Disulfides can also be made by the reaction of Bunte salts with acid solution of iodide, thiocyanate ion or thiourea, or by pyrolysis or by treatment with hydrogen-peroxide[144].

$$2R\text{-}S\text{-}S\text{-}O_3^- \xrightarrow{\hat{O}} R\text{-}S\text{-}S\text{-}R$$

3.2 Reactions and Applications of Disulfides

3.2.1 Chlorinolysis. Chlorinolysis of a disulfides by sulfuryl chloride in acetic acid and subsequent treatment with water, produced the aliphatic thiosulfonates 16[146].

$$R\text{-}S\text{-}S\text{-}R + AcOH + 2SO_2Cl_2 \longrightarrow RS(O)Cl + RSCl + AcCl + HCl + 2SO_2$$

$$RS(O)Cl + RSCl + AcCl \xrightarrow{H_2O} \underset{16}{RSO_2SR} + AcOH + 3HCl$$

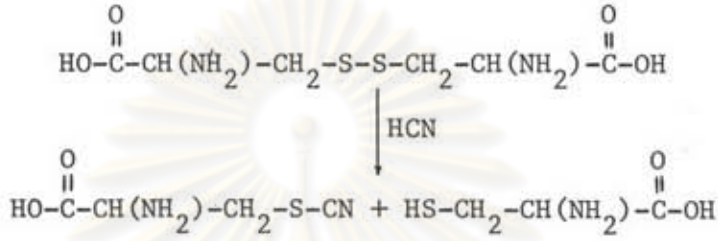
3.2.2 Oxidation. Oxidation of disulfides by superoxide ion affords their sulfinic 17 and sulfonic 18 acids[147].

$$R\text{-}S\text{-}S\text{-}R \xrightarrow{\hat{O}} \underset{17}{RSO_2^-} + \underset{18}{RSO_3^-}$$

The formation of hypotaurine (2-aminoethanesufinic acid) from cystamine is one of the example in the oxidation of disulfides[148].

$$(H_3\overset{+}{N}-CH_2-CH_2-S-)_2 + Hg^{++} + Cl^- \longrightarrow H_3\overset{+}{N}-CH_2-CH_2SO_2H + H_3\overset{+}{N}CH_2CH_2SHgCl$$

3.2.3 Reaction with cyanide ion. In the reaction of HCN with cystine disproportionation of the S-S linkage takes place with the formation of thiocyano amino acid 19 and cysteine[19].



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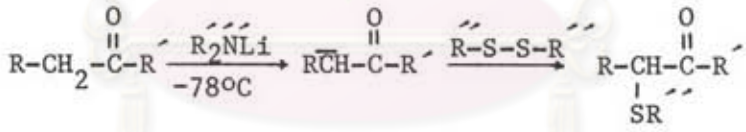
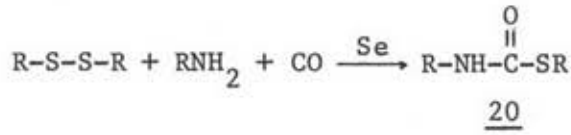
3.2.4 Sulfenylation of ketones and esters. Ketones and esters (including lactones) can be sulfenylated in the α-position by conversion to the enolate ion with a base such as lithium N-isopropylcyclohexylamide and treatment of this with a disulfide[144].



3.2.5 Thiocarbamates formation. Thiocarbamates 20 are formed on treatment of primary aliphatic amines with CO and a disulfide in the presence of selenium[144].



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3.2.6 Reaction with boranes. Reaction of trialkylborans with disulfides resulted a formation of unsymmetrical sulfides[144].

$$R_3B + R'-S-S-R'' \xrightarrow{O_2 \text{ or } h\nu} R-S-R' + R_2-B-S-R''$$

3.2.7 Conversion to alkenes with KOH. Disulfides can be eliminated to form alkenes when heated with KOH in polar aprotic solvent[144].

$$RCH_2-CH_2-S-S-CH_2-CH_2R \xrightarrow{OH^-} 2CH_2=CH-R + S_2^{2-}$$

3.2.8 Reduction of disulfides to mercaptans. Disulfides can be reduced to mercaptans by mild reducing agent such as zinc and dilute acid or Ph_3P and H_2O. The reaction can also be accomplished simply by heating with alkali $LiAlH_4$[144].

$$R-S-S-R \xrightarrow{\hat{H}} 2RSH$$

Hydrogenolysis with Raney nickel resulted a desulfurization as follow[144]:

$$R-S-S-R' \xrightarrow{H_2,\ Ni} RH + R'H$$

3.2.9 Some of the N-acyl-2-mercaptoethylamines and disulfides have been made as potential antiradiation agents and the biological mechanism has been proposed to form a mixed disulfide[142,149,150].