# The Synthesis and Characterization of Some Amidines, Ureas and Biguanides.

## Citation

Detweiler, William Kenneth. *The Synthesis and Characterization of Some Amidines, Ureas and Biguanides.* 1951, https://preserve.lehigh.edu/lehigh-scholarship/graduate-publications-theses-dissertations/theses-dissertations/synthesis-38.

# THE SYNTHESIS AND CHARACTERIZATION OF SOME AMIDINES, UREAS AND BIGUANIDES

by

William Kenneth Detweiler

A DISSERTATION

Presented to the Graduate Faculty

of Lehigh University

in Candidacy for the Degree of

Doctor of Philosophy

Lehigh University
Bethlehem, Pennsylvania
May, 1951

This dissertation is presented to the Graduate Faculty of Lehigh University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

William Kenneth Detweiler

May 17, 1951 William Kenneth Detweiler

This dissertation is approved and recommended for acceptance in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

E D Amstutz

May 18, 1951 E. D. Amstutz
(Professor in Charge)

Accepted, June 8, 1951

Special committee directing the doctoral work of Mr. Detweiler

E D Amstutz
E. D. Amstutz (Chairman)
Professor of Organic Chemistry

Warren W. Ewing
W. W. Ewing
Professor of Physical Chemistry

Earl J Serfass
E. J. Serfass
Professor of Chemistry

B. W. Parker
B. W. Parker
Associate Professor of Biology

## Acknowledgment

The investigation which is described in this dissertation was proposed by Dr. E. D. Amstutz and was carried out under his supervision. The author is especially indebted to Dr. Amstutz and also to Dr. Fish for much helpful advice during the course of this work. The author also wishes to express his appreciation to The Wm. S. Merrell Company for the financial aid which made this work possible and to Dr. Van Campen, Jr., for his interest in this work. The determination of the infrared spectra in this dissertation was made possible through the generosity of Samuel P. Sadtler and Son, Inc.

# Table of Contents

# Part I

# Introduction

# Part I

## Introduction

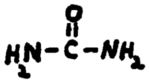
Diuretics are of primary importance because of their value and use in the treatment of cardiac edema. Mercurial diuretics were introduced into general use about thirty years ago and have been generally accepted as the most efficient therapeutic agents for the stimulation of urine production in such cases (1). The mercurial diuretics are the most effective known today and are used because of this potency, but they are toxic and dangerous.

These compounds remove the excess intracellular fluid by overcoming the failure of the edematous patient to excret sodium (2). The changes produced in the kidney by such drugs consist chiefly in degeneration of the epithelium of the tubules (3). It was early demonstrated that kidney diseases were definite contraindications to their employment (3, 4).

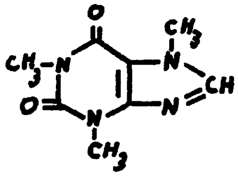
Stanley has reported (5) that the literature contains twenty-seven cases in which death occurred immediately after the injection of a mercurial diuretic. The organic portion of the molecule is of considerable significance in such cases since the various mercurial drugs differ decidedly in their lethal doses and ability to produce reactions (3).

Prior to 1942, there had been no systematic quantitative study done on diuretics. In that year, Lipschitz (6) published the first of a series of papers (7, 8, 9) which described a method of diuretic assay and its application in the determination of the dose-action relationship of various diuretics. With urea as a reference standard, the activities of many known diuretics were determined. Urea was chosen as the standard because of its relatively weak non-toxic diuretic action and stability *in vivo* as well as *in vitro*. *Diuretic activity* was defined (6) as the diuretic potency of a substance referred to that of urea, the activity of which was taken as equal to one.

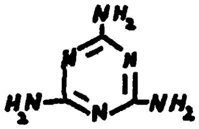
This work revealed several non-mercurial compounds as unusually potent diuretics. As shown by their formulas (Fig. I) they are related to urea and the xanthines chemically in so far as they contain the group $=N-\underset{\|}{C}-N=$ in their molecule. Of the seventy amides, amines and related compounds tested, formoguanamine was found to be the most potent (347.1 times that of urea) and to have the same order of activity as salyrgan, a potent mercurial compound. Since this compound compared favorably with the xanthine diuretics (for example theophylline) and the organic mercury compounds (for example salyrgan) concerning potency and degree of toxicity, it has encouraged much experimental activity.



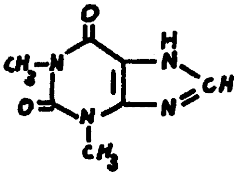
Urea
(1)



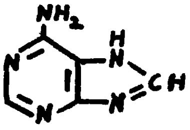
Caffeine
(32)



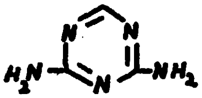
Melamine
(76.5)



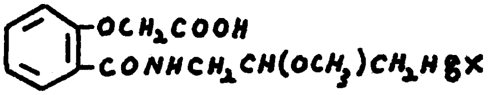
Theophylline
(115)



Adenine
(139)



Formoguanamine
(347.1)

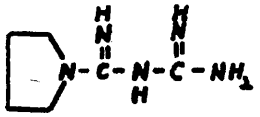


Salyrgan
(400)

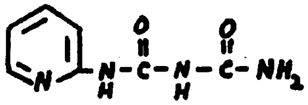
Fig. I

The creditable position of The Wm. S. Merrell Company in the field of hypertension, coupled with a real desire to remain in such a position, has led them to sponsor the present investigation of non-mercurial diuretics. The long-range objective of this research was to synthesize a potent diuretic having the activity of formoguanamine and without any objectionable side reactions.

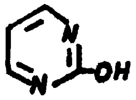
The investigations described in Parts II, III, and IV of this dissertation are concerned with the synthesis of heterocyclic nitrogen compounds containing the amidine ($-\overset{N}{\overset{\|}{C}}-N=$ ), guanidine ( $=N-\overset{N}{\overset{\|}{C}}-N=$ ) and urea ($=N-\overset{O}{\overset{\|}{C}}-N=$) structures. A careful inspection of the structural features of the following compounds (Fig. II), which were prepared during the course of this investigation, will readily reveal that all of them contain various combinations of the amidine, guanidine or urea structures.



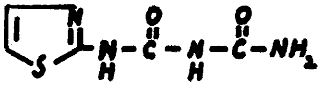
1,1-Tetramethylene
biguanide



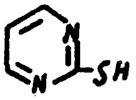
1-(2-Pyridyl)biuret



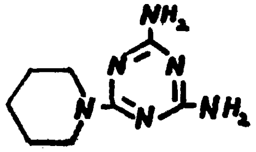
2-Pyrimidol



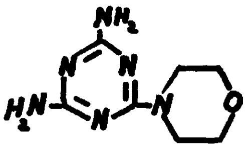
1-(2-Thiazolyl)biuret



2-Thiopyrimidol

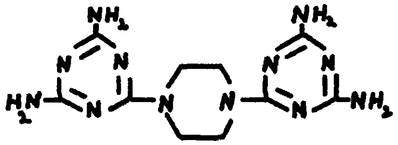


2-(1-Piperidyl)-4,6-
diamino-s-triazine

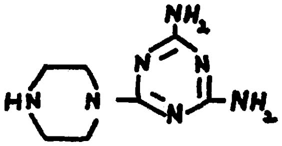


2-(4-Morpholinyl)-4,6-
diamino-s-triazine

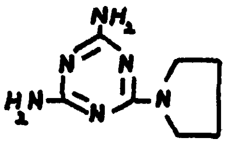
Fig. II



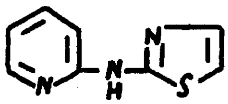
2-(1,4-Piperazinyl) bis (4,6-diamino-s-triazine)



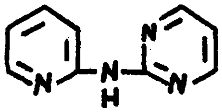
2-(1-Piperazinyl)-4,6-
diamino-s-triazine



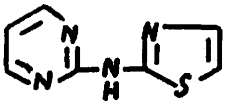
2-(1-Pyrrolidyl)-4,6-
diamino-s-triazine



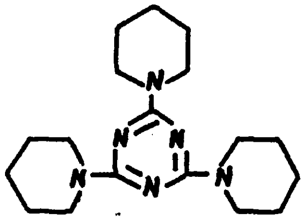
2-Pyridyl-2'-
thiazolylamine



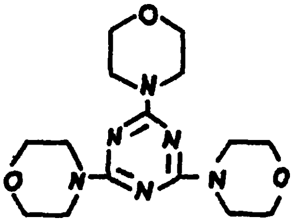
2-Pyridyl-2'-
pyrimidylamine



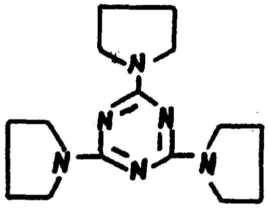
2-Pyrimidyl-2'-
thiazolylamine



2,4,6-Tri-1-piperidyl-s-
triazine



2,4,6-Tri-4-morpholinyl-s-
triazine



2,4,6-Tri-1-pyrrolidyl-s-
triazine

Fig. II

In view of the known diuretic activity of other compounds which possessed these structural features, it was hoped that one of these compounds would be a very potent diuretic. The results of the diuretic and toxicity tests on these compounds will be reported elsewhere.

# Part II

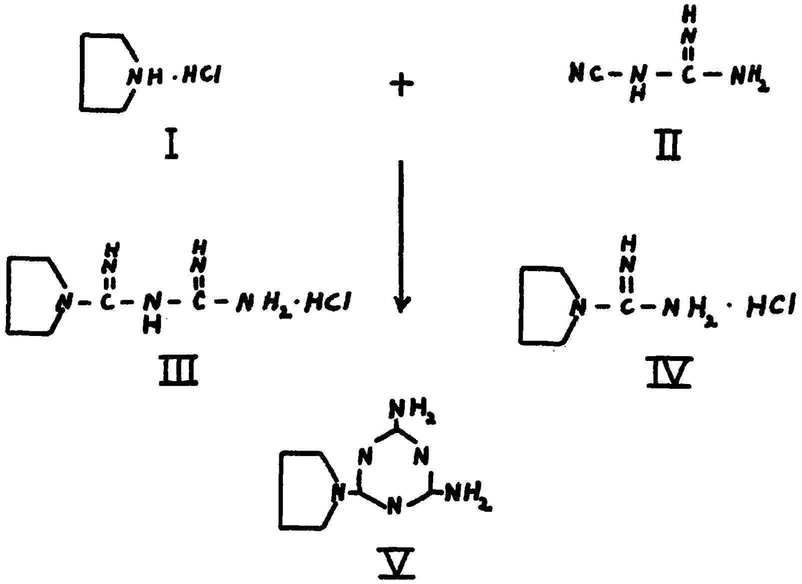
## Some Substituted Biguanides and s-Triazines

# Part II

## Some Substituted Biguanides and s-Triazines

The discovery of Paludrine as a potent antimalarial by Curd and Rose (10) was followed by the development of a keen interest in the field of substituted biguanide derivatives as potential antimalarials. The great activity in this field has led to the general employment of a standard method for the preparation of $\omega$-substituted biguanides through the interaction of an amine with dicyandiamide (11, 12, 13). This process appeared to offer an attractive method of preparing a variety of potential diuretics of the biguanide type in spite of the inherent tendency of these compounds toward cyclization and the formation of guanidines.

The fusion of pyrrolidine hydrochloride (I) with dicyandiamide (II) at approximately 130° for 24 hours permitted the isolation of 1,1-tetramethylenebiguanide hydrochloride (III) in 44% yield. For some unknown reason, the same reactants under apparently the same conditions have been found to rapidly evolve ammonia and produce 1,1-tetramethylene guanidine hydrochloride (IV) and 2-(1-pyrrolidyl)-4,6-diamino-s-triazine (V) in addition to a very poor yield of 1,1-tetramethylenebiguanide hydrochloride when only heated for as little as 6½ hours.



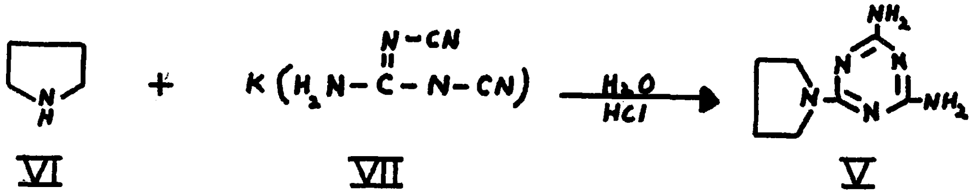
Although this method of reacting an amine hydrochloride with dicyandiamide to prepare substituted biguanides appears to be a general reaction for aliphatic, cycloaliphatic and aromatic amine hydrochlorides, it does not appear to be general for heterocyclic primary amine hydrochlorides which contain a guanidine or amidine structure*.

Potassium dicyanoguanidine has been reported (14) to react with aliphatic, cycloaliphatic and aromatic secondary amine salts in aqueous solution to form N,N-disubstituted melamines. Pyrrolidine (VI) was successfully reacted

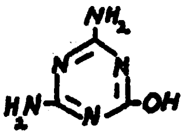
---

*The fusion of 2-aminopyridine hydrochloride with dicyandiamide at 178° produced a pitch which could not be purified; the same reaction in refluxing butanol did not yield any product which could be identified. The fusion of 2-aminothiazole hydrochloride with dicyandiamide resulted in the evolution of ammonia and hydrogen sulfide.

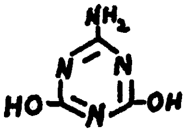
with potassium dicyanoguanidine (VII) in acidic solution to produce a 14% yield of 2-(1-Pyrrolidyl)-4,6-diamino-s-triazine (V). In contrast, the reaction of several hetero-



cyclic primary amines such as 2-aminopyridine, 2-aminopyrimidine and 2-aminothiazole produced products which were infusible and insoluble in the common organic reagents and water. After considering the physical properties and the data obtained from complete analyses of the products obtained from this reaction, the conclusion has been reached that if the desired products were initially formed, they hydrolyzed to produce a mixture of ammeline (VIII) and ammelide (IX).



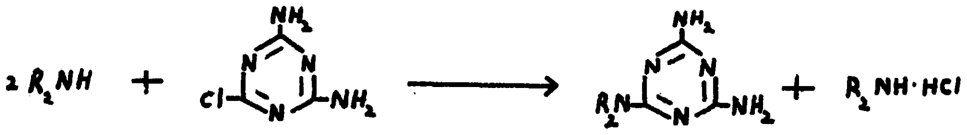
VIII



IX

The most satisfactory method of producing N,N-disubstituted melamines was found to be through the interaction of

2-chloro-4,6-diamino-s-triazine with an excess of the appropriate cycloaliphatic amine according to the reaction

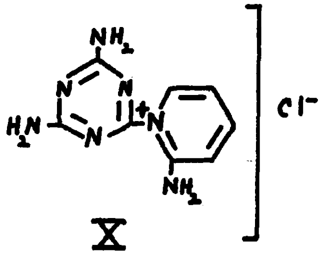


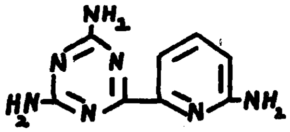
This method produced 2-(1-pyrrolidyl)-, 2-(1-piperidyl)- and 2-(4-morpholinyl)-4,6-diamino-s-triazine in yields ranging between 75 and 79%. After this work had been completed the latter two s-triazines were reported (15) to have been prepared in yields of 22 and 48% respectively. These yields and the vigor in which our reactions took place seem to indicate that this type of reaction should be run in such an excess of the amine that it can act as its own solvent.

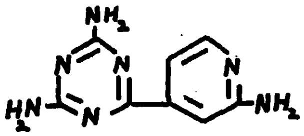
An excess of piperazine reacted vigorously with 2-chloro-4,6-diamino-s-triazine to give a mixture of the mono-and disubstituted-s-triazines; the disubstituted product, 2-(1,4-piperazinyl) bis (4,6-diamino-s-triazine), was isolated in 48% yield from this mixture.

The fusion of a large excess of 2-aminopyridine with 2-chloro-4,6-diamino-s-triazine produced what appeared to be a quantitative yield of 2-(2-pyridylamino)-4,6-diamino-s-triazine hydrochloride. It seemed to be unlikely that this apparent hydrochloride should be able to be isolated from the reaction mixture which contained a large excess of 2-aminopyridine. A dry pyridine extraction of this substance removed 11% of the total weight; from this pyridine extract a water insoluble free base was isolated. This substance analyzed rather closely for 2-(2-pyridylamino)-4,6-diamino-s-triazine or an isomer of it. The pyridine insoluble portion of the reaction product gave, after further purification, a precipitate with acidified silver nitrate solution. This water soluble halogen containing compound analyzed rather closely to the theoretical values required for 2-(2-pyridylamino)-4,6-diamino-s-triazine hydrochloride or an isomer of it.

This data made it appear that the initial product of this reaction was probably the pyridinium salt X which partially rearranged under the influence of heat to produce 2-(2-pyridylamino)-4,6-diamino-s-triazine or one of

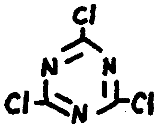

X

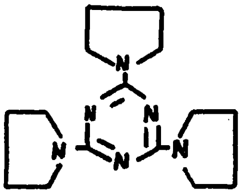

XI

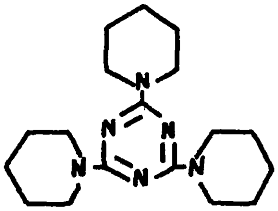

XII

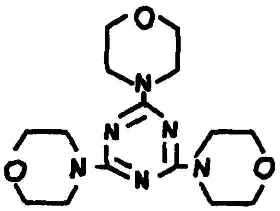
its ring substituted isomer XI and XII. The structures X, XI and XII appear to be consistent with the experimental findings of Saure (16) who has investigated the reactions of cyanuric chloride with pyridine in aqueous solution.

Cyanuric chloride (XIII) reacted with an excess of pyrrolidine, piperidine and morpholine to produce 2,4,6-tri-1-pyrrolidyl- (XIV), 2,4,6-tri-1-piperidyl- (XV) and 2,4,6-tri-4-morpholinyl-s-triazine (XVI) respectively in yields which varied between 93 and 97%.


XIII


XIV


XV


XVI

## Experimental*

1,1-Tetramethylenebiguanide hydrochloride (III). - Dry pyrrolidine hydrochloride (I) (65.6 g., 0.61 mole) and dicyandiamide (II) (51.4 g., 0.61 mole) were intimately mixed and fused in an oil bath at 125-135° for 24 hours. The product of this fusion was treated with 325 ml. of boiling absolute ethanol, filtered from a trace of insoluble material, concentrated to approximately 250 ml. and allowed to crystallize. The colorless granular crystals obtained were

---

*All melting points are corrected for thermometer stem-emergence unless otherwise noted.

filtered, washed with a 1:1 mixture of absolute ethanol and dry ether followed by several portions of dry ether. After drying under vacuum over phosphorous pentoxide, the yield of III was 42.5 g. (36.3%), m.p. 220.2-224.2°. Concentration of the ethanolic mother liquor yielded an additional 9 g. (7.7%) which had a slightly lower melting point. The melting point of these crystals can be raised to 225.8-226.6° by recrystallization from absolute ethanol. Anal. Calcd. for $C_6H_{14}N_5Cl$: C, 37.60; H, 7.36; N, 36.54; Cl, 18.50. Found: C, 37.44; H, 7.34; N, 36.58; Cl, 18.34. Trituration of this hydrochloride with 48% sodium hydroxide followed by filtration, drying, and a dry ether extraction in a Soxhlet extractor yielded the free base of III, m.p. 153.5-154.4°. Anal. Calcd. for $C_6H_{13}N_5$: C, 46.43; H, 8.44; N, 45.13. Found: C, 46.21; H, 8.23; N, 45.12.

On several occasions, the fusion of I and II under conditions apparently identical with these already described led to the evolution of ammonia after only 6½ hours to produce 2-(1-pyrrolidyl)-4,6-diamino-s-triazine (V) and 1,1-tetramethyleneguanidine hydrochloride (IV) in addition to 1,1-tetramethylenebiguanide hydrochloride (III). The products III, IV, and V were separated by fractional crystallization. The major portion of V was separated from the remainder of the reaction mixture by its insolubility in boiling absolute ethanol. The colorless plates V melted 294.9-296.5° (from water). Anal. Calcd. for $C_7H_{12}N_6$:

C, 46.65; H, 6.71; N, 46.64. Found: C, 46.49; H, 6.77; N, 46.77.

Fractional concentration of the alcoholic solution from which V had been separated ultimately yielded colorless crystals of III. Additional concentration yielded a viscous mass of crystals which were extracted with boiling acetone. Concentration of this acetone extract yielded colorless square platelets IV which melted at 88.8-89.8°. Anal. Calcd. for $C_5H_{12}N_3Cl$: C, 40.13; H, 8.09; N, 28.08; Cl, 23.70. Found: C, 40.25; H, 8.00; N, 27.98; Cl, 24.04.

2-Substituted-amino-4,6-diamino-s-triazines were prepared by methods (A) and (B): 2-(1-Pyrrolidyl)-4,6-diamino-s-triazine (V) (Method A). - Concentrated hydrochloric acid was added to a mixture of pyrrolidine (VI) (10 g., 0.141 mole), potassium dicyanoguanidine (VII) (20.8 g., 0.141 mole), and 100 ml. of water to produce a solution have a pH 7.5. This aqueous solution was heated at just below reflux for 20 hours. The light tan colored reaction product was filtered from the chilled solution, washed with water, and dried at 100°, yield 3.42 g. (13.5%), m.p. 295.8-297.5°. A mixed melting point of this sample with the sample V obtained from the dicyandiamide reaction showed no depression. This method yielded mixtures of ammeline (VIII) and ammelide (IX) when 2-aminopyridine, 2-aminopyrimidine, and 2-aminothiazole were reacted with VII.

2-(1-Piperidyl)-4,6-diamino-s-triazine (Method B). - Piperidine (66.5 g., 0.78 mole) and 2-chloro-4,6-diamino-s-triazine (17) (37.9 g., 0.26 mole) were maintained below 40° during the first ½ hour by occasionally cooling the stirred mixture in an ice bath; after this time the temperature rose to 106° over a 5 minute period. The reaction mixture was extracted with 70 ml. of boiling water after standing 3 hours at room temperature. The colorless powder remaining from the extraction was treated with approximately 650 ml. of a 1:1 mixture of ethanol and water, filtered through a heated funnel, and allowed to crystallize. The yield of fine colorless needles was 37.7 g. (74.8%) after drying under vacuum, m.p. 218.7-221.4°. After further recrystallization and vacuum sublimation at 2mm. the melting point* was 222.2-223.6°. Anal. Calcd. for $C_8H_{14}N_6$: C,49.46; H, 7.27; N, 43.27. Found: C, 49.43; H, 7.24; N, 43.28.

2-(4-Morpholinyl)-4,6-diamino-s-triazine (Method B). - Morpholine (71.3 g., 0.82 mole) and 2-chloro-4,6-diamino-s-triazine (17) (29.7 g., 0.20 mole) were mechanically stirred as the temperature gradually rose due to the exothermic reaction taking place. After approximately three minutes of mixing, the reaction mixture suddenly became explosively exothermic causing the morpholine to go to reflux and the loss of a small quantity of product. The reaction then sub-

---

*Walker et al. (15) report m.p. 216-217°, yield 22%.

sided and was allowed to react one additional hour. The colorless crystalline product was dissolved in 1100 ml. of boiling water and filtered through a heated funnel to remove any mechanical impurities and unreacted starting material. The fine colorless needles which crystallized from the cold solution were filtered, washed with two 50 ml. portions of cold water, dried at 100°, yield 31.34 g. (79.3%), m.p. 250-253.7°. Recrystallization of these crystals from 95% ethanol followed by a 1:1 mixture of water and ethanol gave colorless platelets which melted* 250-252.4°. Anal. Calcd. for $C_7H_{12}N_6O$: C, 42.85; H, 6.16; N, 42.84. Found: C, 43.08; H, 6.32; N, 42.81.

2-(1-Piperazinyl) bis (4,6-diamino-s-triazine) (XVII) and 2-(1-piperazinyl)-4,6-diamino-s-triazine (XIX) (Method B). - Piperazine (5.18 g., .06 mole) and 2-chloro-4,6-diamino-s-triazine (17) (4.37 g., .03 mole) gradually produced an exothermic reaction upon mixing; this reaction was accelerated by heating in an oil bath at 93° for a few seconds. After a rapid exothermic reaction had taken place, the reaction mixture was heated with 10 ml. of pyridine until it became paste-like. This paste was extracted with 100 ml.of boiling water and filtered from the insoluble portion (XVII) which was washed with water and dried at 100°, yield 2.18 g. (47.7%) m.p. 380-385° (uncorr.) with

---

*Walker et al (15) report m.p. 236-240°, yield 48%.

decomposition. XVII gave a negative ionic halogen test. The purification of XVII through vacuum sublimation was resorted to since the products obtained from recrystallization did not appear to be suitable for a quantitative analysis. A nearly colorless highly crystalline fraction was obtained by fractional sublimation of XVII from a salt bath at 320° under 4½ mm. pressure. This fraction melted 398-400° (uncorr.) with decomposition gradually taking place at 340°. Anal. Calcd. for $C_{10}H_{16}N_{12}$: C, 39.46; H, 5.30; N, 55.24. Found: C, 39.61; H, 5.51; N, 55.36, 55.03.

The yield of colorless crystalline solid XVIII obtained from the concentration of the aqueous filtrate of XVII was 2.42 g., m.p. 285-295°. This substance is believed to be mainly the hydrochloride of 2-(1-piperazinyl)-4,6-diamino-s-triazine. Recrystallization of XVIII from a few ml. of water gave 1.36 g., of colorless crystals, m.p. 300-320° with decomposition; these crystals gave a positive ionic halogen test. A .07 g. sample of this fraction was dissolved in 75 ml. of cold water, filtered from a small quantity of insoluble white powder and precipitated by the addition of 15 ml. of 48% sodium hydroxide. The white powdery precipitate was filtered, washed with cold water and dried, m.p. 255-260° with decomposition. Vacuum sublimation of this sample from a salt bath at 256° under a pressure of 7 mm. gave a minute yield of colorless crystals

XIX, m.p. 263-271°. An analysis of XIX gave results that indicate it to be 2-(4-piperazinyl)-4,6-diamino-s-triazine. Anal. Calcd. for $C_7H_{13}N_7$: N, 50.23. Found: N, 49.50.

2-(1-Pyrrolidyl)-4,6-diamino-s-triazine (V) was prepared by method B in approximately 75% yield, m.p. 295.2-297.2°.

The fusion of 2-aminopyridine with 2-chloro-4,6-diamino-s-triazine followed by a pyridine extraction gave two compounds XXI and XXII which analyzed for the empirical formulas $C_8H_9N_7$ and $C_8H_{10}N_7Cl$ respectively. Since the structure of these compounds is open to doubt, the experimental procedure is given: 2-aminopyridine (4.71 g., .05 mole) and 2-chloro-4,6-diamino-s-triazine (2.91 g., .02 mole) were fused in an oil bath at 91° for 1 hour followed by 1 additional hour at 140-145°. The yellow paste was suspended in cold absolute ethanol, filtered, washed with cold absolute ethanol and dried at 100°; the yield of fine granular yellow crystals XX was 4.25 g.; m.p. 296-316° (uncorr.) with gaseous decomp. This substance gave a flocculent precip. with an acidified $AgNO_3$ soln., was soluble in water and practically insoluble in boiling absolute ethanol.

Addition of absolute alcohol to a dry pyridine extract of XX yielded 0.35 g. of XXI, m.p. 270.6-279.2°. Solution of XXI in dry pyridine and precipitation with absolute alcohol followed by an alcoholic wash raised the melting point to 277-281.8° (decomp). Anal. Calcd. for $C_8H_9N_7$: C, 47.28; H, 4.46; N, 48.26. Found: C, 46.96; H, 5.24; N, 48.35, 48.03.

A 2.76 g. yield of XXII remained from the pyridine extraction of XX, m.p. 298-301° (decomp.). XXII was extracted with boiling dry pyridine, filtered, washed with absolute ethanol and dried at 100° over phosphorous pentoxide, m.p. 295.2-301.8°. XXII was found to be soluble in water and to give a precipitate with acidified $AgNO_3$ soln.; it could be recovered unchanged upon treatment with .05 N sodium hydroxide solution; hydrochloric acid could be distilled from a solution of it acidified with $H_2SO_4$. Anal. Calcd. for $C_8H_{10}N_7Cl$: C, 40.09; H, 4.21; N, 40.91; Cl, 14.79. Found: C, 40.56; H, 4.51; N, 40.65, 41.04; Cl, 14.67.

<u>2,4,6-Tri-1-pyrrolidyl-s-triazine</u> (XIV). - Cyanuric chloride (XIII) (25.83 g., 0.14 mole) was added over a 25 minute period with stirring to pyrrolidine (99.56 g., 1.4 mole) which had been cooled to 10°; the temperature of the reaction mixture was maintained below 55° during this process. This slurry was stirred an additional ½ hour, diluted with 100 ml. of cold water, filtered, washed with cold water and dried under vacuum at 95°, yield 37.91 g. (94.6%), m.p. 185-188°. After several recrystallizations from 95% ethanol the melting point was 186.6-189.8°. Anal. Calcd. for $C_{15}H_{24}N_6$: C, 62.47; H, 8.39;

N, 29.14. Found: C, 62.71; H, 8.48; N, 29.14.

2,4,6-Tri-1-piperidyl-s-triazine* (XV). - Cyanuric chloride (XIII) (22.20 g., 0.12 mole) was added over a half-hour period with stirring to freshly dried and distilled piperidine (170.3 g., 2 mole) which had been cooled to 0° by means of an ice-salt bath; the temperature was maintained below 25° during this addition. After standing 20 hours the light cream colored slurry was diluted with 100 ml. of cold water, thoroughly mixed, and filtered. This reaction mixture was thoroughly washed several times by suspending it in cold water and then dried under vacuum at 93°, yield 37.44 g. (93%), m.p. 217-220.6°. Long colorless needles were obtained by recrystallization from a toluene-ethanol mixture and then acetone, m.p. 219-221.1°. Anal. Calcd. for $C_{18}H_{30}N_6$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.65; H, 9.28; N, 25.41.

2,4,6-Tri-4-morpholinyl-s-triazine (XVI). - Cyanuric chloride (XIII) (22.15 g., 0.12 mole) was added with stirring over a 35 minute period to morpholine (174.5 g., 2.00 mole) which had been cooled to 0° in an ice-salt bath. The temperature was maintained below 40° during this addition. After an additional half-hour the reaction mixture was suspended in 100 ml. of cold water, filtered,

---

*Hofmann (18) prepared this compound in poor yield by the reaction of the trimethyl ester of trithiocyanuric acid with piperidine. He reported a melting point of 213°.

washed with four generous portions of cold water and dried under vacuum at 85°, yield 39 g. (96.5%), m.p. 279-287°. This compound can be recrystallized from benzene, toluene, morpholine, dioxane and ethanol. Recrystallization from 95% ethanol gave fine colorless needles, m.p. 284-289.4°. Anal. Calcd. for $C_{15}H_{24}N_6O_3$: C, 53.55; H, 7.19; N, 24.99. Found: C, 53.87, 53.63; H, 7.38, 7.31; N, 24.96, 25.04.

## Summary

The products arising from the fusion of dicyandiamide with pyrrolidine hydrochloride were discussed. The reactions of cycloaliphatic amines and primary heterocyclic amines of the amidine or guanidine type with potassium dicyanoguanidine and 2-chloro-4,6-diamino-s-triazine were presented. The preparation of several 2,4,6-trisubstituted-amino-s-triazines by the use of cyanuric chloride were also given.

# Part III

## Compounds Related to Urea.

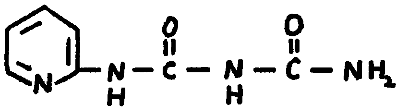
## Some Heterocyclic Biurets and 2-Pyrimidol

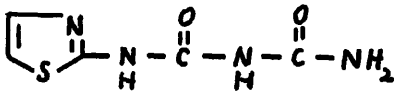
# Part III

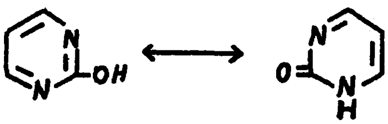
## Compounds Related to Urea.

### Some Heterocyclic Biurets and 2-Pyrimidol

The diuretic activity of substances such as caffeine and theophylline (page 4) which contain the recurring urea structure made it desirable to prepare several compounds containing this structure in order to gain a further insight into the relationship between structure and diuretic activity. With this objective in mind, an attempt was made to prepare 1-(2-pyridyl)biuret (I), 1-(2-thiazolyl)-biuret (II) and 2-pyrimidol (III). It should be noted that 2-pyrimidol is related to urea through its tautomeric isomer 2-pyrimidone.


I


II


III

A search of the literature did not reveal any heterocyclic biurets of the type illustrated by I and II. The Davis-Blanchard (19) method of synthesizing $\omega$-substituted biurets from nitrobiuret was successfully employed in the preparation of these heterocyclic biurets. Reduced to its simplest terms, this reaction may be represented by the equation

$$RNH_2 + H_2NCONHCONHNO_2 \longrightarrow RNHCONHCONH_2 + N_2O + H_2O$$

In this way 1-(2-pyridyl)biuret and 1-(2-thiazolyl)biuret were prepared in yields of 34 and 13% respectively.

Fisher (20) reported that the reaction of 2-aminopyridine hydrochloride with potassium cyanate in aqueous solution yielded 1-(2-pyridyl)urea, melting point 195°. Every attempt to duplicate this reaction has led to products which partially melted with gaseous decomposition over a range of 168-195°. Complete analyses in conjunction with the melting points of three different samples obtained from this reaction has led to the conclusion that the products isolated from this reaction are actually 1-(2-pyridyl)biuret in various states of purity*. It has been impossible to obtain an analytically pure sample from this reaction; however, an analytically pure sample of

---

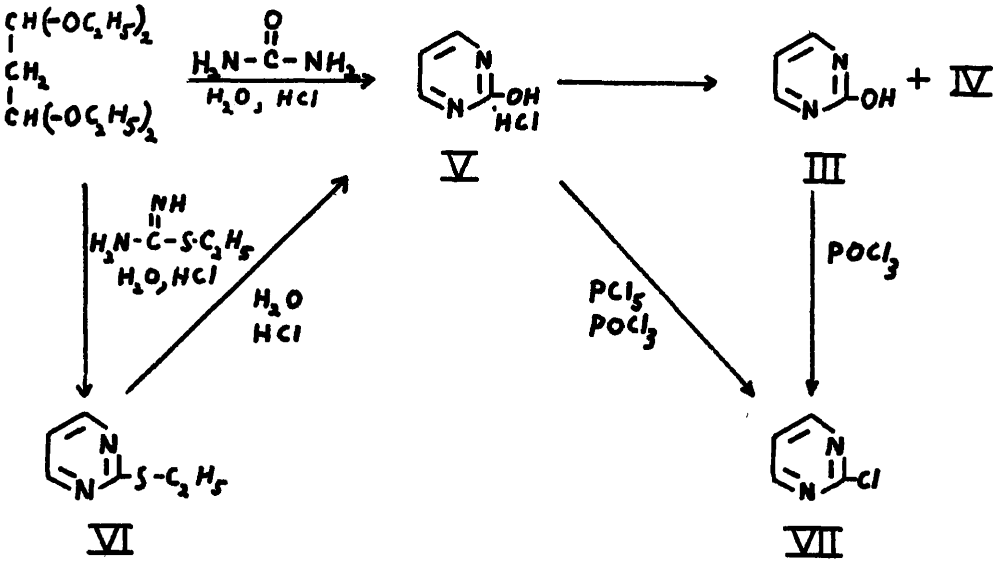
*The behavior of these materials in the biuret test tend to substantiate this conclusion. An inspection of the theoretical values required for 1-(2-pyridyl)urea and 1-(2-pyridyl)biuret will reveal that in addition to a nitrogen analysis (as carried out by Fisher (20) ), a carbon and hydrogen analysis is required to positively differentiate these compounds.

1-(2-pyridyl)biuret (melting point 197-198°) was obtained from the nitrobiuret reaction previously mentioned.

My theory finds support in the work of two Russian investigators (21) who also report that this reaction produces 1-(2-pyridyl)biuret, melting point 175°. The discrepancy between their melting point and my melting point immediately suggested the possibility that either their product was impure or that they had obtained a different form of 1-(2-pyridyl)biuret. The latter possibility was eliminated when the melting point of my compound was essentially unaltered by recrystallization from the solvent prescribed by these investigators.

Johnson and Joyce (22) have reported a four step synthesis of 2-pyrimidol (III) by the reaction of ethyl-$\gamma$-diethoxyacetoacetate with ethylisothiourea which involved the intermediate 2-ethylmercaptopyrimidine (VI). In order to eliminate this lengthy synthesis, 2-pyrimidol hydrochloride (V) was prepared from urea and malonaldehyde (bis-diethylacetal) in a 90.2% yield.

Contrary to the work of Johnson and Joyce (22), 2-pyrimidol did not separate as a yellow infusible amorphous substance when the aqueous solution of the hydrochloride was neutralized with sodium hydroxide. However, evaporation of the neutralized solution to dryness and extraction



with chloroform* yielded two substances (III and IV). The chloroform soluble substance (III) was a colorless and highly crystalline compound melting 182-183° which has been identified as 2-pyrimidol by analysis and conversion to and analysis of the 2-chloro derivative (VII). The physical properties (i.e. melting point and solubility in water) of this compound III are those that one would expect for a monohydroxypyrimidine. These facts have been confirmed by Brown (23) whose work was published at a time when this work was essentially complete.

Brown (23), who prepared 2-pyrimidol (III) by the

---

*I wish to acknowledge my considerable debt to Mr. T. E. Young for developing this method of extracting 2-pyrimidol.

alkaline hydrolysis of 2-aminopyrimidine, made no mention of encountering the yellow substance* erroneously described by Johnson and Joyce (22) as 2-oxypyrimidine. In the course of my work, substantial quantities of the yellow substance (IV) were isolated from the residue of the chloroform extraction previously mentioned.

The important steps in the Johnson-Joyce synthesis have been duplicated insofar as possible, in this laboratory, by starting with their intermediate, 2-ethylmercaptopyrimidine (VI). This mercapto compound was prepared in a 30.8% yield by the condensation of ethylisothiourea hydrobromide with malonaldehyde (bis-diethylacetal). The hydrolysis of 2-ethylmercaptopyrimidine with concentrated hydrochloric acid proceeded as described in the literature (22) to produce what appeared to be a nearly quantitative yield of

---

*The most important characteristics of the yellow spurious 2-pyrimidol (IV) may be summarized as follows: The dried hygroscopic powder is insoluble in common organic solvents but is slightly soluble in aqueous acid and base. Hot water extraction removes most of the color; when heated the material chars but does not melt up to 360°. This substance is formed (a) by recrystallization of colorless 2-pyrimidol hydrochloride from 95% ethanol (but not from methanol), (b) by evaporation to dryness of a sodium hydroxide neutralized solution of 2-pyrimidol hydrochloride (along with much free pyrimidol). (Neutralization of the hydrochloride with ammonia in methanol does not produce the spurious 2-pyrimidol). (c) When 2-pyrimidol hydrochloride is fused the yellow body may be isolated from the charred residue; ammonia is evolved during this heating. The spurious 2-pyrimidol produces only a trace of ether soluble product when treated in the usual way with a phosphorous oxychloride-pentachloride mixture. The infrared spectrum of this substance shows no similarity to the spectra of compounds containing the pyrimidine structure (see Part V).

2-pyrimidol hydrochloride (V). Contrary to the work of Johnson and Joyce (22), no precipitation of the yellow amorphous substance (IV) occurred upon neutralization of the hydrochloride with aqueous sodium hydroxide; therefore, the neutralized solution was evaporated to dryness on a steam bath and extracted with chloroform. In this manner, the true 2-pyrimidol was isolated from the neutralized solution. This proves that the Johnson-Joyce synthetic method is capable of producing 2-pyrimidol.

2-Chloropyrimidine (VII) was prepared by the reaction of phosphorous oxychloride alone or in combination with phosphorous pentachloride on 2-pyrimidol hydrochloride. The reaction was much more rapid and the yield slightly better when the mixture of chlorinating agents was employed. Matsukawa and Ohta (24) have reported a 93% yield of crude 2-chloropyrimidine by the interaction of phosphorous pentachloride and phosphorous oxychloride on the hydrochloride (V); it has been possible to obtain only a 61% yield of purified product using a comparable method.

## Experimental*

1-(2-Pyridyl)biuret (I). - 2-Aminopyridine (47 g. 0.5 mole) and nitrobiuret (25) (74.1 g., 0.5 mole) were dissolved in 830 ml. of water which had been heated to 70°. The

---

*All melting points have been corrected for thermometer stem-emergence unless otherwise noted.

temperature of the stirred solution was raised from 65 to 75° over a period of 2 3/4 hours; during this time gaseous evolution and precipitation occurred. The temperature of the reaction mixture was then raised to 90° over a period of 1 hour. The colorless granular crystals were filtered from the cooled solution and dried under vacuum over phosphorous pentoxide, yield 30.5 g. (33.8%), m.p. 194-195.5° with gaseous decomposition. Recrystallization from 95% ethanol gave an 87% recovery of colorless platelets, m.p. 197-198° with slight gaseous decomposition. Recrystallization of these crystals from water gave fine crystals, m.p. 196.2-197.2°. Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.46; H, 4.50; N, 31.56, 30.76.

1-(2-Thiazolyl)biuret (II). - 2-Aminothiazole (63.5 g., 0.635 mole) and nitrobiuret (25) (94.1 g., 0.635 mole) were dissolved in one liter of water which had been heated to 70°. The temperature of the stirred solution was held at 70 to 73° over a period of 3 hours during which gaseous evolution and precipitation of a white solid occurred. The temperature of the reaction mixture was increased at such a rate as to raise the temperature from 73 to 90° over a period of ½ hour; during this operation the reaction product became cream colored. The reaction mixture was then quickly cooled to 10° in an ice bath, filtered, and the light cream colored product dried under vacuum over phosphorous pentoxide, yield 14.73 g. (12.5%), m.p. 205-214° with gaseous decomposition and resolidification. This substance is heat labile and has a tendency to decompose upon recrystallization. The melting point of these crystals may be raised to 217-218° by rapid recrystallization from 95% ethanol. Anal. Calcd. for $C_5H_6N_4O_2S$: C, 32.25; H, 3.25; N, 30.09; S, 17.22. Found: C, 32.37; H, 3.43; N, 29.74; S, 17.05.

2-Aminopyridine hydrochloride was reacted with potassium cyanate according to the method of Fisher* (20), Potassium cyanate (43 g., 0.531 mole) was added to an aqueous solution of 2-aminopyridine (50 g., 0.531 mole) which had been converted to its hydrochloride by the addition of 246.4 ml. of 2.1562 N hydrochlorid acid. The reaction mixture was heated at just below reflux for 1 hour and cooled. The precipitated white powder (VIII) was filtered, washed with ice water and dried, yield 4.47 g., partially melted 194° with gaseous decomposition and resolidification. The adjustment of the aqueous filtrate to a pH 6 with concentrated hydrochloric acid caused a white powder (IX) to be precipitated, yield 5.19 g., partially melted 188-190° with gaseous decomposition and resolidification. Upon standing, another precipitate X was obtained from the aqueous mother liquor, yield 8.80 g.,

---

*The experimental results presented in this part are typical of those obtained from three different runs.

partially melted 168-171° with gaseous decomposition.

Fractions VIII, IX and X were combined, dissolved in 500 ml. of water which had been previously heated to boiling, and rapidly chilled in an ice bath. The yield of white powder (XI) was 6.30 g., m.p. 175-177° with gaseous decomposition. Upon standing another fraction of white powder (XII) precipitated from the aqueous mother liquor, yield 3.07 g., partially melted 180-182° with gaseous decomposition and resolidification. Fractional recrystallization of XI from absolute ethanol gave fractions XIII (yield .12 g., m.p. 194-195° with gaseous decomposition and resolidification) and XIV (yield 2.10 g., m.p. 180-183° with gaseous decomposition and resolidification). Anal. Found for XII: C, 44.89; H, 4.43; N, 30.80. Anal. Found for XIII: C, 43.12; H, 4.32; N, 30.32. Anal. Found for XIV: C, 42.75; H, 4.29; N, 30.30.

A comparison of this analytical data with the theoretical values required for 1-(2-pyridyl)urea and 1-(2-pyridyl)biuret indicates that these samples (XII, XIII, XIV) are the latter compound in varying degrees of purity. Anal. Calcd. for $C_6H_7N_3O$: C, 52.55; H, 5.15; N, 30.64. Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10.

Biuret tests. - Phenylbiuret and all the samples of 1-(2-pyridyl)biuret obtained from the nitrobiuret and potassium cyanate reactions gave a blue-violet color when treated with dilute copper sulfate and dilute sodium hydroxide. 1-(2-Thiazolyl)biuret gave an emerald green color with these reagents.

2-Pyrimidol hydrochloride (V). - A stirred solution of malonaldehyde (bis-diethylacetal) (239.75 g., 1.086 moles), urea (65.4 g., 1.086 mole), water (18 ml.) and acetone free methanol (500 ml.) was treated with a rapid stream of dry hydrogen chloride for seventy-five minutes. The orange colored reaction mixture was refluxed on a steam bath with stirring for one hour, cooled in an ice-salt bath, filtered and washed with three portions of dry ether. The yield of light cream-colored crystals (V) was 130 g. (90.2%) after drying under vacuum over potassium hydroxide and phosphorous pentoxide, m.p.* 205-207° with gaseous decomposition. Almost colorless crystals of V may be obtained by using a larger volume of methanol and deletion of the reflux periods; this modification reduces the initial yield to 76%; concentration of the mother liquor yields an additional 16.6%. Recrystallization of V from 99.5% methanol does not significantly alter its appearance of melting point.

2-Pyrimidol (III). - A warm solution of 2-pyrimidol hydrochloride (10 g., .0754 moles) in 100 ml. of 99.5% acetone free methanol was treated gradually with 50 ml. of methanol which had been saturated with dry ammonia gas.

---

*Johnson and Joyce (22) have reported a m.p. 203-205°

The mixture was evaporated to dryness under reduced pressure after dry ammonia had been bubbled into the methanolic solution for several minutes. The 2-pyrimidol - ammonium chloride mixture was pulverized, dried under vacuum over $P_2O_5$, mixed with 30 g. of dry sand and extracted with 100 ml. of dry chloroform in a Soxhlet extractor for a total of twenty-eight hours. (The mixture was repulverized three times during this process in order to facilitate the extraction process.) Evaporation of the chloroform extract to dryness under reduced pressure yielded 7.17 g. (99%) of light cream colored crystals (III), m.p. 181-183°. Recrystallization of these crystals from 80 ml. of absolute ethanol yielded 6.3 g. of long spear-shaped crystals, m.p.* 182.2-183.1°. Anal. Calcd. for $C_4H_4N_2O$: N, 29.15. Found: N, 29.22.

The <u>titration curve</u> of 2-<u>pyrimidol hydrochloride</u> (V) has been found to be that of a salt of a weak base followed by that of a weak acid. An electrometric titration of a 0.03155 N solution of V with 0.12620 N sodium hydroxide showed a very sharp change in pH between pH 4.3 and pH 6.8. The first equivalence point occurred at a pH 5.6. Further titration converted the liberated 2-pyrimidol (III) into its sodium salt; the second equivalence point occurred at pH 10.2.

---

*Brown (23) reported a m.p. 178-180°.

The yellow amorphous powder (IV) may be prepared by any of the methods previously described. The following method illustrates the conditions required for the transformation to take place. 2-Pyrimidol hydrochloride (10 g.) dissolved in 175 ml. of 95% ethanol was refluxed for a total of 61 hours over a period of nine days. The yellow-brown crystalline solid (XV) precipitated during this period was periodically filtered off in order to prevent bumping, yield 4.35 g.; it did not melt at 360°. This substance was suspended in 40 ml. of cold water and adjusted to a pH 7.5 with aqueous sodium hydroxide. The insoluble yellow powder (IV) thus obtained was filtered, washed with water and dried at 100°, yield 1.3 g., gradually darkened but did not melt at 360°; it was insoluble in water and the common organic solvents. An additional 0.9 g. of this yellow substance was obtained by evaporation of the ethanolic mother liquor of XV to dryness and treating the residue as described for XV.

The following analytical data was obtained from five different samples of this yellow substance (IV) which were isolated under various conditions during the course of this investigation. Found for IV: C, 42.56, 43.56; H, 5.72, 5.43; N, 25.71, 25.29, 25.16, 25.39, 25.52.

2-Chloropyrimidine* (VII). - 2-Pyrimidol hydrochloride

---

*By using essentially this same method, 2-pyrimidol itself was chlorinated to produce VII: since this modification does not offer any advantage, it is not included.

(V) (132.6 g., 1 mole), phosphorous pentachloride(251 g., 1.2 mole) and phosphorous oxychloride (450 g., 2.9 mole) were heated in an oil bath at 135° for 3¼ hours. Approximately 560 g. of the chlorination mixture was distilled off under reduced pressure; colorless crystals were observed in the distillate near the end of this distillation process. Approximately 5 g. of these crystals were filtered from the chilled distillate; after treatment in the manner described for the residue of the distillation, a 1.5 g. yield (1.3%) of 2-chloropyrimidine (VII) was obtained, m.p. 69.0-70.3°.

The residue from the concentration was poured on ice and adjusted to a pH 7 by slowly adding 48% sodium hydroxide to the cooled solution. The aqueous solution was decanted from a pitch-like substance which was suspended in water and adjusted to a pH 10 in order to dissolve it. The two solutions were combined, readjusted to a pH 7 and extracted with ether. Distillation of the dried solution gave 69 g. (60.3%) of 2-chloropyrimidine b.p.$_{17}$ 81°, m.p. 65-69.5°. Recrystallization from 250 ml. of petroleum ether (b.p. 60-68°) gave 53.1 g. of large colorless crystals, m.p.* 67.8-70.2°. Anal. Calcd. for $C_4H_3N_2Cl$: N, 24.46. Found: N, 24.38.

2-Ethylmercaptopyrimidine (VI). - Ethylisothiourea hydrobromide** (49.6 g., 0.268 mole), 70 ml. of Baker's

---

*Matsukawa and Ohta (24) reported a m.p. 65°, b.p.$_{26}$ 91°.

**Prepared in 99.3% yield according to Wheeler, Merriam and Bristol (26,27).

acetone free methanol and malonaldehyde (bis-diethylacetal) (59.2 g., 0.268 mole) were treated with a rapid stream of dry HCl gas for 1 3/4 hours while stirring; during this time the reaction mixture went to reflux and became dark brown in color. The reaction mixture was cooled in an ice bath for ½ hour without effecting crystallization. The reaction mixture was concentrated to a heavy brown oil under reduced pressure while heating in a hot water bath. The dark brown oil was dissolved in 150 ml. of cold water and adjusted to a pH 8 by adding solid sodium carbonate. The dark solution was extracted with ten 100 ml. portions of ether and the extract dried over $MgSO_4$. The dried ether solution was concentrated and distilled. The yield of light yellow liquid was 11.58 g. (30.8%), b.p.*$_{18}$ 110 to 113°.

## Summary

Two new heterocyclic biurets were prepared from the corresponding amines and nitrobiuret. The reaction of 2-aminopyridine with potassium cyanate was shown to produce 1-(2-pyridyl)biuret in various states of purity rather than 1-(2-pyridyl)urea as reported in the literature.

The isolation of 2-pyrimidol and the factors responsible

---

*Johnson and Joyce (22) reported a boiling point of 115° at 20 mm. pressure. They reported the melting point of the hydrochloride to be 98-99°. The hydrochloride prepared from this sample of 2-ethylmercaptopyrimidine melted 100.8-102.7°.

for the production of a yellow amorphous substance, incorrectly described in the literature as 2-oxypyrimidine, were discussed. It was shown that the yellow material previously believed to be 2-pyrimidol is actually a mixture of partially hydrolyzed and polymerized pyrimidines. New syntheses of 2-pyrimidol hydrochloride, 2-chloropyrimidine and 2-ethylmercaptopyrimidine were also given.

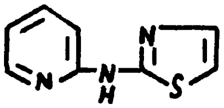
# Part IV

## Some Heterocyclic Secondary Amines

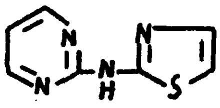
## Part IV

### Some Heterocyclic Secondary Amines

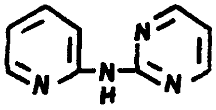
As part of the program on the synthesis of potential diuretics, an attempt has been made to prepare the following basically substituted heterocyclic compounds containing the amidine structure. Of these six secondary amines, only the unsymmetrically substituted ones were successfully synthesized.



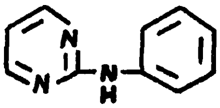
2-Pyridyl-2'-
thiazolylamine



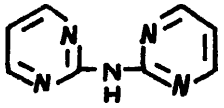
2-Pyrimidyl-2'-
thiazolylamine



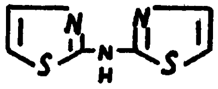
2-Pyridyl-2'-
pyrimidylamine



2-Anilino-
pyrimidine

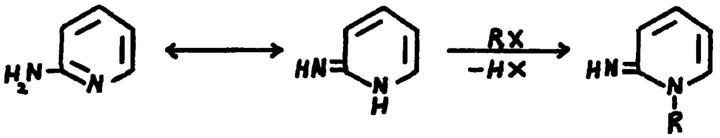


2,2'-Dipyrimidyl-
amine



2,2'-Dithiazolyl-
amine

These compounds were prepared by the reaction of the sodium salt of a primary amine with an "active" heterocyclic halide. The sodium salt of the amine was employed since it has been established (28) that the ring nitrogen of 2-aminopyridine, for example, is capable of substitution via the imino form of the amine. The necessity of employ-



ing the sodium salt of the amine has been substantiated during the course of this investigation.*

Although this method of synthesis employed appears to be straightforward, the actual preparation of pure samples of these amines has involved considerable difficulty. It has been impossible to develop one set of conditions which would satisfactorily lead to all the desired products. The great differences in reactivity and stability among the sodio salts of 2-aminopyridine, 2-aminothiazole and 2-aminopyrimidine are undoubtedly factors contributing to this problem. Adams and Whitmore (29) noted that the sodium

---

*The direct fusion of 2-chloropyrimidine with 2-aminopyridine for 42 hours at approximately 100° gave an ionic halogen compound which upon treatment with base liberated a substance which melted 182-184°; in contrast, the reaction of the sodium salt of the amine with the same halide gave 2-pyridyl-2'-pyrimidylamine which melted at approximately 150-152°. The higher melting material was not investigated further but may have been an isomeric compound formed by the reaction of a ring nitrogen.

derivative of 2-aminopyrimidine is so unreactive that it is stable in ordinary laboratory air. It has been frequently noted, during the course of this work, that this substance has a very low reactivity in halogen replacement reactions. Another factor of importance in complicating the picture is the great difference in reactivity of the 2-halo-derivatives of the same heterocycles. Thus, in fusion reactions 2-chloropyrimidine has been found to produce charred, infusible, apparently polymeric materials which could not be purified. Other work done in this laboratory (30) has shown that this compound is very considerably more reactive than either 2-bromopyridine or 2-chlorothiazole.

Anhydrous solvents such as benzene were successfully employed in certain cases; however, in other cases it was necessary to react the sodium salt of the amine directly with the halogen compound. The lack of consistency in this field is illustrated by the work of Maggiolo, Phillips and Hitchings (31). They found that 2-aminopyridine would not react with 2-methyl-4-amino-6-chloropyrimidine either in aqueous solution or by direct heating in the absence of a solvent while a variety of aliphatic and aromatic amines reacted easily and in good yield.

The sodium salt of 2-aminopyridine reacted with 2-chlorothiazole in refluxing benzene to produce a 40% yield of 2-pyridyl-2'-thiazolylamine. Similarly, the sodium salt of aniline reacted with 2-chloropyrimidine to give a 22% yield of 2-anilinopyrimidine.* In contrast, the reaction of the sodium salt of 2-aminopyrimidine with 2-chlorothiazole in benzene led to no reaction; the same reactants in para-cymene produced an insoluble and infusible substance which probably arose from ring rupture. This latter reaction was successfully carried out in 9.5% yield by the direct reaction of the sodium salt of the amine with the heterocyclic halide. Correspondingly, the sodium salt of 2-aminopyrimidine and 2-aminopyridine did not produce 2-pyridyl-2'-pyrimidylamine when refluxed in benzene with 2-bromopyridine and 2-chloropyrimidine respectively; however, the direct reaction of the sodium salt of 2-aminopyrimidine with 2-bromopyridine produced a 27% yield of 2-pyridyl-2'-pyrimidylamine.

Ten individual attempts were made to prepare 2,2'-dipyrimidylamine through the interaction of 2-aminopyrimidine or its sodium salt with 2-chloropyrimidine. The conditions employed involved the direct fusion of the reactants or the use of anhydrous solvents such as benzene, toluene, ether, ethanol and liquid ammonia. In all cases either unreacted starting materials or charred infusible substances were isolated from the reaction mixtures.

---

*This reaction was run in order to determine the stability of 2-chloropyrimidine in the presence of a sodium salt of an active primary amine.

The reaction of the sodium salt of 2-aminothiazole with 2-chlorothiazole in refluxing toluene produced an infusible brown substance which evolved hydrogen cyanide and hydrogen sulfide upon acidification.

The halides employed in these reactions were prepared by diazotization of the corresponding amines with the exception of 2-chloropyrimidine which was prepared from 2-pyrimidol hydrochloride as described in Part III of this dissertation.

The sodium salt of 2-aminopyrimidine was more effectively prepared by the reaction of the amine with freshly prepared sodium amide in liquid ammonia rather than in an aromatic solvent.*

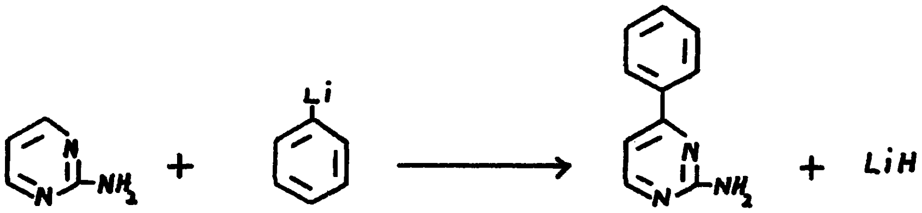
An attempt was made to prepare the lithium salt of 2-aminopyrimidine by the reaction of phenyllithium with the amine in refluxing toluene. Instead of obtaining the lithium salt, 2-amino-4-phenylpyrimidine was isolated in 20% yield from this reaction. This compound has been prepared by several investigators (32, 33, 34) through the use of ring closure methods on guanidine salts.

Although such compounds as pyridine (35) and quinoline (36) have been reported to give ring substituted products with phenyllithium, this reaction is unique in the respect

---

*Adams and Whitmore (29) have prepared this sodium salt in refluxing toluene.

that it was carried out in the presence of an amino group. It is possible that this substituted pyrimidine was formed



by a 1,2-addition of phenyllithium at the nitrogen to carbon double bond of the pyrimidine ring; however, there does not appear to be any evidence to exclude a 1,4-addition to the conjugated system of the imino dihydro form of 2-aminopyrimidine.

## Experimental*

Sodium Salt of 2-aminopyrimidine and 2-aminopyridine.- 2-Aminopyrimidine (19.02 g., 0.2 mole) was added over a 10 minute period to a solution of sodium amide** (.2 mole) in approximately 200 ml. of anhydrous liquid ammonia. After 2 additional hours of stirring, the solvent was evaporated, the gray-white salt pulverized, extracted with two 100 ml.

---

*All melting points have been corrected for thermometer stem-emergence.

**Prepared from sodium and liquid ammonia according to T. H. Vaughn, R. R. Vogt and J. A. Nieuwland (37).

portions of boiling anhydrous benzene and dried under vacuum over phosphorous pentoxide, yield 19 g. (85%).

The sodium salt of 2-aminopyridine was prepared in an analogous manner except for the extraction process which was deleted; this salt was dark blue in color.

<u>2-Pyridyl-2'-thiazolylamine</u>. - The sodium salt of 2-aminopyridine (35.9 g., 0.3 mole) was refluxed in 50 ml. of anhydrous benzene with stirring for ½ hour in order to insure complete reaction. 2-Chlorothiazole* (30 g., 0.25 mole) in 40 ml. of anhydrous benzene was added over a 10 minute period to the warm suspension of the sodium salt while the reaction flask was being cooled in a cold water bath. The reaction mixture was then stirred and heated at gentle reflux for 10 hours. The dark brown mixture was cooled and extracted with 250 ml. of a 1:1 mixture of concentrated hydrochloric acid and water. The acidic extract was cooled and adjusted to a pH 10 with 48% sodium hydroxide. The tan colored precipitate was filtered, washed with four 50 ml. portions of cold water and dried at 100°, yield 22 g., m.p. 191.8-193°. Recrystallization from 95% ethanol after treatment with charcoal gave 17.9 g. (40.3%) of light tan colored needles, m.p. 195.8-196.6°; sublimation at 15 mm. pressure and recrystallization from ethanol gave colorless needles which had essentially the same melting point as the

---

*Prepared from 2-aminothiazole according to Ganapathi and Venkataraman (38).

discolored crystals. Anal. Calcd. for $C_8H_7N_3S$: C, 54.22; H, 3.98; N, 23.72; S, 18.09. Found: C, 54.32; H, 4.13; N, 23.75; S, 17.95.

2-Pyridyl-2'-pyrimidylamine. - The sodium salt of 2-aminopyrimidine (22.65 g., 0.193 mole) and 2-bromopyridine (30.6 g., 0.193 mole) were heated in an oil bath at 150-170° for 45 minutes. The cooled reaction mixture was thoroughly extracted by shaking it with several portions of cold water; the addition of a cold 1:1 mixture of ethanol and ether converted the sticky mixture into a light cream colored powder which was filtered, washed with ether and dried under vacuum over phosphorous pentoxide, yield 9.1 g. (27.2%) m.p. 149.6-151.7°. Recrystallization from ethanol gave light cream colored hexagonal plates, m.p. 149.3-152.1°; vacuum sublimation under 2 mm. pressure produced colorless crystals, m.p. 150.2-152.1°. Anal. Calcd. for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.82; H, 4.68; N, 32.47.

2-Anilinopyrimidine*. - A mixture of aniline (3.26 g., .035 mole) and sodium amide (1.37 g., .035 mole) in 35 ml. of dry benzene were heated and stirred for 3¼ hours in an oil bath at 92° under an atmosphere of nitrogen. 2-Chloropyrimidine** (4 g., .035 mole) in 200 ml. of anhydrous

---

*Johnson and Heyl (40) prepared this compound by the reduction of 4-chloro-2-anilinopyrimidine. They reported a melting point of 116°.

**This compound was prepared from 2-pyrimidol hydrochloride; see page 36 of this dissertation.

benzene was added to the cooled reaction mixture. After this addition, the mixture was heated and stirred at gentle reflux for 4½ hours, cooled, and then steam distilled. The distillate was acidified with concentrated hydrochloric acid and shaken to extract the amine from the benzene layer of the distillate. A brown colored solid was precipitated from the acidic solution upon adjusting it to a pH 10, yield 2.7 g. Solution of this substance in boiling water and filtration from insoluble impurities gave 1.3 g. (22%) of colorless needles, m.p. 114.3-115.2°.

<u>2-Pyrimidyl-2'-thiazolylamine</u>. - The sodium salt of 2-aminopyrimidine (22.18 g., 0.189 mole) and 2-chlorothiazole (22.58 g., 0.189 mole) were heated in an oil bath at 95° for 2 3/4 hours when it became necessary to cool the reaction mixture in order to moderate an exothermic reaction which had developed; the reaction mixture was then heated for an additional 6 hours at 95°, cooled, suspended in 50 ml. of water and steam distilled (6 g. of 2-chlorothiazole were recovered). The residue from the steam distillation was filtered, washed with cold water and dried at 100°, yield 3.1 g. (9.5%), m.p. 209-211.8°. Cream colored crystals were obtained upon recrystallization from ethanol, m.p. 211-212.1°. Vacuum sublimation under 6 mm. pressure and recrystallization from ethanol gave colorless crystals, m.p. 212.1-212.6°. Anal. Calcd. for $C_7H_6N_4S$: C, 47.18;

H, 3.39; N, 31.44; S, 17.99. Found: C, 47.22; H, 3.44; N, 31.44; S, 17.89.

2-Amino-4-phenylpyrimidine*. - 2-Aminopyrimidine (9.51 g., 0.1 mole) in 500 ml. of hot dry toluene was added over a half hour period to phenyllithium** (prepared from 31.4 g. of bromobenzene and 2.78 g. of lithium metal) in 140 ml. of anhydrous ether. The ether was allowed to distil from the reaction mixture during this addition; when the bath temperature reached 115°, the condenser was set for reflux and the residual mixture was refluxed with stirring for 7 hours. While cooling the reaction mixture in an ice bath, a few ml. of water and 300 ml. of a 1:1 mixture of concentrated hydrochloric acid and water were cautiously added with stirring. The acidic extract was separated from the toluene and adjusted to a pH 9 by cautiously adding 48% sodium hydroxide to the cooled solution. The precipitated tan solid was filtered, washed with cold water and dried, yield 6.9 g., m.p. 146-157°. Recrystallization from 95% ethanol after treatment with decolorizing charcoal gave 3.4 g. (20%) of cream colored needles, m.p. 162-164°. Two additional recrystallizations from ethanol gave nearly colorless needles, m.p. 164.4-165.1°. The last trace of

---

*Other investigators (32, 33, 34) have reported preparing this compound in poor yield by ring closure methods; they reported melting points at 164 and 165°.

**The phenyllithium used in this reaction was prepared according to "Organic Syntheses" (35).

color was removed by vacuum sublimation at 9 mm. pressure; the melting point was not significantly altered. Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70,11; H, 5.37; N, 24.47.

## Summary

The preparation of four unsymmetrical heterocyclic secondary amines was given. These amines were prepared by the reaction of the sodium salt of the amine with a heterocyclic halide alone or in refluxing benzene. The reaction of 2-aminopyrimidine with phenyllithium has been shown to produce 2-amino-4-phenylpyrimidine in fair yield.

# Part V

## Some Infrared Spectra

# Part V

## Some Infrared Spectra

The infrared absorption spectra of many of the compounds prepared during the course of this investigation have been determined in an effort to supplement the few existing spectra in this field. The long range objective of this part of the program was to identify the vibrational frequencies corresponding to the substituents and to identify the characteristic vibrational frequencies of the pyrimidine, pyridine, thiazole and s-triazine rings.

In this connection, it became desirable to have a complete spectrum of pyrimidine for reference*. A search of the literature disclosed the fact that pyrimidine had only been synthesized by three methods which were considered to be cumbersome and unsatisfactory from the standpoint of yield and availability of starting materials. The three methods that have been reported to produce pyrimidine are: decarboxylation of pyrimidine-5-carboxylic acid (43) and the reduction of either tri- (44) or tetrachloropyrimidine (45) with zinc dust and water.

An unsuccessful attempt was made to reduce 2-chloropyrimidine with zinc dust and water. The failure of 2-

---

*A limited portion of the spectrum of pyrimidine has been previously reported by Barnes, Liddel and Williams (41) and also by Brownlie (42).

chloropyrimidine to be reduced by this method is not too surprising after one inspects the existing literature (44-48) on the reduction of chloropyrimidines with zinc and water. This data reveals the fact that the chlorine in 2-chlorosubstituted pyrimidines is reduced with great difficulty or not at all under these conditions.

The work of Childress and McKee (49) on the preparation of chloroaminopyrimidines from tetrachloropyrimidine appears to be pertinent. These investigators found that tetrachloropyrimidine reacted more readily with ammonia than 2,4,6-trichloropyrimidine. They also found that ammonolysis of tetrachloropyrimidine yielded a mixture of 2,4,6-triaminopyrimidine and 4,6-diamino-2,5-dichloropyrimidine; this reaction showed the 2-chloro substituant to be less reactive than the 4 or 6. It appears as though the 2-position rivals the 5-position in resisting reaction with ammonia. In order to reduce 2,4,6-triamino-5-chloropyrimidine, it was necessary to carry out the reduction under pressure in the presence of Palladium on charcoal and Adams Catalyst.

This collection of data made it appear that a low pressure reduction was required to reduce 2-chloropyrimidine. The reduction was carried out in the presence of a platinum oxide - palladium on charcoal catalyst and also with the latter catalyst alone under a hydrogen pressure of forty pounds per square inch. The ethanolic solution of the halogen compound underwent an exothermic reaction and rapidly absorbed approximately four moles of hydrogen. The highly hydroscopic crystalline basic ionic halogen compound isolated by the concentration of the ethanolic solvent did not have the properties anticipated for pyrimidine hydrochloride. Although this substance had approximately the melting point required for 1-amino-3-methylaminopropane hydrochloride (50, 51) it did not act as expected upon treatment with base; concentration of an ether extract of the basic solution yielded a colorless oil which decomposed upon distillation. A picrate of the distillate melted too high for the dipicrate of 1-amino-3-methylaminopropane (51, 52). These are the properties that Titherly and Branch (53, 54) have ascribed to hexahydropyrimidine which is supposedly in equilibrium with its open chain tautomer, methylene-$\alpha,\gamma$-diaminopropane. The present work lacks conformation of this structure since it has been impossible to prepare their dibenzoylderivative.

In 1937, several investigators (55, 56) reported the removal of the sulfhydryl group from some trisubstituted pyrimidines. It appeared that this reaction could be used for the removal of the sulfhydryl group of 2-pyrimidinethiol in the preparation of pyrimidine. In this connection, 2-pyrimidinethiol hydrochloride was synthesized in an 84% yield by the condensation of malonaldehyde (bisdiethylacetal) with thiourea under the influence of hydrogen chloride. No reference to this procedure has been noted in the literature. This compound is so slightly basic that recrystallization of it from water produces the free base. Just recently Roblin and Clapp (57) have reported that 2-pyrimidinethiol can be prepared in a 30% yield by the reaction of 2-chloropyrimidine with sodium hydrosulfide. Their product melted 219-220° with decomposition; the sample of 2-pyrimidinethiol prepared and analyzed during the course of this investigation melted 238° with decomposition. The oxidation of 2-pyrimidinethiol hydrochloride with 12% hydrogen peroxide appeared to go as anticipated; however, only a small quantity of a substance having an aldehydic odor was isolated from the reaction mixture. It appears as though the pyrimidine ring must have been destroyed during this reaction.

The sulfhydryl group of 2-pyrimidinethiol was successfully removed by the Mozingo reaction (58) which involved the use of highly active Raney nickel catalyst. This new synthesis produced a 31% yield of pyrimidine in a relatively easy manner. The purification of pyrimidine was complicated by the presence of a highly basic substance which was produced by the undesired hydrogenation of the pyrimidine ring. Application of the same reaction to 2-ethylmercaptopyrimidine produced a mixture of pyrimidine and this basic substance which was even more difficult to separate. A comparison of the physical properties of pyrimidine with those previously reported (43) appears in Table I.

Table I

| Compound | Reported by Gabriel and Coleman | This work. |
|---|---|---|
| Pyrimidine<br>($C_4H_4N_2$) | narcotic odor<br>b.p.$_{762}$ 123.5-124°<br>m.p. 20-22°<br>long crystals | pyridine-like odor<br>b.p.$_{767}$ 125-125.5°<br>m.p. 18.4-20.4°<br>long crystals |
| Picrate<br>($C_{10}H_7N_5O_7$) | m.p. 156°<br>yellow needles | m.p. 153.5-154.5°<br>yellow needles |
| $C_4H_4N_2 \cdot HgCl_2$ | white needles | white needles. |

The infrared absorption spectra of thirty compounds containing the amidine structure are given on pages 61 to 66. Table II contains a key to the spectra and lists the absorption frequencies* (in microns) which have been tentatively assigned to N-H and C-H stretching vibrations. Since some of the correlations are tentative and much overlapping of band positions occurs in these compounds, this data is presented mainly as a starting point for future work.

---

*The determination of these spectra was carried out on a Baird Infrared Spectrophotometer. Since all of these compounds were only soluble in solvents which absorb strongly, most of them were examined as a capillary layer of a fine suspension of the compound in "Nujol". All compounds which were liquid at room temperature, were examined in a .01 mm. cell.

The interpretation of these spectra has been complicated by the symmetry, tautomeric isomerism and hydrogen bonding which many of these compounds exhibit. Furthermore, the bands due to one group in one compound occupy approximately the same position assigned to another structural element in a similar compound. This is particularly true in the case of the carbon-nitrogen double-bond and the carbon-carbon double-bond. In view of this difficulty, it is not surprising that such simple compounds as urea, thiourea and guanidine have not had their infrared absorption frequencies assigned to specific structures. To a large extent, the inherent difficulty of this problem arises out of the similarity in mass of carbon and nitrogen, and in the strength of the bonds which they form.

The carbon-carbon double-bond vibrations are usually such that the intensity of the infrared absorption is very low; however, it is impossible to predict the extent to which these vibrations will be shifted and intensified by a change in dipole moment created by a conjugated carbon-nitrogen double-bond entering strongly into the same mode of vibration.

Since the frequencies observed in these highly conjugated compounds appear to have been altered, it has been impossible to make use of the accepted (41, 59, 60, 61, 62) frequencies of the carbon-carbon double-bond and the carbon-nitrogen double-bond to unambiguously locate and differentiate the bands due to these structural elements. Authoritative references (59, 60, 63) have indicated that absorption bands arising from the nitrogen-hydrogen bending vibrations are also expected to be found in the double-bond region. It appears that the spectra of the double-bond region in many of these compounds is complicated by such bonds or by ionic forms of such bonds. The spectra of the trisubstituted-s-triazines makes it appear as though the carbon-nitrogen double-bond stretching vibration is to be found in the vicinity 6.2 microns. Because of the lack of time and insufficiency of properly substituted compounds, no attempt will be made to identify these structural elements at this time.

Brownlie (42) has reported that his sample of pyrimidine did not show a band at 1775 $cm.^{-1}$ while that of Barnes (41) did show such a band; the sample of pyrimidine (curve #24) prepared during the course of this investigation has produced a band at 1770 $cm.^{-1}$ (5.63 microns). The sample of pyrimidine synthesized during the course of this investigation has produced a strong sharp band at 3067 $cm.^{-1}$. (3.26 microns) which corresponds to the benzene carbon-hydrogen aromatic valency vibration at 3065 $cm.^{-1}$; Brownlie has failed to observe this band.

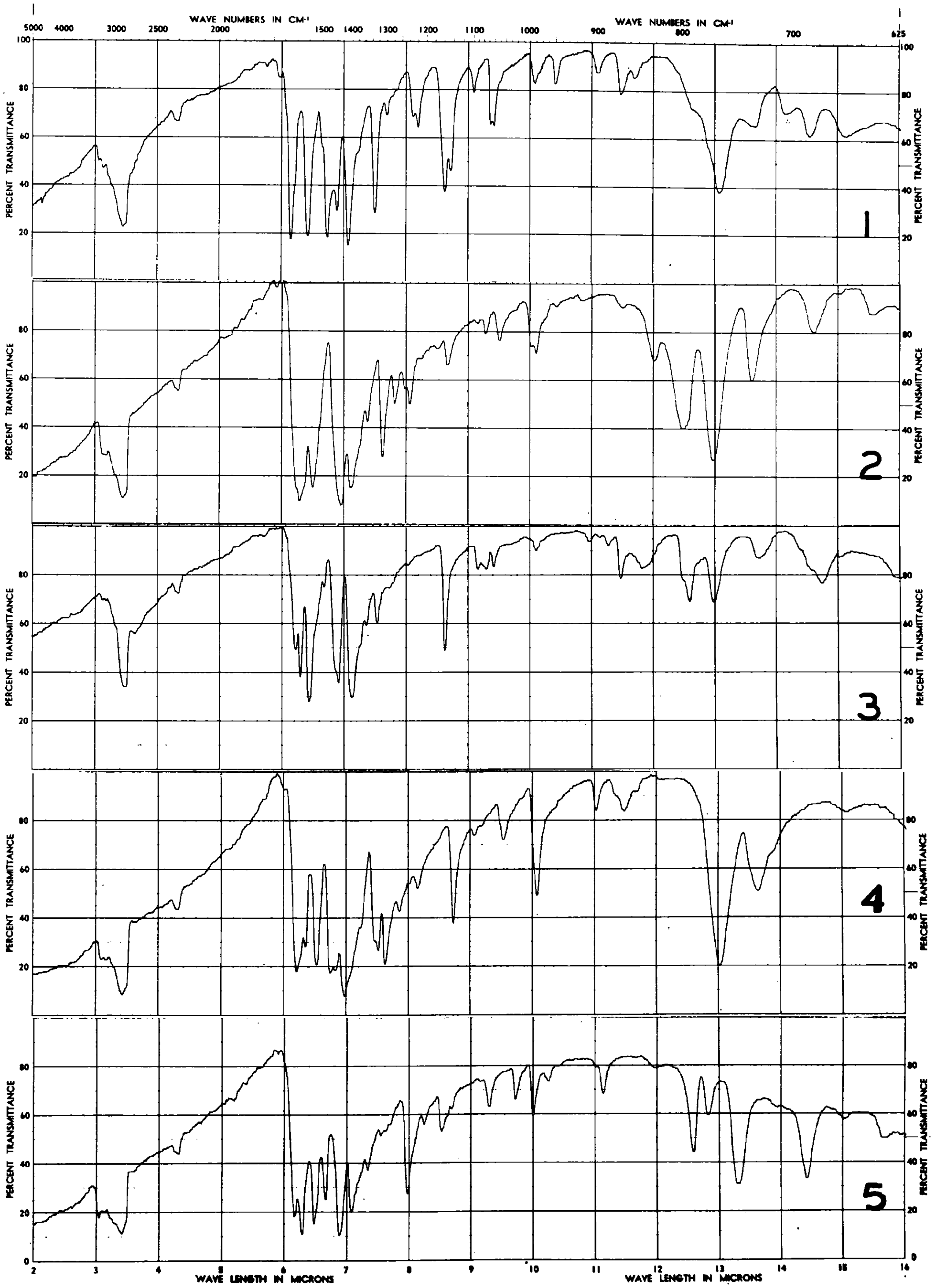
Marion, Ramsay and Jones (63) have stated that unassociated hydroxyl groups show a sharp absorption band in the region 3700-3500 $cm.^{-1}$. 2-Pyrimidol hydrochloride (curve #29) shows a sharp band at 3480 cm.$^{-1}$ (2.87 microns); it is likely that this band is due to a trace of water since the compound is hygroscopic and its parent compound 2-pyrimidol (curve #30) did not show such a band. It appears that the common nomenclature of these compounds is misleading since 2-pyrimidol and its hydrochloride show strong sharp absorption bands due to the carbon-oxygen double-bond at 1724 cm.$^{-1}$ (5.80 microns) and 1745 cm.$^{-1}$ (5.73 microns) respectively. Randall, Fowler, Fuson and Dangl (59) have made the statement that any strong band between 5.5 and 5.9 microns is almost certainly due to a carbonyl bond. The strong broad band in these two compounds in the 3.3 to 3.8 micron region is probably due to association. It is believed that this association band is overlapped by a band arising from the hydrogen chloride group in the case of the salt. Several investigators (63, 64) have reported that a strong band at 6.01 microns is characteristic of a cyclic amide. 2-Pyrimidol has a strong band at 6.01 microns (1665 cm.$^{-1}$) and its hydrochloride has a weak band at 6.05 microns (1653 cm.$^{-1}$) which may be due to this group.

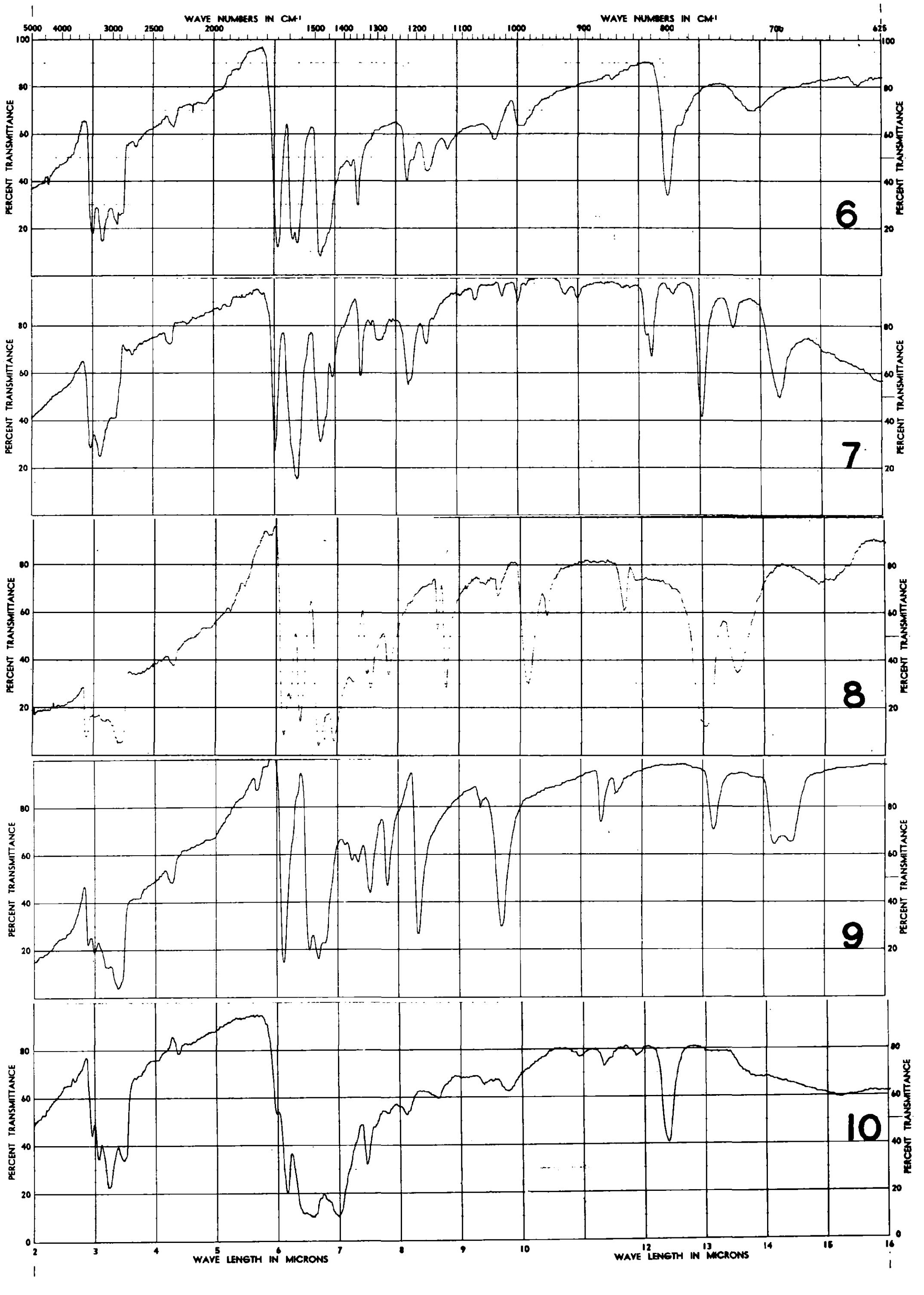
2-Pyrimidinethiol (curve #26) has a strong broad band at 4.00 microns (2500 cm.$^{-1}$) which is probably due to the associated sulfhydryl group.

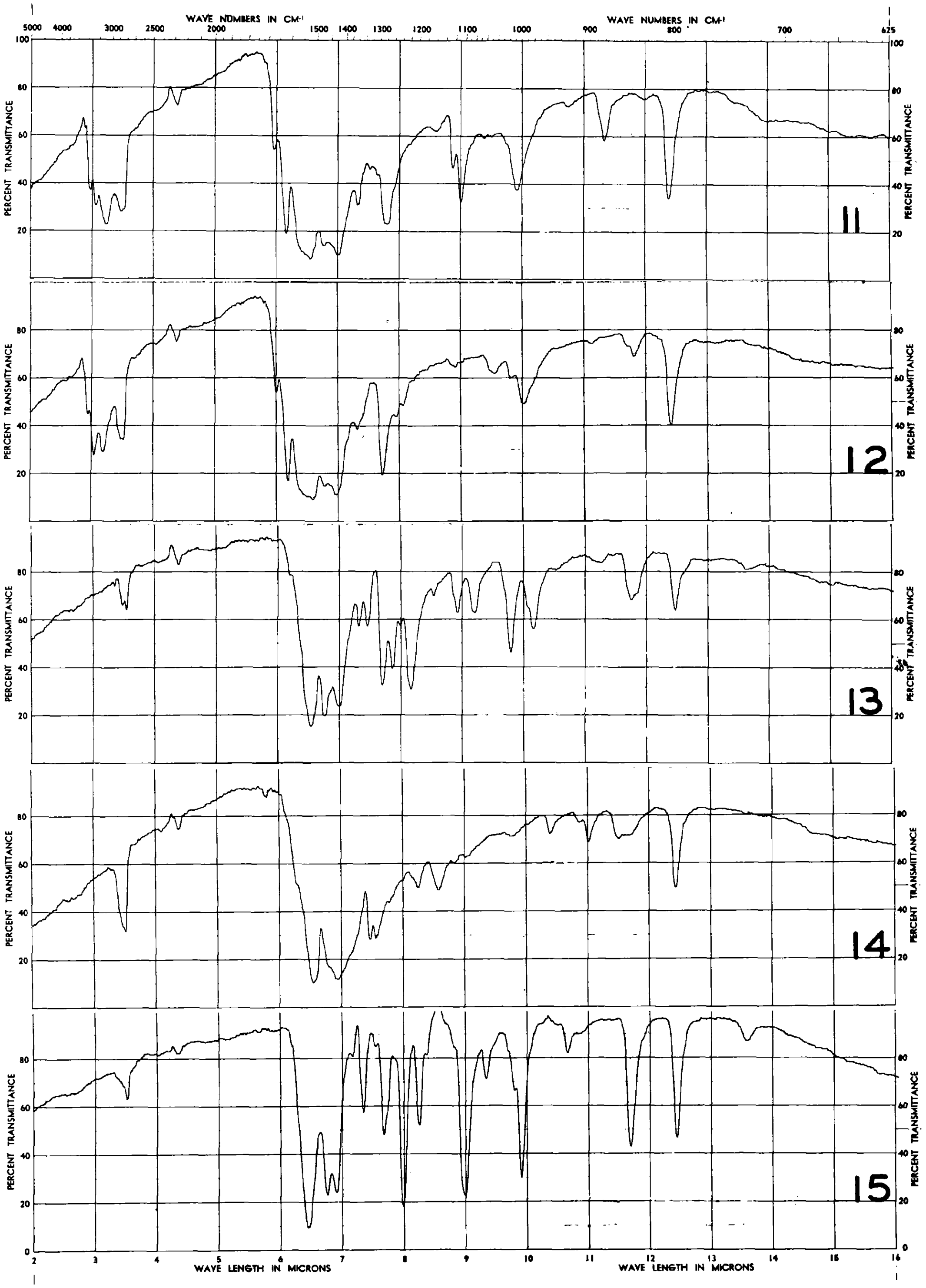
The single bond vibration due to the C-O-C vibration in 2-(4-morpholinyl)-4,6-diamino-s-triazine (curve #11)

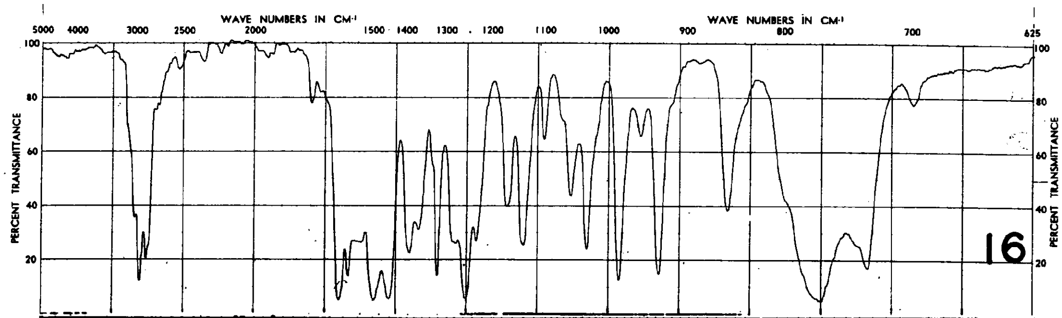
## Table II

| No. | Compound | N-H Str. | C-H Str. |
|---|---|---|---|
| 1 | 2-Pyridyl-2'-thiazolylamine | 3.05, 3.13 | 3.43 |
| 2 | 2-Pyrimidyl-2'-pyridylamine | 3.10, 3.20 | 3.43 |
| 3 | 2-Pyrimidyl-2'-thiazolylamine | 3.11, 3.18 | 3.46 - 3.50 |
| 4 | 2,2'-Dipyridylamine | 3.08, 3.18 | 3.42 |
| 5 | 2-Anilinopyrimidine | 3.04 | 3.41 |
| 6 | 2-Aminopyrimidine | 3.00, 3.18 | 3.42, 3.44 |
| 7 | 2-Amino-4-phenyl-pyrimidine | 2.98, 3.11 | 3.30, 3.39 |
| 8 | 2-Aminopyridine | 3.02, 3.19 | 3.40 - 3.47 |
| 9 | 2-Aminothiazole | 3.00, 3.19 | 3.39 |
| 10 | 2-(1-Pyrrolidyl)-4,6-diamino-s-triazine | 2.96, 3.06 | 3.23, 3.48 |
| 11 | 2-(4-Morpholinyl)-4,6-diamino-s-triazine | 2.98, 3.05 | 3.22, 3.48 |
| 12 | 2-(1-Piperidyl)-4,6-diamino-s-triazine | 2.94, 3.03 | 3.19, 3.50 |
| 13 | 2,4,6-Tri-1-piperidyl-s-triazine | | 3.35, 3.48, 3.54 |
| 14 | 2,4,6-Tri-1-pyrrolidyl-s-triazine | | 3.52 |
| 15 | 2,4,6-Tri-4-morpholinyl-s-triazine | | 3.52 |
| 16 | 2-(1-Piperidyl)-pyridine | | 3.32, 3.39, 3.48 |
| 17 | 2-(1-Piperidyl)-pyrimidine | | 3.36, 3.42 3.52 |
| 18 | 2-(1-Piperidyl)-quinoline | | 3.53 |
| 19 | 2-(1-Piperidyl)-benzothiazole | | 3.44, 3.52 |
| 20 | 2-Chloroquinoline | | 3.42 |
| 21 | 2-Chloropyridine | | 3.27 |
| 22 | 2-Chlorothiazole | | 3.23 |
| 23 | 2-Chlorobenzothiazole | | 3.28 |
| 24 | Pyrimidine | | 3.26, 3.34, 3.40, 3.46 |
| 25 | 2-Ethylmercapto-pyrimidine | | 3.32, 3.39, 3.47 |
| 26 | 2-Pyrimidinethiol | | 3.19, 3.42-3.49 |
| 27 | Spurious pyrimidol | | |
| 28 | 2-Chloropyrimidine | | 3.48 |
| 29 | 2-Pyrimidol·HCL | 3.19 | 3.48 |
| 30 | 2-Pyrimidol | 3.23 | 3.38 |

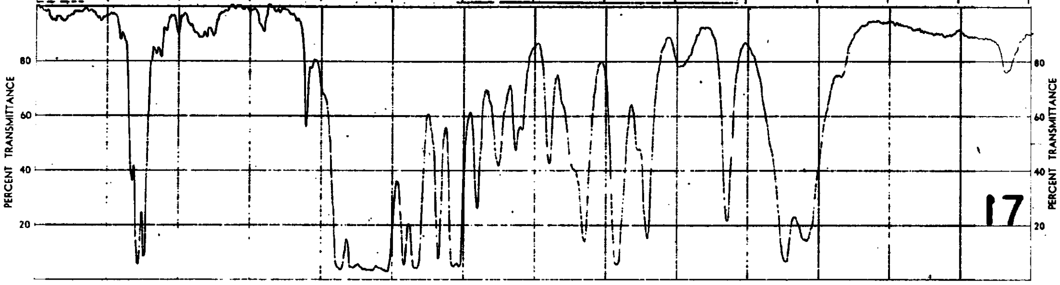

WAVE NUMBERS IN CM⁻¹
5000
4000
3000
2500
2000
1500
1400
1300
1200
1100
1000
900
800
700
625
PERCENT TRANSMITTANCE
0
20
40
60
80
100
1
2
3
4
5
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM-1
5000
4000
3000
2500
2000
1500
1400
1300
1200
1100
1000
900
800
700
625
PERCENT TRANSMITTANCE
0
20
40
60
80
100
6
7
8
9
10
2
3
4
5
6
7
8
9
10
12
13
14
15
16
WAVE LENGTH IN MICRONS

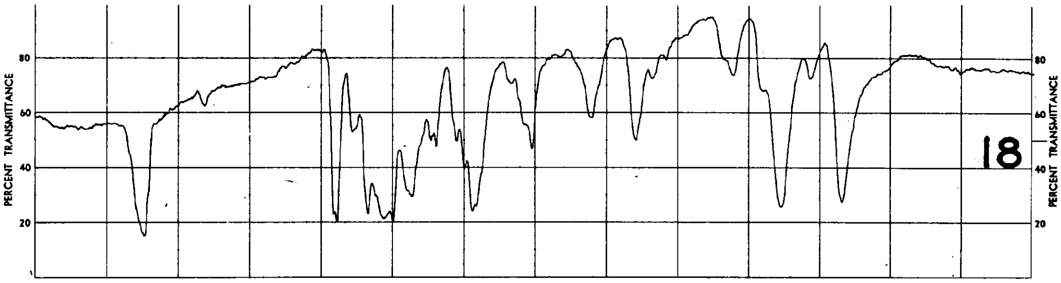

WAVE NUMBERS IN CM⁻¹
5000
4000
3000
2500
2000
1500
1400
1300
1200
1100
1000
900
WAVE NUMBERS IN CM⁻¹
800
700
625
PERCENT TRANSMITTANCE
100
80
60
40
20
0
11
12
13
14
15
2
3
4
5
6
WAVE LENGTH IN MICRONS
7
8
9
10
11
12
13
WAVE LENGTH IN MICRONS
14
15
16


WAVE NUMBERS IN CM⁻¹
5000
4000
3000
2500
2000
1500
1400
1300
1200
1100
1000
WAVE NUMBERS IN CM⁻¹
900
800
700
625
PERCENT TRANSMITTANCE
100
80
60
40
20

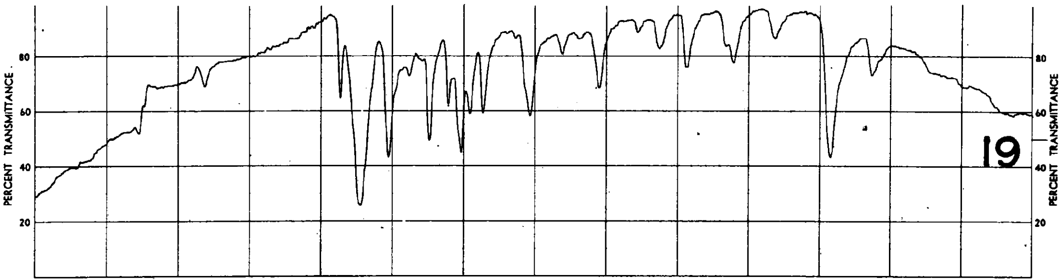
16


PERCENT TRANSMITTANCE
80
60
40
20

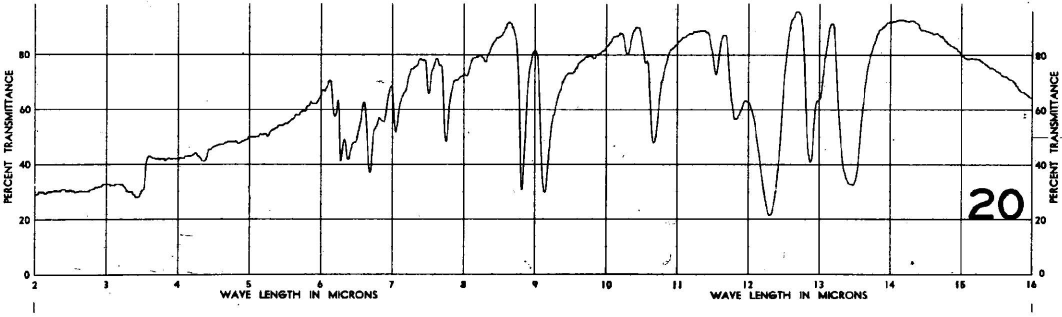
17


PERCENT TRANSMITTANCE
80
60
40
20

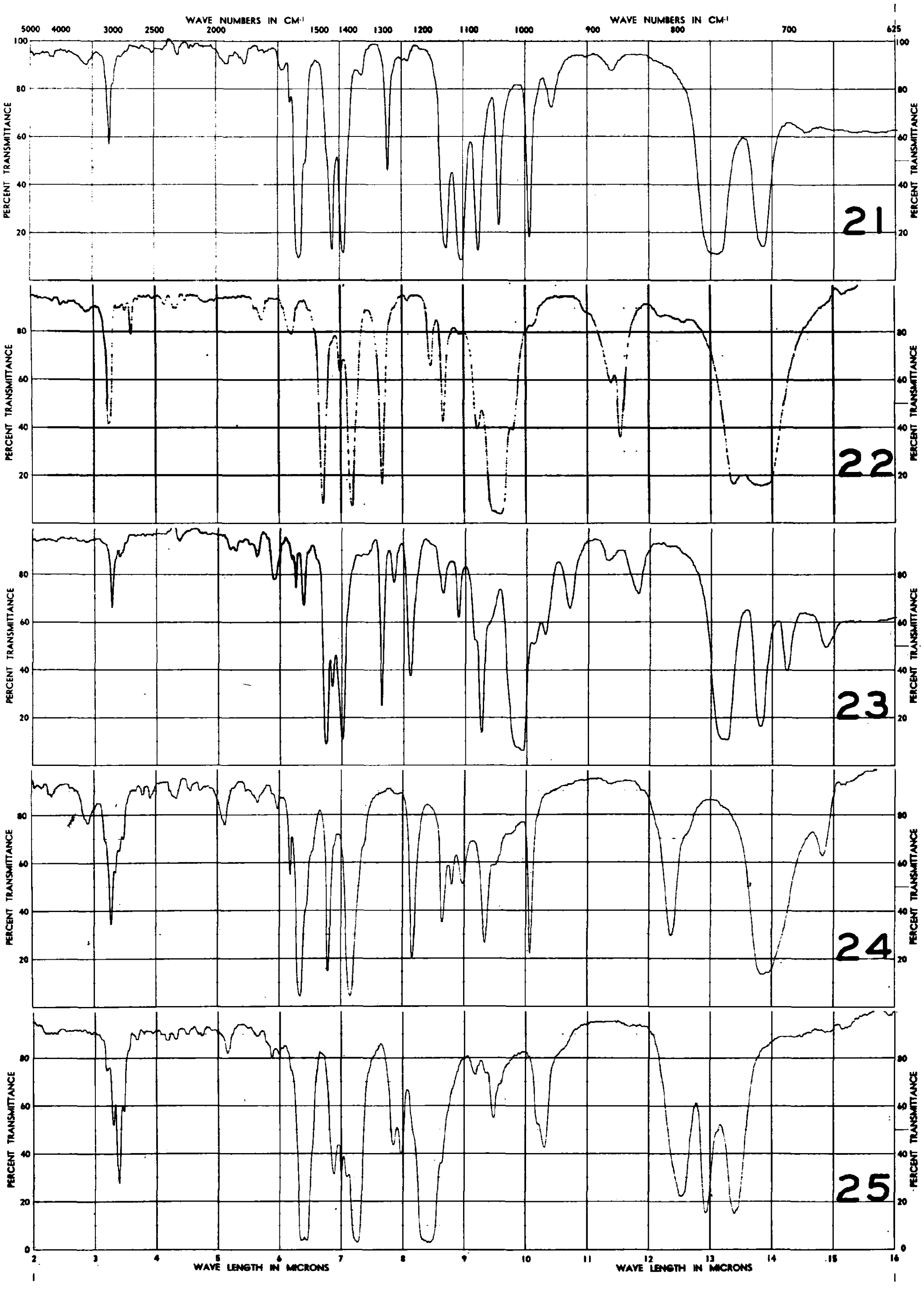
18

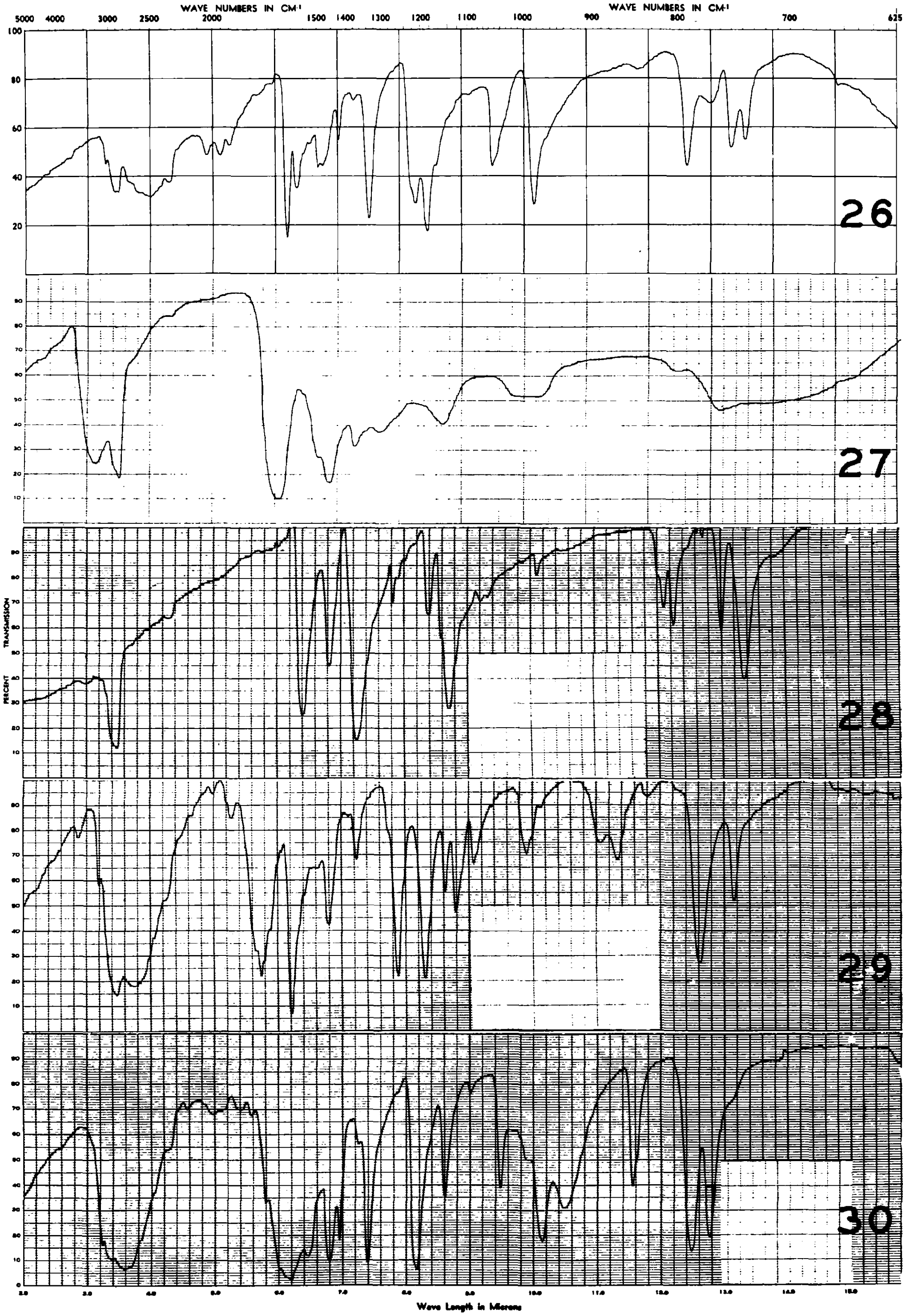

PERCENT TRANSMITTANCE
80
60
40
20

19


PERCENT TRANSMITTANCE
80
60
40
20
0
2
3
4
5
6
WAVE LENGTH IN MICRONS
7
8
9
10
11
12
13
WAVE LENGTH IN MICRONS
14
15
16

20


WAVE NUMBERS IN CM⁻¹
5000
4000
3000
2500
2000
1500
1400
1300
1200
1100
1000
900
800
700
625
PERCENT TRANSMITTANCE
100
80
60
40
20
0
21
22
23
24
25
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
WAVE LENGTH IN MICRONS


WAVE NUMBERS IN CM⁻¹
5000
4000
3000
2500
2000
1500
1400
1300
1200
1100
1000
900
WAVE NUMBERS IN CM⁻¹
800
700
625
100
80
60
40
20
26
27
PERCENT TRANSMISSION
28
29
30
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
14.0
15.0
Wave Length in Microns

and 2,4,6-tri-4-morpholinyl-s-triazine (curve #15) has been located at 9.01 microns (1110 cm.$^{-1}$) and 9.00 microns (1111 cm.$^{-1}$) respectively. This band was recognized by its sharpness and intensity as compared with the other s-triazines.

## Experimental*

Reduction of 2-Chloropyrimidine**. - 2-Chloropyrimidine (16.1 g., .14 mole), 4 g, of 5% Pd on carbon catalyst and 150 ml. of absolute alcohol were placed in a low pressure hydrogenation bottle and subjected to a hydrogen pressure of forty pounds per square inch. The reaction mixture became very hot and the pressure dropped to seven pounds per square inch during the first fifteen minutes. The pressure was then adjusted to forty pounds and did not drop below thirty-seven and a half pounds. The reaction mixture was hydrogenated a total of 1 3/4 hours; no drop in pressure was noted after the first 25 minutes.

The catalyst was filtered under gravity and washed with two 25 ml. portions of hot absolute alcohol. The filtrate and washings were concentrated to dryness under reduced pressure while heating on a steam bath. The sticky

---

*All melting points have been corrected for thermometer stem-emergence.

**See the theoretical discussion in Part V concerning the nature of this reduction.

colorless crystals obtained were washed with two 50 ml. portions of dry ether and dried under vacuum over KOH pellets, m.p. 184.6-186.2°, yield 16.5 g. These crystals were very hygroscopic, gave a strong ionic halogen test with acidic silver nitrate solution and a basic test with litmus. Upon treatment with 25% sodium hydroxide, extraction with ether and evaporation of the ether, a colorless liquid was obtained, which gave a picrate m.p. 158-160°. This liquid decomposed upon distillation. A picrate made from the distillate had a melting point of 259.8° after recrystallization from 95% ethanol*.

The reaction of 10% sodium hydroxide and benzoyl chloride with a sample of the original reaction product gave a trace of a substance m.p.**249-255°. This substance was insoluble in ether, soluble in water and gave a positive ionic halogen test; it appeared to be a quaternary salt.

2-Pyrimidinethiol. - Malonaldehyde (bis-diethylacetal) (262.5 g., 1.19 mole), thiourea (90.7 g., 1.19 mole), 43 ml. of water and 600 ml. of acetone free methanol were treated with a rapid stream of dry hydrogen chloride for 1 3/4 hours

---

*Johnson and Joyce (50) have reported 1-amino-3-methylaminopropane hydrochloride as melting 185-190°; Braun et al (51) report a melting point of 185° for the hydrochloride and a melting point of 227° for the picrate; Tarbell et al (52) have reported the dipicrate as melting 224.5-226.5°.

**Titherly and Branch (53) report 1,3-dibenzoylhexahydropyrimidine as melting 95°.

at such a rate as to cause the methanol to reflux gently. The reaction mixture was heated to reflux on a steam bath for 2 3/4 hours, cooled to 5°, filtered, and washed with two 200 ml. portions of ether. After drying under vacuum over phosphorous pentoxide and potassium hydroxide, the yield of yellow crystals was 126.4 g. These crystals charred at 229° but do not melt at 300°. An additional 22 g. was obtained by refluxing the mother liquor for an additional 1 3/4 hours on a steam bath. Assuming a monohydrochloride, this represented a combined yield of 83.9%. Rapid recrystallization of these crystals from 1250 ml. of water which had been previously heated to boiling gave 62.9 g. of fine yellow platelets, m.p.* 234-235°. Anal. Calcd. for $C_4H_4N_2S$: C, 42.83; H, 3.60; N, 24.98. Found: C, 42.82; H, 3.60; N, 24.90.

Pyrimidine. - The Raney nickel catalyst used in this reaction was prepared as directed in "Organic Syntheses" (65) except for the final heating of the catalyst which was carried out at 50° as directed by Mozingo (58).

2-Pyrimidinethiol (17.2 g., 0.153 mole) was dissolved in 1020 ml. of hot 63% ethanol. Raney nickel catalyst (84 g., 140 ml.) as a paste in absolute ethanol was added in teaspoon portions to the hot solution over a period of 5

---

*Roblin and Clapp (57) have reported a melting point of 219-220°.

minutes (the catalyst must be kept moist at all times!). A condenser was put in place and the reaction mixture was heated at reflux on a steam bath for 4 hours.

The warm reaction mixture was filtered through a large fine sintered glass funnel to remove the catalyst which was extracted with two 100 ml. portions of water. The ethanolic filtrate was treated with 200 ml. of 95% ethanol which contained 65 gm. of mercuric chloride; a 37.25 gm. yield of salt was precipitated (dried at 85° under vacuum). The aqueous extract of the catalyst was treated with 100 ml. of warm water which contained 6 g. of mercuric chloride. The pure white needles precipitated were filtered off, dried under vacuum, yield .82 g.

The two fractions of the mercuric chloride salt were placed in a 500 ml. Claisen flask with 100 ml. of aqueous sodium sulfide (saturated at 20° C). This addition caused the precipitation of mercuric sulfide and the separation of a liquid having the odor of pyridine. Approximately 63 ml. of distillate was collected while heating in an oil bath at 136-170°.

The distillate was treated with 75 g. of potassium carbonate which caused a layer of pyrimidine to separate.

The aqueous mixture was extracted with four 25 ml. portions of ether. The ether extract was dried over KOH and concentrated to produce a light yellow colored liquid which crystallized in an ice bath. Distillation gave a fraction boiling 122.5-126.2° (bath 161 to 166°); yield 3.8 g. (31%). This fraction was a colorless liquid at room temperature and had a pyridine like odor. A picrate of this substance melted 153.5-154.5°.

Further purification by fractionation through a Todd column after drying an anhydrous ether solution of it over potassium hydroxide pellets gave 2.4 g. of pyrimidine* b.p.$_{767}$ 125-125.5°, m.p. 18.4-20.4°.

A similar reduction on 2-ethylmercaptopyrimidine gave a poorer yield of pyrimidine.

## Summary

A new synthesis of pyrimidine was presented. This preparation involved the use of the Mozingo reaction on 2-pyrimidinethiol. Several unsatisfactory attempts to prepare pyrimidine were discussed. The infrared absorption spectra of thirty heterocyclic nitrogen compounds were given. Some of the absorption bands of these compounds were tentatively identified.

---

*See page 56 for a comparison of this sample of pyrimidine with the one reported in the literature.

# References

# References

1. C. T. Ray and G. E. Burch, Am. J. Med. Sci., 217, 96 (1949).
2. N. M. Keith, J. Am. Med. Assoc., 107, 2047 (1936).
3. A. C. De Graff and J. E. Nadler, ibid., 119, 1006 (1942).
4. W. H. Higg, ibid., 119, 1182 (1942).
5. T. E. Stanley, Virginia Medical Monthly, 76, 416 (1949); J. Am. Med. Assoc., 142, 136 (1950).
6. W. L. Lipshitz, Z. Hadidian and A. Kerpcsar, J. Pharmacol., 79, 97 (1943).
7. W. L. Lipschitz and Z. Hadidian, ibid., 81, 84 (1944).
8. W. L. Lipschitz and E. Stokey, ibid., 83, 235 (1945).
9. W. L. Lipschitz and E. Stokey, ibid., 92, 131 (1949).
10. F. H. S. Curd and F. L. Rose, J. Chem. Soc., 1946, 729.
11. H. King and I. Tonkin, ibid., 1946, 1063.
12. E. Bamberger and L. Sieberger, Ber., 24, 899 (1891).
13. I. Strukov, N. Sychra and B. Smirnov, J. Chem. Ind. (U. S. S. R.), 18, 22 (1941).
14. D. E. Nagy, U. S. Patent, 2,392,608 (1946); C.A., 40, 3480 (1946).
15. D. F. Walker, Y. J. L'Italien, W. M. Pearlman and C. K. Banks, J. Am. Pharm. Assoc., 39, 393 (1950).
16. S. Saure, Ber., 83, 225 (1950).
17. C. K. Banks, O. M. Gruhzit, E. W. Tillitson and J. Controulis, J. Am. Chem. Soc., 66, 1771 (1944).
18. A. W. Hofmann, Ber., 18, 2779 (1885).
19. T. L. Davis and K. C. Blanchard, J. Am. Chem. Soc., 1803 (1929).

20. O. Fisher, Ber., 32, 1301 (1899).

21. M. P. Gerchuk and S. Z. Taits, Zhur. Obshchei Khim., 20, 910 (1950); C. A., 44, 9443 (1950).

22. T. B. Johnson and A. W. Joyce, J. Am. Chem. Soc., 37, 2151 (1915).

23. D. G. Brown, Nature, 165, 1010 (1950).

24. T. Matsukawa and B. Ohta, J. Pharm. Soc. Japan, 69, 491 (1949); C. A., 44, 3456 (1950).

25. J. Thiele and E. Uhlfelder, Ann., 303, 93 (1893).

26. H. L. Wheeler and H. F. Merriam, Am. Chem. J., 29, 483 (1903).

27. H. L. Wheeler and H. S. Bristol, ibid., 33, 440 (1905).

28. A. E. Tschitshibabin, R. A. Konowalowa and A. A. Konowalowa, Ber., 54, 814 (1921).

29. R. R. Adams and F. C. Whitmore, J. Am. Chem. Soc., 67, 737 (1945).

30. T. E. Young and E. D. Amstutz, ibid., in press.

31. A. Maggiolo, A. P. Phillips and G. Hitchings, ibid., 73, 106 (1951).

32. E. Benary, Ber., 63B, 2601 (1930).

33. J. M. Sprague, L. W. Kissinger and R. M. Lincoln, J. Am. Chem. Soc., 63, 3028 (1941).

34. K. Bowden and E. R. H. Jones, J. Chem. Soc., 1946, 953.

35. J. C. W. Evans and C. F. H. Allen, "Organic Syntheses", Coll. Vol. II, John Wiley and Sons, Inc., N. Y., 1947, p. 517.

36. K. Ziegler and H. Zelser, Ann., 485, 174 (1931).

37. T. H. Vaughn, R. R. Vogt and J. A. Nieuwland, J. Am. Chem. Soc., 56, 2120 (1934).

38. K. Ganapathi and A. Venkataraman, Proc. Indian Acad. Sci., 22A, 343 (1945); C. A., 40, 4059 (1946).

39. C. F. H. Allen and J. R. Thirtle, "Organic Syntheses," Vol. 26, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 16.

40. T. B. Johnson and F. W. Heyl, Am. Chem. J., 38, 244 (1907).

41. R. W. Barnes, U. Liddel and V. Z. Williams, Ind. Eng. Chem., Anal. Ed., 15, 702 (1943).

42. I. A. Brownlie, J. Chem. Soc., 1950, 3062.

43. S. Gabriel and J. Colman, Ber., 32, 1537 (1899).

44. S. Gabriel, Ber., 33, 3667 (1900).

45. W. O. Emery, Ber., 34, 4178 (1901).

46. T. Matsukawa and B. Ohta, J. Pharm. Soc. Japan., 70, 134 (1950); C. A., 44, 5886 (1950).

47. T. Matsukawa and B. Ohta, ibid., 70, 137 (1950); C. A.; 44, 5886 (1950).

48. T. B. Johnson and A. W. Joyce, J. Am. Chem. Soc., 37, 2162 (1915).

49. S. J. Childress and R. L. McKee, ibid., 72, 4271 (1950).

50. T. B. Johnson and A. W. Joyce, ibid., 38, 1859 (1916).

51. J. W. Braun, R. Lotz, K. C. Warne, W. Pinkernelle, W. Pohland, A. Pohl, F. Dengel and H. Arnold, Ber., 70B, 979 (1937).

52. D. S. Tarbell, N. Shakespeare, C. J. Claus and J. F. Bunnett, J. Am. Chem. Soc., 68, 1217 (1946).

53. A. W. Titherly and G. E. K. Branch, J. Chem. Soc., 103, 330 (1913).

54. G. E. K. Branch, J. Am. Chem. Soc., 38, 2466 (1916).

55. A. Wheeler, A. E. Ruehle and J. Finkelstein, ibid., 59, 526 (1937).

56. R. R. Williams, A. E. Ruehle and J. Finkelstein, ibid., 59, 529 (1937).

57. R. O. Roblin, Jr. and J. W. Clapp, ibid., 72, 4890 (1950).

58. R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, ibid., 65, 1013 (1943).

59. H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949.

60. N. B. Colthup, J. Opt. Soc. Am., 40, 397 (1950).

61. R. B. Barnes, R. C. Gore, R. W. Stafford and V. Z. Williams, Anal. Chem., 20, 402 (1948).

62. W. R. Brode, "Chemical Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1945, p. 273.

63. L. Marion, D. A. Ramsay and P. N. Jones, J. Am. Chem. Soc., 73, 305 (1951).

64. M. Gates, R. B. Woodward, W. F. Newhall and R. Kunzli, ibid., 72, 1141 (1950).

65. R. Mozingo, "Organic Syntheses," Vol. 21, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 15.

# Index of New Compounds

# Index of New Compounds

# Vita

# Vita

William Kenneth Detweiler, the son of William Samuel and Olive Godshall Detweiler, was born on January 27, 1923, in Quakertown, Pennsylvania. He attended the Trumbauersville Grammar School and graduated in the academic course from the Quakertown Junior-Senior High School in 1941.

Having been awarded an athletic scholarship from Albright College, Reading, Pennsylvania, he entered this college in September, 1941. During the next two years, he pursued the Chemistry-Biology Curriculum and received his letter for participation with the varsity football team.

From June, 1943, until November, 1945, Mr. Detweiler served with the Air Wing of the United States Navy. He entered the Naval service as an Aviation Cadet; after having satisfactorily completed this course of study, he was designated a Naval Aviator and received his commission as Ensign in December, 1944. Upon completion of advanced training, Mr. Detweiler was released to inactive duty in November, 1945. From that time until the present he has served as a Lieutenant (j.g.) in a photographic squadron of the United States Naval Reserve based at the Willow Grove Naval Air Station.

In March, 1946, Mr. Detweiler entered Ursinus College, Collegeville, Pennsylvania, and graduated from there with the degree Bachelor of Science in June, 1947.

The following September, Mr. Detweiler enrolled in the Graduate School of Lehigh University and received the degree Master of Science in Chemistry in February, 1949. Continuing at the same institution, he spent the next two and one-half years working toward the degree Doctor of Philosophy on a project sponsored by The Wm. S. Merrell Company of Cincinnati, Ohio. The results of this investigation comprise the foregoing dissertation.

Mr. Detweiler is co-author with Dr. E. D. Amstutz of a scientific paper, "Acyl Aldehydes. The Synthesis of Para-Acetylbenzaldehyde.," J. Am. Chem. Soc., 72, 2282 (1950), which was abstracted from Detweiler's master's thesis.

Mr. Detweiler is a member of the American Chemical Society and the Lehigh Chapter of the Society of the Sigma Xi.

On June 21, 1944, Mr. Detweiler was married to the former Ann Celeste Ranken of Ridge Valley, Pennsylvania.

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 - 1346 USA