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A STUDY OF THE SYNTHESIS OF  
2-TRIFLUOROMETHYL PYRIMIDINES

JOHN A. KING

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A STUDY OF THE SYNTHESIS OF  
2-TRIFLUOROMETHYL PYRIMIDINES

by

John A. King  
//  
Captain, United States Air Force

Submitted in partial fulfillment of  
the requirements for the degree of

MASTER OF SCIENCE

United States Naval Postgraduate School  
Monterey, California

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A STUDY OF THE SYNTHESIS OF  
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John A. King

This work is accepted as fulfilling  
the thesis requirements for the degree of

MASTER OF SCIENCE

from the

United States Naval Postgraduate School



## ABSTRACT

Phenylbutanedione-1,3 and 2,4-pentanedione were reacted with trifluoroacetamide in the presence of sodium ethoxide. A crystalline product melting at 38.4°C was recovered from the reaction of 2,4-pentanedione and trifluoroacetamide and tentatively identified by its infrared spectra as 2-trifluoromethyl-4,6-dimethylpyrimidine. The reaction of trifluoroacetamide and phenylbutanedione-1,3 in the presence of sodium ethoxide yielded a white crystalline product melting at 90.3°C which was also tentatively identified as the 2-trifluoromethyl-4-methyl-6-phenylpyrimidine. The amidine of trifluoroacetic acid reacted in a manner described for the reaction of an amidine with a beta-diketone. Yields obtained (19-34%) were within the limits reported for many other pyrimidine syntheses, influenced in part by the instability of trifluoroacetamide.

The writer wishes to express his appreciation for the assistance and counselling given to him by Professors George H. McFarlin and John W. Schultz of the U.S. Naval Postgraduate School.



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## 1. Introduction

The synthesis of 2-substituted pyrimidines was investigated in the 19<sup>th</sup> century. This method [1] involved the reaction of an amidine with a beta diketone-like compound to yield the substituted pyrimidine. The reaction has been expanded to permit the use of other poly-functional nitrogen compounds and is today the primary method for obtaining 2-substituted pyrimidines.

In a review of the literature, it was noted that extensive research has been conducted on pyrimidines. Since pyrimidines are one of the constituents of nucleic acids, the majority of work is directed toward those compounds that are of physiological interest, such as the amino and hydroxypyrimidines. Recently, three groups of investigators [5, 6, 7] have reported the synthesis of trifluoromethylpyrimidines. Their efforts were also directed to those compounds of biological interest and involved the standard methods similar to those devised by Pinner. Of the trifluoromethyl-compounds reported only four were of the 2-trifluoromethylpyrimidine type acquired through the use of trifluoroacetamide.

Trifluoroacetamide, a nitrogen derivative of trifluoroacetic acid, has been synthesized by the amination of trifluoroacetonitrile. Similar derivatives are formed by other acids and have been used in pyrimidine syntheses. However, trifluoroacetic acid has been readily available for only a decade, and limited research has been done using its derivatives.



Since the highly electronegative trifluoromethyl group may impart unusual properties to a reaction, such as involved in the synthesis of pyrimidines, an investigation was directed toward the study of the synthesis of 2-trifluoromethylpyrimidines, specifically those pyrimidines that may be formed by the reaction of trifluoroacetamide with 2,4-pentanedione or phenylbutanedione-1,3 in the presence of sodium ethoxide. Since such pyrimidines would be free of the amino, hydroxy and keto substituents, infrared spectroscopy was planned as a means of characterizing the reaction products.



## 2. Background

Pinner [1] investigated the synthesis of amidines and the reaction of amidines with beta diketone-like materials to form the heterocyclic 1,3-diazines, the pyrimidines. Various modifications have evolved since the initial work. The synthesis has been expanded [1, 3, 4] to incorporate other poly-functional nitrogen compounds such as urea, guanidine, and thiourea. Sodium hydroxide has been replaced by a solution of a sodium alkoxide as the condensing medium, but his work is the classic in the field and remains today the important synthetic method of obtaining 2-substituted pyrimidines.

Amidines are usually formed by treating the iminoether hydrochloride with an alcoholic solution of ammonia [1, 2], however, trifluoroacetamide has been synthesized by the direct reaction of trifluoroacetonitrile with liquid ammonia. [9]



Schriner and Neumann [1] describe amidines as monoacid bases. In contrast to this, Reilly and Brown [9] report that trifluoroacetamide is sufficiently acidic to form metal salts. However, they also report that addition products were formed by reacting perfluoroacids with the trifluoroacetamide which would conform to the expected reaction of an amidine.

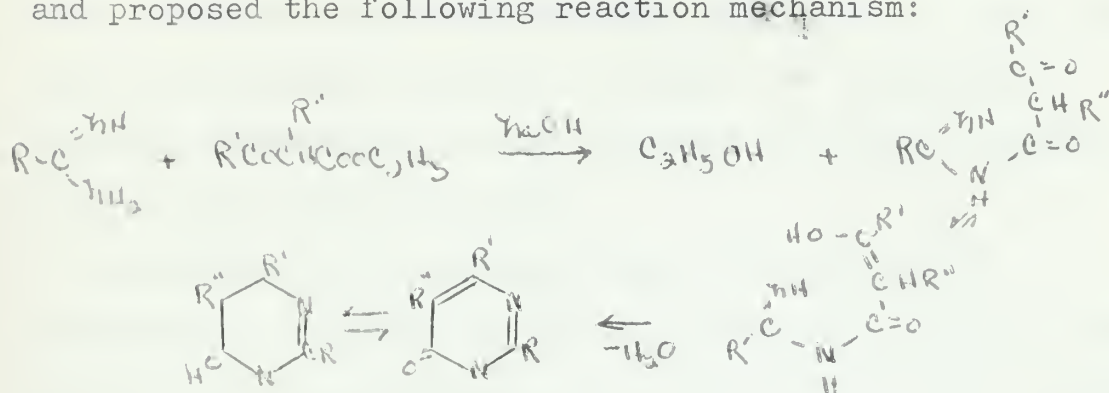


The trifluoroacetamide is hygroscopic in the crude state



and readily hydrolyzes. Distillation to remove the residual ammonia is reported to improve the stability.

Pinner [1] investigated the reaction of amidines with beta-ketonic esters in the presence of sodium hydroxide and proposed the following reaction mechanism:



Later investigation showed that beta-diketones could be used to replace the ester to form a pyrimidine.



The nature of the condensing medium was found to have a profound effect on the yield and sodium alkoxides appear to be the preferred condensing medium. Reported yields range from 20% to 95% using sodium methoxide or sodium ethoxide. Yields as low as 10% are reported when sodium hydroxide is used as the condensing medium. Although extensive pyrimidine research has been reported using this approach, relatively few trifluoromethyl substituted pyrimidines have been synthesized.

The first trifluoromethylpyrimidines were reported





by Giner - Borolla and Bendich in 1958. [6] A series of 6-trifluoromethylpyrimidines including the uracils, 2-thio-uracils, isocytosine and some 5-phenylazo derivatives of these compounds were synthesized. This was accomplished by reacting guanidine, thiourea, or urea with ethyl trifluoroacetoacetate or ethyl ( $\alpha$  phenylazo)-trifluoroacetoacetate in the presence of sodium butoxide. Yields range from 70% to 95%.

In latter work, Bergman, Cohen and Shahak [7], synthesized 6-trifluoromethyl-4-hydroxypyrimidines in which the 2- and 5- positions were substituted with  $-\text{CH}_3$ ,  $-\text{SC}_2\text{H}_5$ , and  $-\text{F}$ . Their approach was to condense ethyl trifluoroacetoacetate or ethyl  $\alpha$  VVV tetrafluoroacetoacetate with urea, acetamidine, or guanidine in the presence of sodium methoxide. Yields ranged from 20% to 70%.

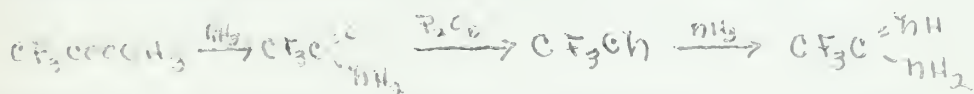
Barone, Peters, and Tieckelman [5] described the synthesis of the only 2-trifluoromethylpyrimidines which were reported in the literature. Their work was directed also to the physiologically active materials. 2-Trifluoromethyl-4-hydroxy-5-carbethoxypyrimidine was synthesized by reacting trifluoroacetamidine with a beta-ketoester in the presence of sodium ethoxide. Subsequent replacement reactions with the 4-hydroxy position yielded the 4-phenoxy-, 4 chloro- and 4-o-chloroanilinc compounds. The condensation with the amidine resulted in a yield of 73%.



### 3. Theoretical Studies

Based on the work reported by Peters et al [5] for the synthesis of 2-trifluoromethylpyrimidines and on the standard methods which have evolved for the preparation of 2-substituted pyrimidines, sodium ethoxide was selected as the condensing medium. Condensation of trifluoroacetamide with 2,4-pentanedione and phenylbutanedione-1,3 was expected to yield the 2-trifluoromethyl-4,6-dimethylpyrimidine and the 2 trifluoromethyl-4-methyl-6-phenylpyrimidine respectively. Specific directions for all syntheses used in this study are included in section 5. The infrared spectra are recorded and discussed in section 4.

Trifluoroacetamide was prepared by amination of either  $\text{CF}_3\text{COOCH}_3$  or  $\text{CF}_3\text{COOC}_2\text{H}_5$ . The resulting amide was dehydrated with phosphorus pentoxide to form trifluoroacetonitrile. Refluxing the nitrile with liquid ammonia yielded the amidine directly, vis



The amidine is reported to hydrolyze in the presence of moisture and will polymerize on standing, with the release of ammonia. The stability is improved, however, by distilling the crude product under reduced pressure. The amidine was also found to be heat sensitive. If the distillation temperature was permitted to rise above  $100^\circ\text{C}$ , the amount of polymer remaining in the distillation flask was increased immeasurably.

a. Reaction of Trifluoroacetamide and 2,4-Pentanedione



Trifluoroacetamide was prepared, distilled, and used fresh. The age of the material in all preparations was less than 24 hours. This was deemed necessary since it had been reported that the freshly prepared material gave the best results. To prevent hydrolysis, all glassware was oven dried and cooled in the assembled condition with a cotton drying tube attached.

50 milliliters of 2 molar sodium ethoxide was prepared with absolute ethanol and trifluoroacetamide was added in one aliquot. Approximately an equal molar quantity of 2,4-pentanedione (Eastman Practical) was diluted 50/50 with absolute ethanol and added dropwise to the amidine-sodium ethoxide mixture. After a slight exothermic reaction, the reactants were refluxed for six hours. The precipitate which formed in the reaction flask was filtered and recrystallized from ethanol to give flaky soap-like leaflets which decomposed without melting at 310-318°C. Acidification with sulfuric acid and extraction with ether, followed by evaporation of the extract, resulted in recovery of 2,4-pentanedione. The original leaflets gave a positive sodium test and it was concluded that this product was the sodium enolate  $\text{Na}^+ [\text{CH}_2\text{COCHCOCH}_2^-]$ . After evaporation of the filtrate from the distillation step, a resinous residue remained which yielded trace amounts of a yellowish fragile crystalline material mp 34°C. Recrystallization from ligroin resulted in a white crystalline product mp 38.4°C.

Sodium fusion of the mp 38.4°C crystals gave a strong qualitative test for nitrogen. Zirconium alizarine test



for the fluoride ion resulted in a positive test. In this respect, it was found that with known materials, the alizarine test paper was sensitive only if the fusion filtrate was evaporated to dryness, made moist with a drop of water, and the concentrated fusion mixture used. This technique was used in all fluoride tests.

Infrared analysis of a nujol mull of mp 38.4°C crystals resulted in a spectrum which showed strong absorption at 1600  $\text{cm}^{-1}$ , 1500  $\text{cm}^{-1}$ , 1200-1140  $\text{cm}^{-1}$ , 1000  $\text{cm}^{-1}$  and 800  $\text{cm}^{-1}$ . Absorption in the amide carbonyl frequency of around 1700  $\text{cm}^{-1}$  was absent as well as the absorption at 1700  $\text{cm}^{-1}$  noted in the amidine. As previously noted [12], pyrimidines are reported to have characteristic absorption frequencies in 1600  $\text{cm}^{-1}$ , 1000  $\text{cm}^{-1}$  and 800  $\text{cm}^{-1}$  areas, while  $-\text{CF}_3$  shows strong absorption in the 1100-1300  $\text{cm}^{-1}$  region. On this basis mp 38.4°C material was tentatively identified as 2-trifluoromethyl-4,6-dimethylpyrimidine and subsequent preparations were designed to improve the recovery of this material.

When 0.1 mole quantities of the amidine and the 2,4-pentanedione were used in the initial preparation, 6.1 grams of the sodium enolate and 2.1 grams of resinous remains were obtained as well as a trace amount of 2-trifluoromethyl-4,6-dimethylpyrimidine. When the material identified as the pyrimidine was permitted to remain in an open vessel overnight, some product was lost. Therefore, in consideration of the material balance, it was concluded that volatility of the product influenced recovery.





The synthesis procedure was modified to incorporate a dry ice trap at the exit of the reflux condenser and also such traps in the vacuum filtration line. In a subsequent preparation, when the residues of the traps were added to the material recovered in fractional crystallization, the yield was increased to 17%.

The material tentatively identified as 2-trifluoromethyl-4,6-dimethylpyrimidine was soluble in ethanol, acetone, ether, petroleum ether, and water-alcohol mixtures. The most satisfactory method which evolved for the separation was: (1) filtration of the voluminous residue, (2) concentration under vacuum to remove ethanol, (3) washing of the precipitate with ligroin, and (4) dissolving the residue of the distillation flask in ligroin and filtering to remove insolubles, (5) washing the trap with ligroin and then adding all ligroin solutions to an evaporating dish, crystallizing and recrystallizing from ligroin, (6) final purification by vacuum sublimation.

Although yield was improved by reducing loss through volatility, resinous portions remaining at the end of each synthesis ranged from 2-3 grams for each 0.1 mole reaction. Since the trifluoroacetamide was heat sensitive, a pyrometer was fitted to the gas-col mantle used to heat the reaction vessel, so that the heating of the reactants could be controlled. Restricting the flask temperature to 75°C and increasing the reaction time to 16 hours resulted in yield of 34%

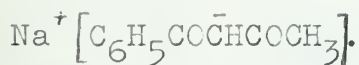
The stripped alcohol was redistilled at atmospheric pressure. After an initial fore-run of 4-5 milliliters, the remaining product was removed at 77-78°C. Qualitative



test of the fore-run resulted in the identification of acetone. Crystallization of the crude  $\text{Na}^+[\text{CH}_3\text{CO}\bar{\text{C}}\text{HCOCH}_3]$  from water gave a material identified as sodium acetate by comparison of the infrared spectrum of the nujol mull with that obtained from standard sodium acetate.

b. Reaction of Trifluoroacetamidine with Phenylbutanedione-1,3

Phenylbutanedione-1,3 was reacted with trifluoroacetamidine using the same procedure and techniques that were described for the 2,4-pentanedione reaction with the exception that dry ice traps were excluded. Water was used to remove the excessive precipitate which formed in the reaction. Neutralization of the water washing resulted in a white solid melting at  $54^\circ\text{C}$ . Mixed melting point with phenylbutanedione-1,3 (mp  $53^\circ\text{C}$ ) was unchanged. Crystals were sampled from the original precipitate and recrystallized from ethanol. Sodium qualitative test was positive and the material decomposed without melting at  $250^\circ\text{C}$ . Therefore, it was concluded that this material was the enolate



The dark red organic liquid yielded a crystalline material melting point  $90.3^\circ\text{C}$ . Qualitative tests for nitrogen and fluorine were positive. An infrared spectrum of this material showed a distinct absorption in the  $1600\text{--}1500\text{ cm}^{-1}$  region which was indicative of a mono-substituted benzene nucleus as well as that expected for a pyrimidine. In addition, the  $\text{-NH}_2$  and  $\text{=NH}$  stretching noted in the amidine were absent. In consideration of the distinct

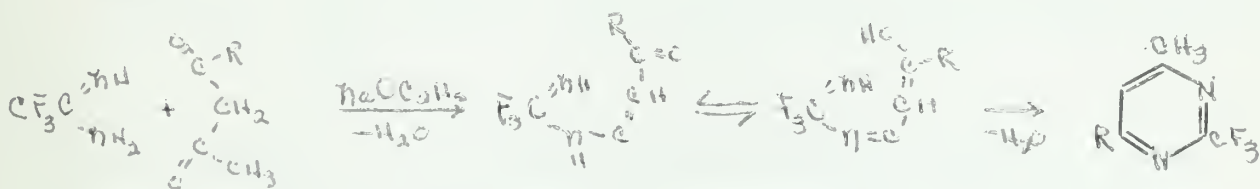


change in the spectra when compared to the amidine and the diketone, the material melting at 90.3°C was tentatively identified as 2-trifluoromethyl-4-methyl-6-phenylpyrimidine. Additional spectral considerations are discussed in section 4.

When equal molar quantities (0.15 mole) of reactants were used, 7.0 grams of 2-trifluoromethyl-4-methyl-6-phenylpyrimidine was obtained which resulted in a yield of 19%. In addition, the red organic residue (3.2 grams) was distilled under reduced pressure and acetophenone and ethyl benzoate were recovered. After recovery of the phenylbutanedione-1,3 from the acidification step, no further examination was made of the water layer.

### c. Reaction Mechanism

Some consideration is in order as to the mechanism of reaction and the nature of the reaction products. The condensation of the amidine with the beta-diketone (either 2,4-pentanedione or phenylbutanedione-1,3) is postulated as:



Where R = CH<sub>3</sub> or C<sub>6</sub>H<sub>5</sub>

It would appear that the Na<sup>+</sup>[CH<sub>3</sub>CO<sup>-</sup>CHCOCH<sub>3</sub>] which was formed in the 2,4-pentanedione reaction was a product of the initial reaction and subsequent addition resulted from this material or it was formed after depletion of the amidine.

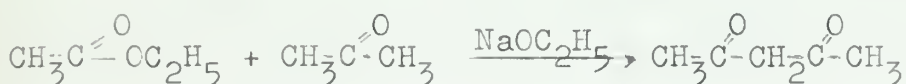


Ingold<sup>1</sup> reports that  $\text{CH}_3\text{COCH}_2\text{COCH}_3$  exists in 49% enolic form with distinct acidic properties. Therefore the following reaction would account for the formation of this material:

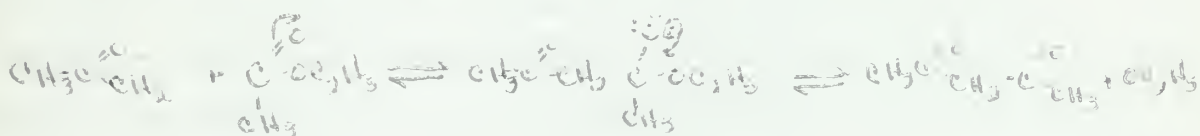


In a similar manner,  $\text{Na}^+ [\text{CH}_3\text{CO}\bar{\text{C}}\text{HCO}\text{C}_6\text{H}_5]$  could also be formed with the phenylbutanedione-1,3 in the synthesis of 2-trifluoromethyl-4-methyl-6-phenylpyrimidine since the beta-diketones have similar properties.

In addition, both 2,4-pentanedione and phenylbutanedione-1,3 are formed by the Claisen condensation of either  $\text{CH}_3\text{COOC}_2\text{H}_5$  or  $\text{C}_6\text{H}_5\text{COOC}_2\text{H}_5$  and  $\text{CH}_3\text{COCH}_3$ , for example:



or postulated in a step wise fashion



Consideration of the above mechanism would account for the  $\text{CH}_3\text{COCH}_3$  and  $\text{CH}_3\text{COONa}$  found in the reaction of 2,4-pentanedione with the amidine. In like manner  $\text{C}_6\text{H}_5\text{COOC}_2\text{H}_5$  could also be accounted for in the reaction of phenylbutanedione-1,3 with the amidine, however, the  $\text{C}_6\text{H}_5\text{COCH}_3$  recovered would have to be formed by alkali cleavage of phenylbutanedione-1,3.

<sup>1</sup>C. K. Ingold, Structure and Mechanism in Organic Chemistry, Cornell University Press, New York, 1953





#### 4. Infrared Spectral Studies

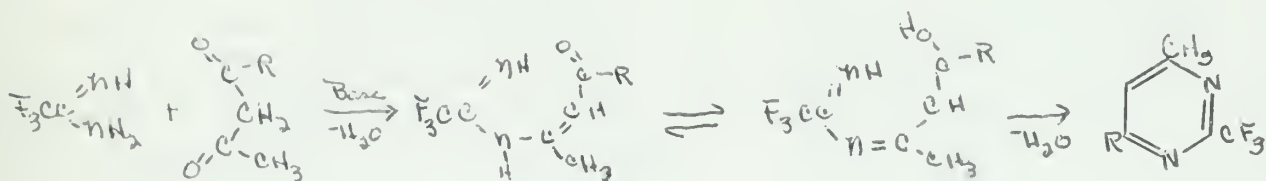
Spectral correlation of the pyrimidine nucleus has not been developed to the extent found in the benzene or pyridine ring systems. The correlations are also complicated by the ability of many of the pyrimidines (hydroxy and aminopyrimidines) to exist in more than one form. In view of this, Bellamy [12] attributes absorption between  $1600\text{ cm}^{-1}$  to the C=C and C=N ring vibrations. Absorption at  $1000$  to  $960\text{ cm}^{-1}$  is assigned to the ring deformation mode while absorption in the  $825$ - $775\text{ cm}^{-1}$  range is considered to be due to either a ring vibration or C-H deformation mode. He also notes that the above absorptions were found in all pyrimidines examined and are considered to be characteristic of pyrimidines.

Thompson et al [15] recorded the spectra of chloropyrimidines and of pyrimidine itself. Pyrimidine shows absorption at  $1675\text{ cm}^{-1}$ ,  $1610\text{ cm}^{-1}$  and  $1580$ - $1560\text{ cm}^{-1}$  regions. The chloro-substituted pyrimidines, however, lacked the absorption in the  $1600$ - $1700\text{ cm}^{-1}$  region, and only a single band was observed in the  $1550\text{ cm}^{-1}$  region. In view of this work and comparing other reported spectra, [12, 13, 14, 15] pyrimidines appear to be sensitive to substitution, and frequency shifts will occur, depending on the nature and placement of substituents.

The reaction encompassed by this study involved the condensation of an amidine with a beta-diketone as described in section 3. The reaction is postulated as a replacement reaction followed by ring closure. The possibility exists



that the intermediate product could be isolated as well as the pyrimidine.



where  $R = \text{CH}_3$  or  $\text{C}_6\text{H}_5$

It should be noted that the amidine, ketone, and the intermediate product have characteristic groups such as  $\text{C}=\text{O}$ ,  $\text{N}-\text{H}$  and  $-\text{NH}_2$ , while the pyrimidines covered by this study would lack such substituents. In addition, trifluoroacetamide is hydrolytically unstable and readily hydrolyzes to the amide. It would be expected that the substituted amidine postulated as an intermediate product would suffer the same instability. In view of this, the spectrum of the amide as well as the spectra of the reactants and reaction products are presented to justify the identification of the pyrimidines.

#### a. Trifluoroacetamide

The spectrum of trifluoroacetamide (Figure 1) has a pair of bands at  $3360\text{-}3200\text{ cm}^{-1}$  due to  $\text{NH}$  stretching vibration. The  $\text{C}=\text{O}$  vibrational frequency occurs at  $1705\text{ cm}^{-1}$  while the weaker  $\text{NH}$  deformation vibration is seen at  $1470\text{ cm}^{-1}$ . A strong absorption is also noted in the  $1230\text{-}1130\text{ cm}^{-1}$  region and is attributed to the  $-\text{CF}_3$  group. These assignments are in agreement with published data [11, 12, 16], as well as that expected of an amide.



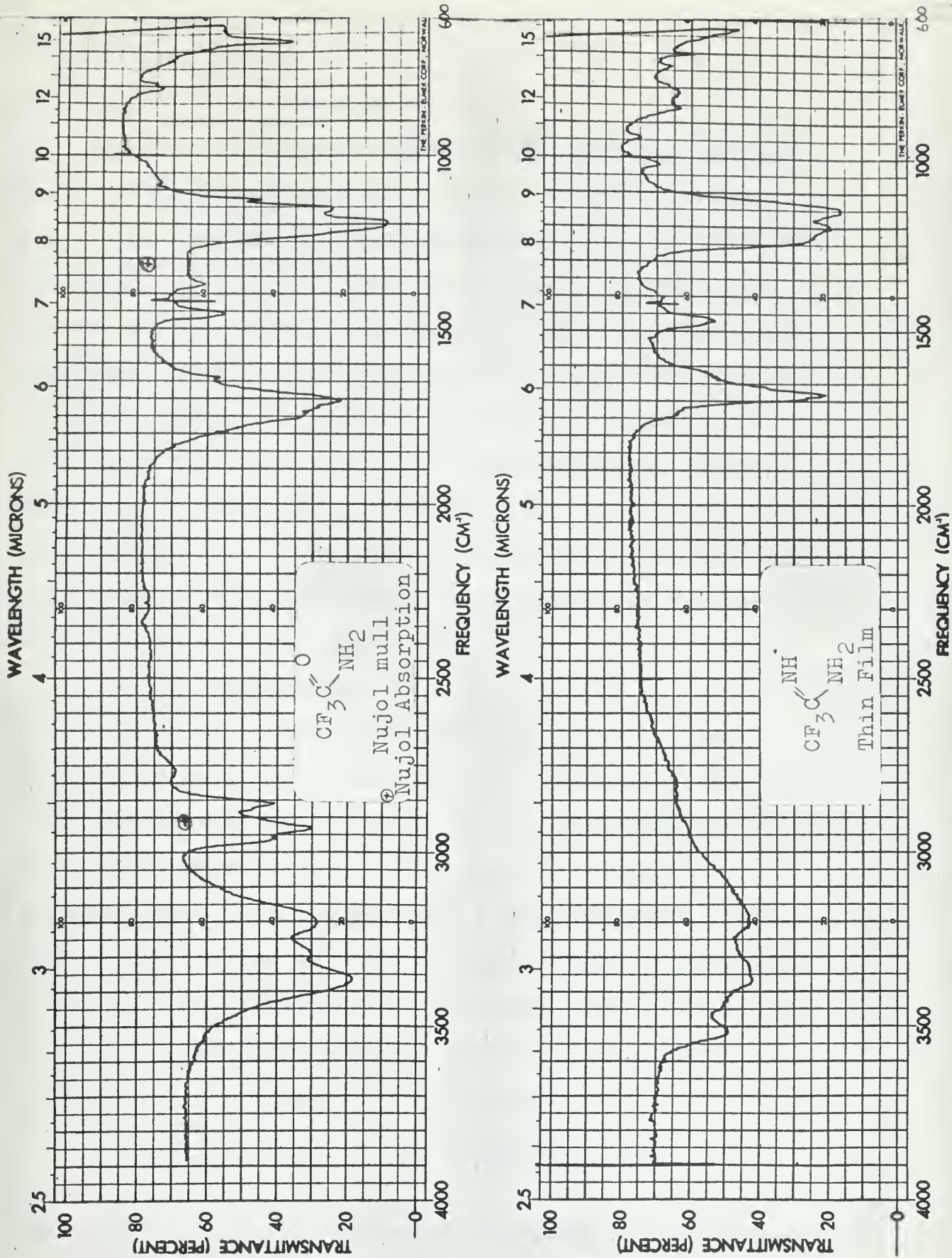


Figure 1

Infrared Spectra of Trifluoroacetamide and Trifluoroacetimidine



b. Trifluoroacetamide

Specific assignments were not available for amidines, however, trifluoroacetamide (Figure 1) shows a strong resemblance to the trifluoroacetamide. The absorption at  $3370\text{ cm}^{-1}$  and  $3200\text{ cm}^{-1}$  conform to the NH stretching seen in the amide. Imines ( $=\text{NH}$ ) [11, 12] show a characteristic absorption in the same range so that a specific assignment cannot be made. The  $3520\text{ cm}^{-1}$  may be due to a free NH with lower frequency due to the bonded NH mode. The similarity in the  $1470\text{ cm}^{-1}$  absorption to that seen in the amide suggests an NH deformation mode, while the  $1680\text{ cm}^{-1}$  may be due to  $=\text{NH}$  mode. The strong absorption is noted at  $1240\text{-}1140\text{ cm}^{-1}$  region due to  $-\text{CF}_3$ .

c. 2,4-Pentanedione

In the 2,4-pentanedione spectrum (Figure 2), weak absorptions are seen in the  $3020\text{ cm}^{-1}$ ,  $2980\text{ cm}^{-1}$ , and  $2930\text{ cm}^{-1}$  regions and are due to CH and  $\text{CH}_3$  stretching vibrations. It would be expected that these absorptions should be stronger since this compound has a high C-H ratio. The pair of absorptions at  $1735\text{ cm}^{-1}$  and  $1720\text{ cm}^{-1}$  correspond to the carbonyl vibration while a broad band at  $1640\text{-}1580\text{ cm}^{-1}$  is described as conjugate chelation due to the resonance occurring in the enolic structure.



Bands around  $1350$  and  $1225\text{ cm}^{-1}$  are common in all ketones while the  $1355\text{ cm}^{-1}$  absorption is due to  $\text{C}-\text{CH}_3$  symmetrical bending vibrations. In the sodium enolate of 2,4-pentane-





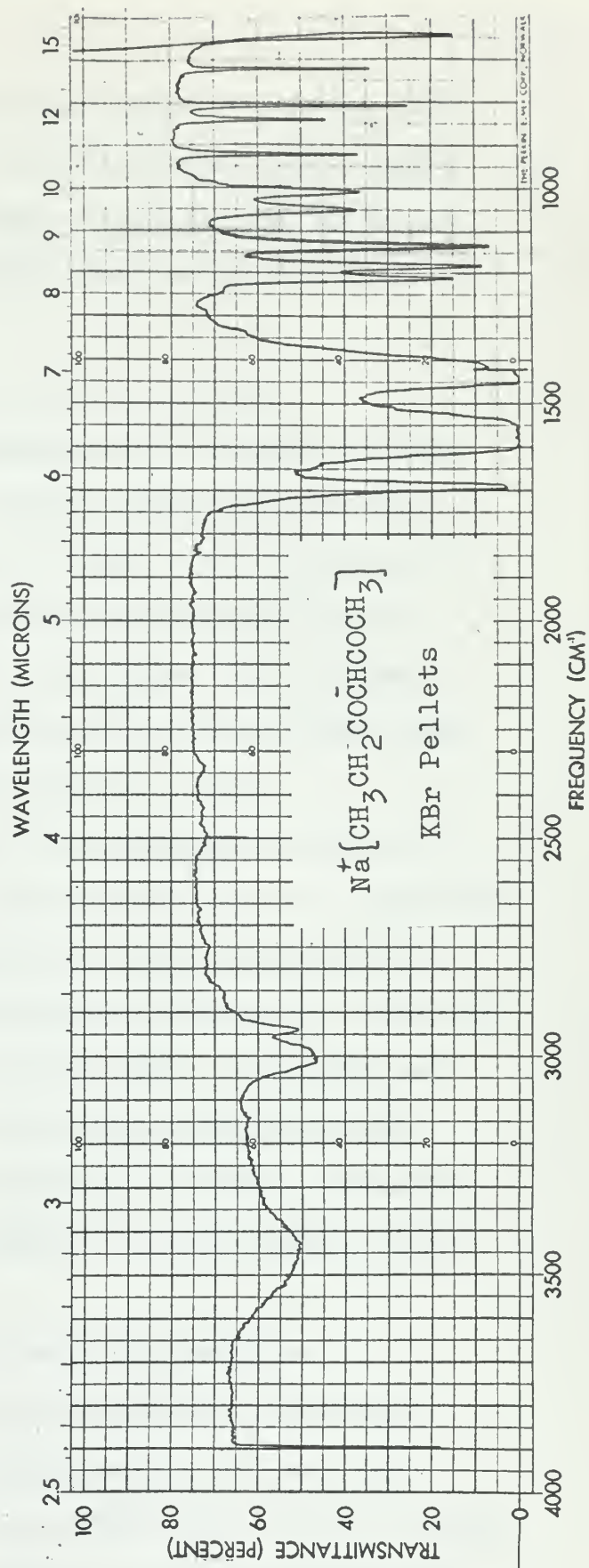
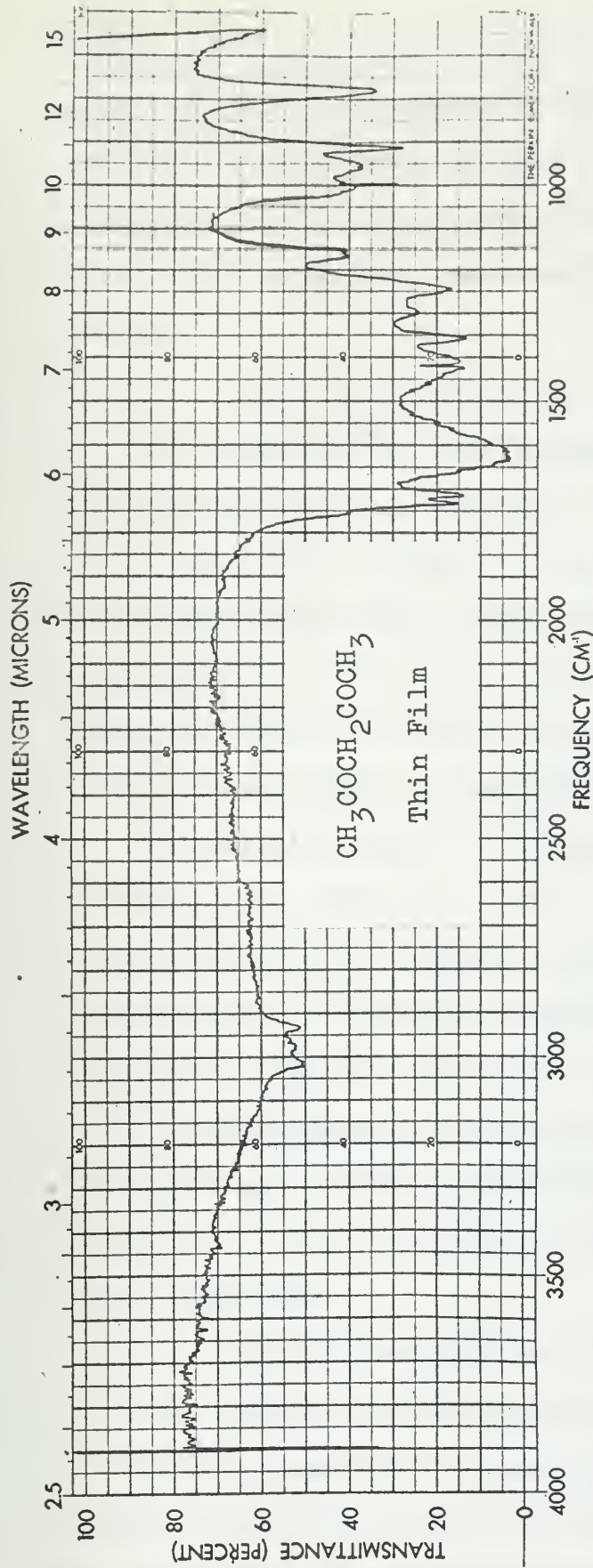


Figure 2

Infrared Spectra of 2,4-Pentanedione and the Sodium Enolate of 2,4-Pentanedione



dione (Figure 2) a strong single absorption occurs at  $1690\text{ cm}^{-1}$  and a broad band is seen in the  $1600\text{-}1500\text{ cm}^{-1}$  region. In addition, the intensity of absorptions due to CH and  $\text{CH}_3$  stretching modes are increased over that noted for the ketone.

d. Phenylbutanedione-1,3

The spectrum of phenylbutanedione-1,3 (Figure 4) does not possess the well defined carbonyl absorption that is seen in 2,4-pentanedione but instead has a broad absorption curve beginning with a sharp shoulder at  $1720\text{ cm}^{-1}$  and continuing to  $1500\text{ cm}^{-1}$ . Better resolution was obtained with a spectrum of a carbon tetrachloride solution than from either a nujol mull or potassium bromide pellet.

The region  $1700\text{ to }1500\text{ cm}^{-1}$  is obscured by the fact that C=C ring vibration, C=O from ketone, C-H, C-C skeletal vibration from the benzene nucleus and characteristic absorptions for a monosubstituted benzene nucleus all occur in this area. The CH stretching for aliphatic compounds and the  $\text{CH}_3$  stretching vibrations are barely discernable at  $3000\text{-}2900\text{ cm}^{-1}$  while a broad absorption of medium intensity at  $3080\text{ cm}^{-1}$  falls within the aromatic CH stretching vibration assignment.

e. 2-Trifluoromethyl-4,6-dimethylpyrimidine

The spectrum of the material tentatively identified as 2-trifluoromethyl-4,6-dimethylpyrimidine (I) was recorded as the nujol mull and as the solid KBr pellet. (Fig. 3) The spectrum of the potassium bromide pellet, continued to give an absorption at  $3500\text{-}3300\text{ cm}^{-1}$ , however, an infrared



spectrum of a nujol mull of I did not show this absorption. Therefore, the absorption was considered to be due to moisture in the potassium bromide. Frequency shifts due to "solvent" interaction of the potassium bromide on I were not significant.

Of considerable interest was the weak absorption noted for the aliphatic CH and CH<sub>3</sub> stretching vibration at 2930 cm<sup>-1</sup> and 2860 cm<sup>-1</sup>. The only comparisons available were the 2-methyl-4,6-dichloropyrimidine, mono, di, and tri-chloropyrimidines and pyrimidine itself reported by Thompson [15]. In this respect with the 2-methyl-4,6-dichloropyrimidine rather weak absorptions were noted in the 3000-2800 cm<sup>-1</sup> region, conforming to the CH aliphatic modes while pyrimidine itself shows stronger multiple absorption in this region.

Absorption at 1608 cm<sup>-1</sup> and 1538 cm<sup>-1</sup> fall within the region referred to by Bellamy [12] as characteristic of -C=C- and -C=N- vibration for pyrimidines. In comparing the spectra of trifluoroacetamide, trifluoroacetamide 2,4-pentanedione and the sodium enolate (see Figures 1 and 2) the C=O C=NH or C-NH<sub>2</sub> absorptions in the 1700 cm<sup>-1</sup> region are noted. If ring closure had not occurred or if some compound not recognized had resulted from the condensation, it is doubtful that the strong C=O for ketone and N-H for the amidine which was seen in the 1700 cm<sup>-1</sup> region could be shifted 100 cm<sup>-1</sup>. Ring closure would eliminate the C=O, =NH and -NH<sub>2</sub> group and result in absorption noted in the spectra. Handling procedure in separation and



purification were not designed to preclude moisture and a compound such as suggested as an intermediate product would have hydrolyzed to at least a substituted perfluoro amide. Such compounds show absorption within the region noted for the C=O of the amide and should be easily determined.

Thompson [15] has drawn attention to the absorption in the  $990\text{ cm}^{-1}$  and  $800\text{ cm}^{-1}$  region for the chloro and ethoxy substituted pyrimidines. The former is assigned to ring vibration and the latter to either ring vibration or deformation. Conforming to this the  $1000\text{ cm}^{-1}$  absorption of I is assigned to vibration of the ring and the strong band at  $800\text{ cm}^{-1}$  due to CH deformation.

Referring to the work of Lacher [13] and Blout and Fields [14] group assignments for C-H bending vibration can be made at  $1450\text{ cm}^{-1}$  with the  $1410\text{ cm}^{-1}$  absorption due possibly to C-CH<sub>3</sub> group vibration. An additional C-CH<sub>3</sub> group vibration was assigned to the  $1380\text{ cm}^{-1}$  region.

The spectra of 6-trifluoromethyl-4-hydroxypyrimidines were reported by Bergman, Cohen and Shahak [7]. Absorptions at  $1280\text{--}1215\text{ cm}^{-1}$ , and  $1170\text{ cm}^{-1}$  were assigned to the -CF<sub>3</sub> group in the compound unsubstituted in the 5 position while absorptions of  $1280\text{ cm}^{-1}$  and  $1215\text{ cm}^{-1}$  were assigned to the 5-fluoro derivative. In the spectrum of I, strong absorptions were noted in  $1190\text{ cm}^{-1}$  and  $1145\text{ cm}^{-1}$  region. The strong absorptions for I in the  $1190\text{ cm}^{-1}$  and  $1145\text{ cm}^{-1}$  are assigned to the CF<sub>3</sub> group. Placement of the substituents gives rise to a frequency shift in other pyrimidines and it is





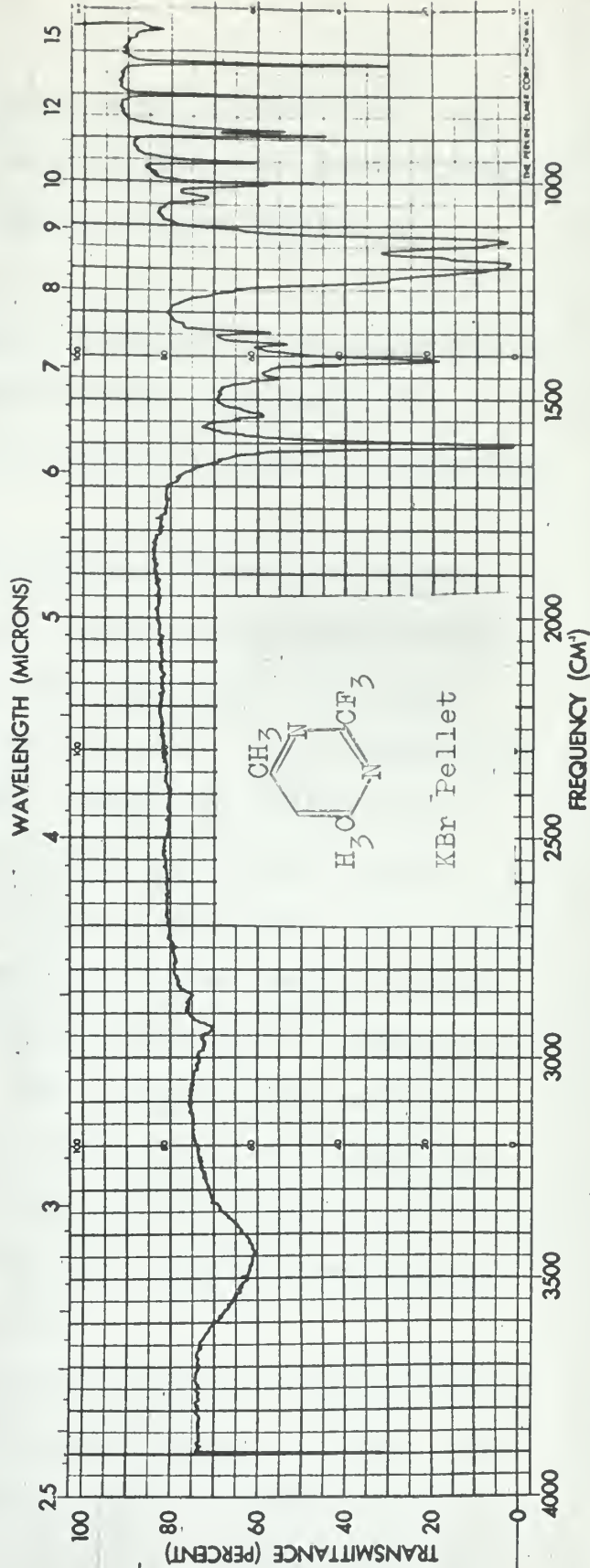
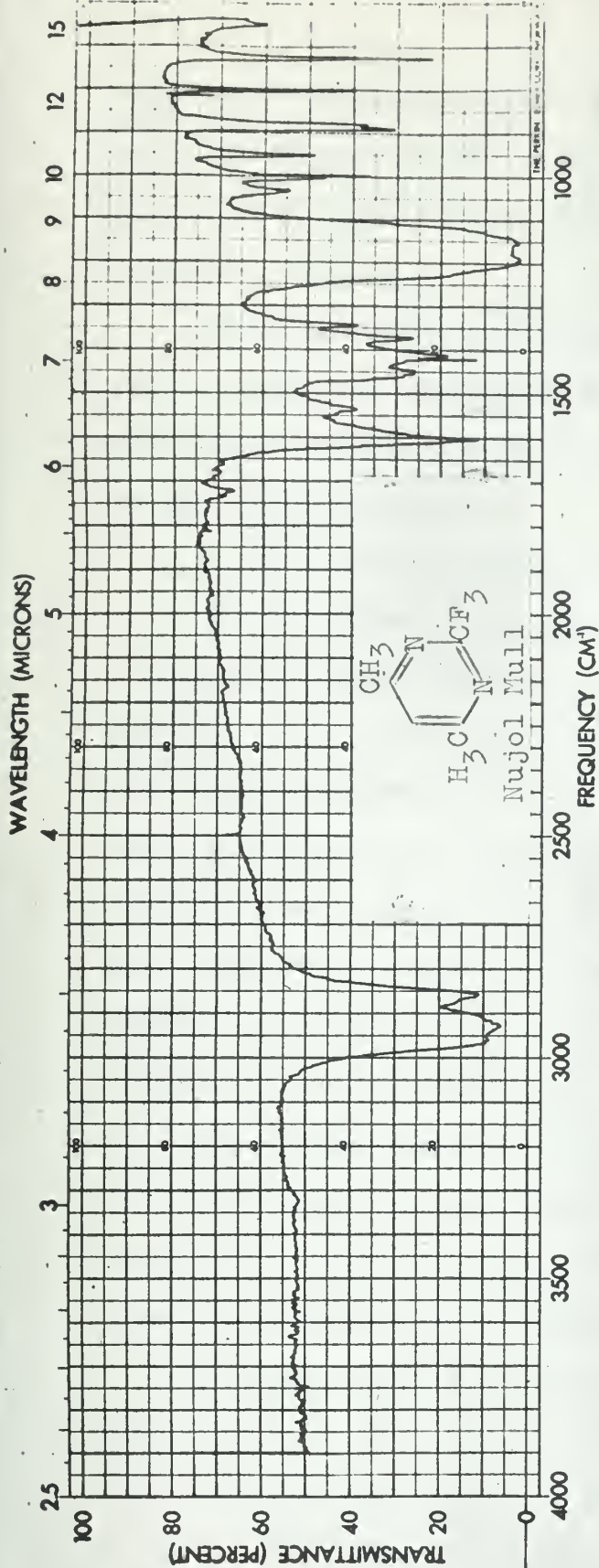


Figure 3

Infrared Spectrum of 2-Trifluoromethyl-4,6-dimethylpyrimidine



expected that such a shift would be valid since the  $-CF_3$  would be placed in the 2 position influenced by both nitrogens rather than vicinal to one as in the spectra of Bergman, loc cit.

Since pyrimidine spectra are primarily characteristic of the specific compound, insufficient information is available for assignment of the other frequencies appearing in the spectrum of I.

f. 2-Trifluoromethyl-4-methyl-6-phenylpyrimidine

The spectrum of a compound tentatively identified as 2-trifluoromethyl-4-methyl-6-phenylpyrimidine (II) was recorded as the potassium bromide pellet. The synthesis of this compound involved the same methods as discussed for the 2-trifluoro-4,6-dimethylpyrimidine with only phenylbutanedione-1,3 replacing the 2,4-pentanedione. It is possible that the intermediate product or some unidentifiable product would be isolated as well as the final condensation product i.e. the pyrimidine. The changes which resulted in the spectral region 1700 to 1600  $cm^{-1}$  of the ketone and the elimination of significant NH and  $NH_2$  vibration of either the amide or amidine suggest that the spectrum represented actually a pyrimidine. (Figure 4)

In comparing the 1700-1500  $cm^{-1}$  region of phenylbutanedione-1,3 with that of II, a striking change is noted. The broad band in the ketone is transferred to three absorptions at 1600  $cm^{-1}$ , 1550  $cm^{-1}$ , and 1500  $cm^{-1}$ . Shoulders on the bands indicate compound absorptions.

The broad band at 3450  $cm^{-1}$  is attributed to moisture



in the potassium bromide. The absorption at 3085  $\text{cm}^{-1}$  is also seen in the ketone and can be compared to the characteristic absorption noted for mono substituted benzenes, however it also occurs in the area assigned for C-H ring vibration noted in some pyrimidines and multiple enhancement cannot be discernable. The weak band at 3115  $\text{cm}^{-1}$  falls within the area expected for CH stretching vibrations of the pyrimidine nucleus. Absorptions at 3030  $\text{cm}^{-1}$  and 3000  $\text{cm}^{-1}$  are also characteristic of the C-H stretching vibration of the benzene nucleus while those at 2930  $\text{cm}^{-1}$  and 2860  $\text{cm}^{-1}$  represent absorption from aliphatic CH and  $\text{CH}_3$  vibrations. The assignments for C-H deformation and ring vibration mode for the 2-trifluoro-4,6-dimethylpyrimidine are also valid for II. The specific absorptions which occur in the 1000  $\text{cm}^{-1}$  and 800  $\text{cm}^{-1}$  region are complicated by the characteristic absorptions in the benzene nucleus. A medium intensity absorption at 1000  $\text{cm}^{-1}$  and a weak absorption at 800  $\text{cm}^{-1}$  are developed from the less definitive spectrum at this region seen in the ketone and are assigned to the ring vibration and C-H deformation modes of the pyrimidine nucleus. The absorption at 1450  $\text{cm}^{-1}$ , 1400  $\text{cm}^{-1}$  and 1380  $\text{cm}^{-1}$  occurs in an area similar to that found in 2-trifluoromethyl-4,6-dimethylpyrimidine for C-H bending vibration and C- $\text{CH}_3$  group vibration. The absorption occurring at 1455  $\text{cm}^{-1}$  is one of the quartet of absorptions in the 1600-1425  $\text{cm}^{-1}$  region which are indicative of the benzene nucleus. The broad band of almost total absorption from 1240 to 1140  $\text{cm}^{-1}$  falls with the area expected of  $-\text{CF}_3$ .



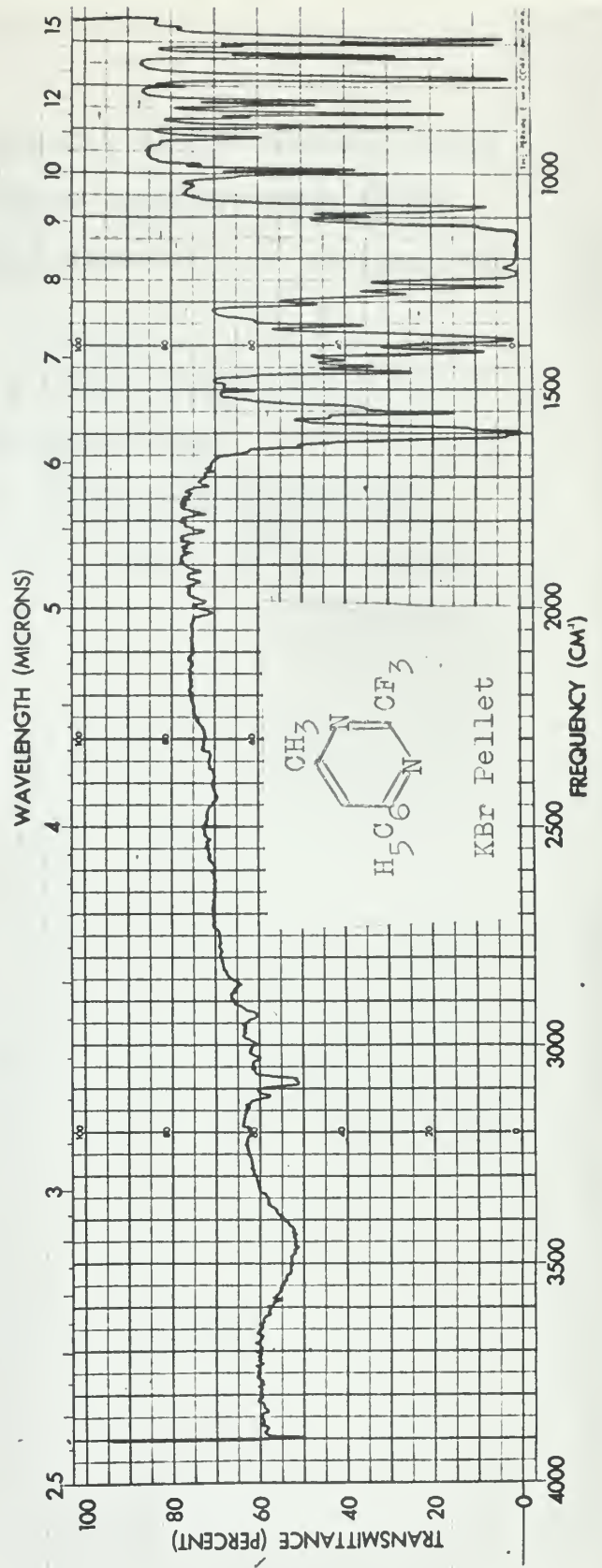
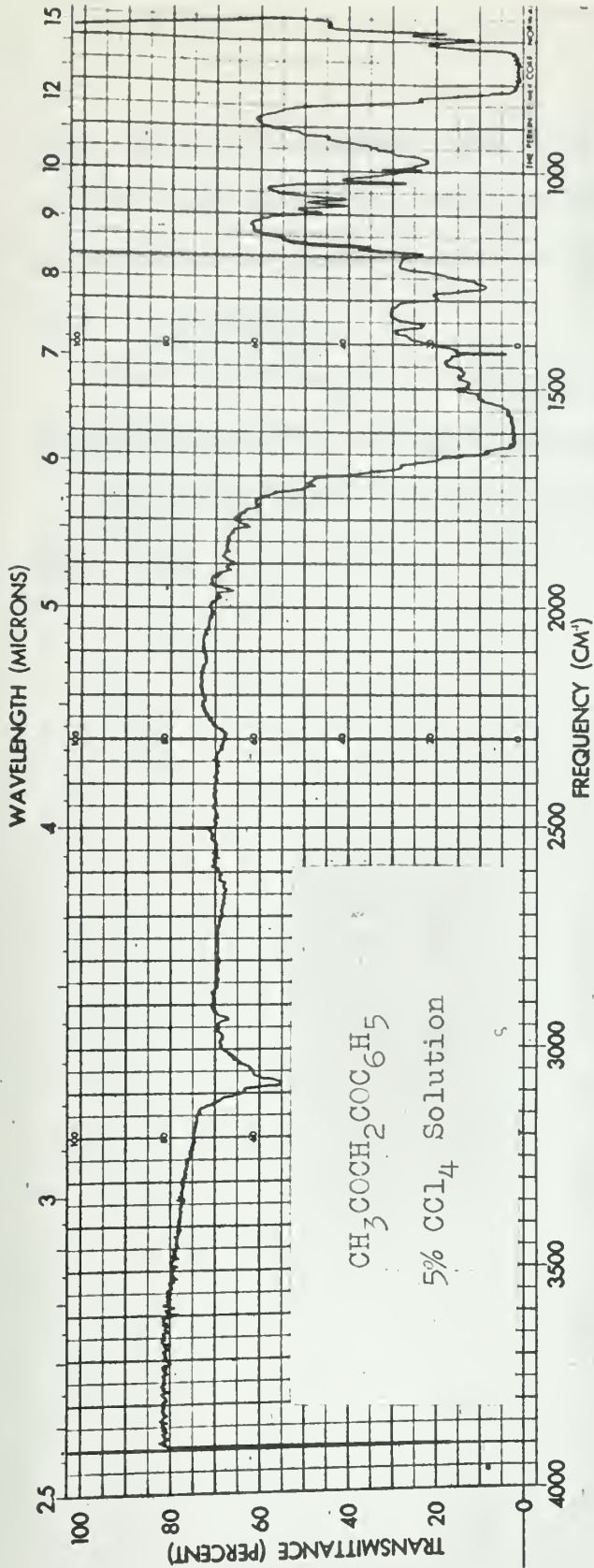


Figure 4  
 Infrared Spectrum of Phenylbutanedione-1,3 and  
 2-Trifluoromethyl-4-methyl-6-phenylpyrimidine.





Also within this same area are usually found characteristic bands - usually weak for the benzene nucleus. The broad absorption suggests multiple enhancement but is assigned to the  $-CF_3$  group.

The spectrum of II conforms to that expected for 2-trifluoromethyl-4-methyl-6-phenylpyrimidine.

To facilitate identification, Table 1 lists the absorptions noted for the pyrimidines covered by this study.



TABLE 1

## Infrared Absorption of 2-Trifluoromethylpyrimidines

<u>Compound</u>	<u><math>\nu</math> Maximum <math>\text{cm}^{-1}</math> (KBr)</u>
2-Trifluoromethyl-4,6-dimethylpyrimidine	2970w, 2935w, 2860w, 1608s, 1535m, 1450w, 1410s, 1372w, 1345m, 1190s, 1140s, 1035w, 1004m, 955m, 890s, 880m, 800m, 730s, 650w
2-Trifluoromethyl-4-methyl-6-phenylpyrimidine	3120w, 3085m, 3030w, 3000w, 2930w, 2860w, 2010w, 1985w, 1940w, 1910w, 1870w, 1850w, 1820w, 1785w, 1710w, 1690w, 1630w, 1600s, 1555s, 1505w, 1460s, 1450m, 1435m, 1415s, 1385s, 1355m, 1305w, 1282m, 1265s, 1240-1130s, 1100m, 1075s, 1030w, 1000s, 990s, 980w, 920m, 890s, 872w, 863s, 842m, 835s, 800w, 782s, 735m, 725s, 700s, 690s

Legend: w = weak, m = medium, s = strong



## 5. Experimental

### a. Preparation of Ethyl Trifluoroacetate ( $\text{CF}_3\text{COOC}_2\text{H}_5$ )

One mole (114 grams) of  $\text{CF}_3\text{COOH}$ , three moles (138 grams) of absolute ethanol and 5 milliliters of concentrated  $\text{H}_2\text{SO}_4$  were added to a 500 milliliter flask. A Friedrichs condenser was attached and the resulting mixture heated at reflux with a glass-rod mantle for three hours. The Friedrichs condenser was replaced with a distillation adapter, West condenser, and delivery tube. The product was stripped to an indicated boiling point of  $70^\circ\text{C}$ ., dried first over  $\text{CaCl}_2$  and then over  $\text{Na}_2\text{SO}_4$  over night. Fractionation at a 10:1 reflux ratio through a 10mm x 76mm glass helices-packed column yielded 89 grams (62.5%), boiling point  $59-61^\circ\text{C}$ .

### b. Preparation of Methyl Trifluoroacetate ( $\text{CF}_3\text{COOCH}_3$ )

$\text{CF}_3\text{COOCH}_3$  was prepared in a manner similar to the  $\text{CF}_3\text{COOC}_2\text{H}_5$  replacing only the three moles of absolute ethanol with absolute methanol. A suitable product was obtained without resorting to rectification. However, it was necessary to siphon ice water through the condenser both during reflux and distillation to reduce product loss. Ester yield based on one mole (114 grams) of  $\text{CF}_3\text{COOH}$  was 109 grams of  $\text{CF}_3\text{COOCH}_3$  (85%) with a boiling point of  $42-44^\circ\text{C}$ .

### c. Preparation of Trifluoroacetamide ( $\text{CF}_3\text{CONH}_2$ )

$\text{CF}_3\text{CONH}_2$  was prepared by reacting either  $\text{CF}_3\text{COOCH}_3$  or  $\text{CF}_3\text{COOC}_2\text{H}_5$  with anhydrous  $\text{NH}_3$  in a manner as first described by Gilman and Jones. [10]

A three-neck 500 milliliter flask was fitted with a



dry ice condenser with a cotton drying tube attached to the exit arm of the condenser. A glass delivery tube was fashioned so as to reach the bottom of the flask and was held in place by passing the tube through a rubber stopper. The delivery tube was inserted through one neck and the remaining neck of the flask was closed by a blank ball joint which served as a means of introducing materials into the flask.

The ester was diluted 50/50 with ethyl ether and introduced into the flask. Dry ice and acetone were added to the condenser and anhydrous ammonia was passed into the flask such that mild refluxing of liquid  $\text{NH}_3$  was noted. The  $\text{NH}_3$  addition was continued for two hours. The flask and products were permitted to come to room temperature and then remain overnight so that the excess ammonia would evaporate. The contents of the flask were poured into an evaporating dish and crystallized, filtered and recrystallized from 95% ethanol. The product was then placed in a 500 milliliter flask equipped with a distillation head and West condenser and heated until liquid  $\text{CF}_3\text{CONH}_2$  was noted to reflux. The flask was then cooled, the product was broken up, removed, and ground with a mortar and pestle for subsequent use in nitrile synthesis. Yield 72 grams (79%), based on 89 grams of  $\text{CF}_3\text{COOC}_2\text{H}_5$ . Note when  $\text{CF}_3\text{COOCH}_3$  was used, a single crystallization yielded an  $83^\circ\text{C}$  melting point product.

d. Preparation of Trifluoroacetonitrile ( $\text{CF}_3\text{CN}$ )

$\text{CF}_3\text{CN}$  was prepared by dehydrating the amide with





$P_2O_5$  [10]. Since the nitrile is a gas at  $-63^\circ C.$ , the following adaptation was utilized:

$P_2O_5$  and  $CF_3CONH_2$  mixture was introduced into a 500 milliliter distillation flask. A second 500 milliliter flask was fashioned as a trap and cooled with crushed ice. Two dry ice traps, fashioned from 50 milliliter test tubes, were connected in series and served as receivers. Tygon tubing was used for all flexible connections. All glassware was oven dried and assembled hot. A cotton filled drying tube was attached at the exit of the dry ice tube bank to permit venting during cooling and was replaced with a freshly dried tube for the dehydration. In the preparation, ice was packed around the trap and the receivers were cooled in a Dewar flask containing dry ice and acetone.

Using the above described setup, 25 grams (0.219 mole) of  $CF_3CONH_2$  and 25 grams (0.178 mole) of  $P_2O_5$  were introduced into the dehydrating flask and mixed by shaking. Approximately 10 gm of  $P_2O_5$  was added as a top layer. The dehydrating flask was heated with a glas-col mantle at 30 volts. All portions of the flask above the mantle were insulated with glass wool. The contents of the flask soon became a frothy plastic mass. Heating was continued until apparent gas evolution ceased. By using insulation and a high mantle temperature, sublimation of  $CF_3CONH_2$  and subsequent plugging of the dehydrating exit tube was avoided. Because of the volatility, yield was not determined but the product was stored in the dry ice-cooled receivers for use in the synthesis of  $CF_3CNHNH_2$ .



e. Preparation of Trifluoroacetamide ( $\text{CF}_3\text{CNH}_2$ )

To a three neck 500 milliliter flask was attached a dry ice condenser and a gas delivery tube as described under the synthesis of  $\text{CF}_3\text{CONH}_2$ . The glassware was oven dried and protected during cooling with a dry cotton drying tube. When cool, dry ice and acetone were added to the condenser and dry ice was packed around the flask. Anhydrous  $\text{NH}_3$  was introduced into the flask until approximately 100 milliliters of liquid  $\text{NH}_3$  had been collected.

$\text{CF}_3\text{CN}$  prepared as previously described was distilled into the liquid  $\text{NH}_3$ . Upon completion of the nitrile addition, the gas tube was replaced by a blank stopper and the dry ice was removed from the outside of the flask. The dry ice trap was of sufficient capacity to permit about two hours of refluxing before the coolant was depleted. The flask assembly was allowed to remain overnight to evaporate the excess ammonia. The liquid remaining in the flask was transferred to a dry 50 milliliter flask and distilled with a vacuum distillation assembly with an air column 10 centimeters long. After an initial forerun to  $30^\circ\text{C}$  at 30 mm Hg, the pressure was reduced to 10 mm Hg and a product of almost constant boiling was removed at  $38^\circ\text{C}$ . Yield 16 grams (64%) based on 25 gm (0.219 mole) of  $\text{CF}_3\text{CONH}_2$ .

f. Synthesis of 2-Trifluoromethyl-4,6-dimethylpyrimidine

Prior to use, all glassware was dried in an oven, assembled as a unit, and cooled with a drying tube attached. This procedure was deemed necessary since  $\text{CF}_3\text{CNH}_2$  is easily hydrolyzed.



50 ml. of anhydrous ethanol was placed in a 200 milliliter three neck flask equipped with a magnetic stirrer, Friedrichs condenser with drying tube attached, and dropping funnel. 2.3 grams of sodium was cut into small pieces and added through a stoppered neck of the flask. The sodium ethoxide was allowed to cool to room temperature. A dry ice cooled trap was connected to the exit of the condenser and the trap exit was protected from moisture with a dry cotton-filled drying tube. 17 grams (0.16 mole) of freshly prepared  $\text{CF}_3\text{C}(\text{NH})\text{NH}_2$ , as previously described, was added in one aliquot to the sodium ethoxide. 16 gram (0.16 mole) of 2,4-pentanedione was diluted with an equal volume of absolute alcohol, placed in the dropping funnel and added dropwise with stirring to the amidine-ethoxide mixture.

A slight evolution of heat was noted during the addition and the flask remained warm for about two hours. The reactants were permitted to remain overnight at room temperature. A gas-col mantle with pyrometer attached was fitted to the flask and the voltage adjusted to a mantle temperature of  $75^\circ\text{C}$ . The reactants were noted to reflux and the mantle was disconnected. What appeared to be an exothermic reaction continued for approximately one and one half hours. When the exothermic reaction was completed, heat was applied to the mantle and a temperature of  $75^\circ\text{C}$  was maintained for an additional twelve hours. The initial color of the reactants was light straw, but the color darkened as the heating progressed.

The flask was cooled, and the precipitate which formed



was vacuum filtered. A dry ice trap was placed between the filter flask and the aspirator. The filtrate was stripped of  $C_2H_5OH$  at 50 mm Hg pressure. Stripping was conducted at as low a temperature as possible to avoid over-heating the products. This was accomplished by connecting a pyrometer to the mantle and maintaining the temperature at less than  $75^\circ C$ . The flask was cooled, 25 milliliters of Eastman 0.64 ligroin was added and the slurry was filtered. The flask and precipitate were washed with two additional 25 milliliter aliquots of ligroin. The ligroin extract was placed in an evaporating dish and the crystalline product collected when the ligroin had evaporated. The traps were washed with ligroin and the washing evaporated. The products of the traps and the other ligroin washing were dissolved in a minimum amount of ligroin and recrystallized. The soft, fragile, easily melted crystals were transferred to a vacuum sublimation device as described by Wheeler<sup>1</sup>. Vacuum was applied to the sublimator and pumping continued for five minutes at about 10 mm Hg to remove solvent. Dry ice was added to the cooling thimble and the sublimator was heated by placing it in a beaker of boiling water. Yield for sublimate 9.6 grams (34%), mp  $38.4^\circ C$ . IR analysis indicated that this material was 4,6-dimethyl-2-trifluoromethyl-pyrimidine. In addition, 5.1 grams of material identified as  $Na^+ [CH_3COFCOCH_3]^-$  and a small amount of  $C_2H_3O_2Na$  were also obtained. Qualitative analysis of the stripped  $C_2H_5OH$  indicated that it contained acetone per 2,4-dinitrophenyl-

<sup>1</sup>Wheeler, E., Scientific Glassblowing, pg 460, Interscience Publishers, Inc., New York, 1958.





hydrazone.  $\text{NH}_3$  was noted in the trap and a small amount (approximately 2 grams) of brown tar-like polymer containing nitrogen was also obtained.

#### g. Synthesis of 2-Trifluoromethyl-4-methyl-6-phenylpyrimidine

A Friedrichs condenser was fitted to a 500 milliliter three-neck flask which was equipped with a magnetic stirrer, and a dry cotton filled drying tube was attached to the exit arm of the condenser. Stoppers were added to the remaining flask necks and served as a means of introducing materials into the flask. All glassware was oven dried prior to use.

50 milliliters of absolute  $\text{C}_2\text{H}_5\text{OH}$  was added to the flask and the stirrer started. 2.3 grams of sodium was cut into small pieces and added to the  $\text{C}_2\text{H}_5\text{OH}$ . When the reaction was complete, 18 grams (0.15 mole) of  $\text{CF}_3\text{CNHNH}_2$  and 25 grams (0.16 mole) of  $\text{C}_6\text{H}_5\text{COCH}_2\text{COCH}_3$  were added each in one aliquot. Slight warming occurred and the reacting mixture turned a dark straw color. The color darkened to a deep red as the reaction continued.

A gas-col mantle with pyrometer attached was fitted to the flask and the reactants were heated to a temperature of  $75^\circ\text{C}$  for 16 hours.

The flask was cooled and the precipitate filtered. The filtrate was then stripped of  $\text{C}_2\text{H}_5\text{OH}$  under vacuum. The precipitate which formed after stripping was again filtered and added to the previous precipitate. The combined precipitate was washed with a minimum amount of water. Acidification of the water extract yielded a white curd-like



precipitate which when dried melted at 54°C. Qualitative test for nitrogen was negative and phenylhydrazine test positive. Mixed melting point with phenylbutanedione-1,3 was unchanged. The precipitate was identified therefore as  $\text{Na}^+ [\text{C}_6\text{H}_5\text{C}\bar{\text{C}}\text{HCOCH}_3]$ . The filtrate was permitted to stand overnight and a precipitate was noted to form. Concentration under vacuum yielded additional product. The organic residues from the water washing previously described were combined with this product. Crystallization in water -  $\text{C}_2\text{H}_5\text{OH}$  of the precipitate acquired from the original filtrate and the residue from the washings yielded a product melting at 90.3°C. Infrared spectra of this material indicated that it was the 2-trifluoromethyl-4-methyl-6-phenylpyrimidine.

The solid recovered from the enolate amounted to 4.2 grams. An additional 3.9 grams of an organic liquid containing predominately  $\text{C}_6\text{H}_5\text{COOC}_2\text{H}_5$  and  $\text{C}_6\text{H}_5\text{COCH}_3$  was obtained from the final stripping reaction. Net yield of 2-trifluoromethyl-4-methyl-6-phenylpyrimidine, 7 grams (19%), mp 90.3°C.



## 6. Conclusions

In view of the conformity to reported spectra for known pyrimidine compounds, it is concluded that the reaction of 2,4-pentanedione and trifluoroacetamide resulted in the synthesis of 2-trifluoromethyl-4,6-dimethylpyrimidine, while the reaction of phenylbutanedione-1,3 with trifluoroacetamide yielded 2-trifluoromethyl-4-methyl-6-phenylpyrimidine. The yields were low partially due to side reactions, however, they were well within those yields reported for other pyrimidine syntheses. Until complete carbon-hydrogen analyses are available to prove or disprove these conclusions, the identification of these materials must remain tentative.



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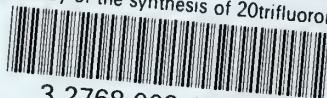






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