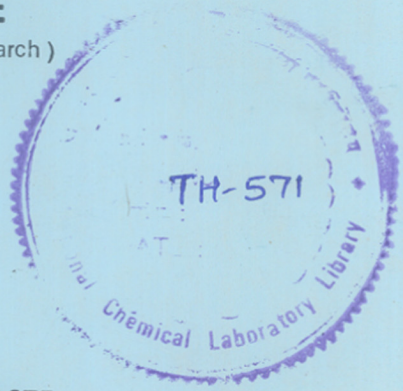
SYNTHESIS REACTIONS AND ANALYSIS OF SUBSTITUTED UREAS AND PURINE ALKALOIDS

COMPUTERISED

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA
FOR THE DEGREE OF
MASTER OF SCIENCE
(Partly by Papers & Partly by Research)
IN CHEMISTRY



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MARCH 1989

DEDICATED

TO

*** MY PARENTS ***

A C K N O W L E D G E M E N T

It is a pleasure to express my profound sense of gratitude to Dr. R.B. Mitra, Director, Central Leather Research Institute, Madras, for his valuable guidance, constant encouragement and enthusiastic supervision throughout the course of my research.

I am indebted to Late Dr. B.B. Ghatge, Late Dr. A. Subbarao and Dr. B.V. Bapat for the invaluable assistance, helpful discussions and suggestions. The assistance rendered by Dr.D.G.Panse, Mr.S.M.Likhite, Mrs.M.V.Mane and Mr.M.M.Gharpure is recorded with high sense of gratitude. My thanks are also due to Mr. P.V. Iyer, for excellent typing of this manuscript.

Finally, I am grateful to Dr. S. Rajappa, Head, Organic Chemistry-I Division and Dr. L.K. Doraiswamy, Director, National Chemical Laboratory, for giving an opportunity to me for submission of this research work in the form of a thesis.

Mr. V.K. Gumaste

Division of Organic Chemistry-I
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Pune - 411 008.
March - 1989

CERTIFICATE

Certified that the work incorporated in the thesis entitled "Synthesis, Reactions and Analysis of Substituted Ureas and Purine Alkaloids" submitted by Mr. VIKAS KALYANRAO GUMASTE was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(Dr. R.B. Mitra)
Supervisor

GENERAL REMARKS

1. All melting points and boiling points are uncorrected. Temperatures are recorded on centigrade scale.

2. PMR spectra were recorded on Varian T-60 and FT-80-A Spectrometers, using TMS as internal standard. The chemical shifts are given in δ values.

3. GLC analysis was carried on a Hewlett-Packard model Serial No.5730-A equipped with Flame Ionisation Detector and 3380-A Integrator. A Carlo-Erba model Fractovap 2450, equipped with Flame Ionisation Detector and 3390-A Integrator was also used.

4. High performance liquid chromatographic analysis was carried out on Waters Associates equipped with Model 440 Absorbance Detector and Data Module Integrator.

5. The numbers assigned to the structures, references, figures and tables refer to that particular chapter only.

C O N T E N T S

CHAPTER - I

INTRODUCTION

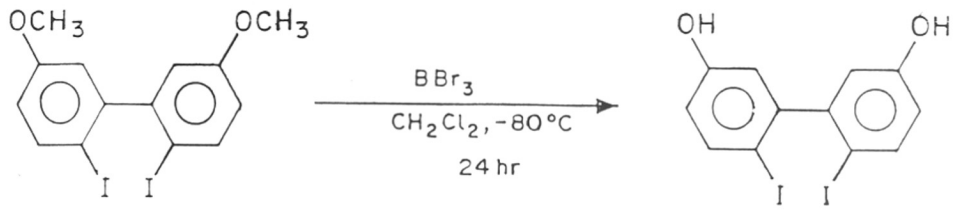
In the Bhopal accident involving methyl isocyanate (MIC), numerous products were formed as a result of high temperature thermal reactions of MIC and its by-products with water and chloroform. Several products involving demethylation of N-methyl groups were observed. The work reported in this thesis forms a part of the larger investigation carried out in our laboratory on this problem.

The process of removal of methyl or alkyl group from heteroatom such as O,N,S, etc. is known as demethylation or dealkylation. Methylation or demethylation can be carried out using a wide variety of reagents.

Methylation of organic compounds such as carboxylic acid can be efficiently and quantitatively done by reacting with diazomethane. Similarly methylation of phenolic compounds can be done by using dimethylsulfate or methyl iodide in presence of alkali. Methylation and demethylation reactions can be used to degrade certain organic molecule to a known product. A well known reaction namely Hofmann[1] degradation involves methylation of nitrogen atom, quaternization of the same and subsequent degradation to a known product. This reaction has been widely used in the field of alkaloids for structure determination.

There are several references available in the literature on demethylation of ethers and esters. Ethers are normally demethylated under acidic or Lewis acid conditions. Thus, 2,2'-Diiodo-5,5' dimethoxy biphenyl (1) when treated with Boron tribromide[2] in methylene chloride at -80°C for 24 hrs. gave demethylated product 2,2'-Diiodo-5,5' dihydroxy biphenyl (2) in 77% yield (Scheme-I). Ethyl 2 acetyl-5-methoxyphenoxy acetate (3) when allowed to react with Boron trichloride[3] in cold methylene chloride at room temperature for just five minutes gave demethylated product 2-hydroxy-4-methoxy-aceto-phenone (4) (Scheme-II). However, Feutrill[4] et al have reported that when methyl ethers of substituted phenol (5) are treated with ethyl sulfide anion in dimethylformamide under nitrogen atmosphere at 102°C, they gave demethylated product (6) in 94% yield (Scheme-III). In 1970, Buncel[5] et al have reported that when 7-methoxy-4-nitrobenzofuroxan (7) was heated at 55°C for 45 minutes in the presence of 0.1 N KOH methyl group from position 7 is knocked off to give 7-hydroxy-4-nitrobenzofuroxan (8) (Scheme-IV). Kelly[6] et al have reported a novel method of demethylation in which the sensitive styrene bond is unaffected. They have demethylated 2-methyl-5-methoxy styrene (9) in the presence of lithium thiomethoxide at 160°C for 7 hrs. which gave 2-methyl-5-hydroxy styrene (10) in good yield (Scheme-V). Lithium n-propyl mercaptide[7] in hexamethylphosphoramide (HMP) is an

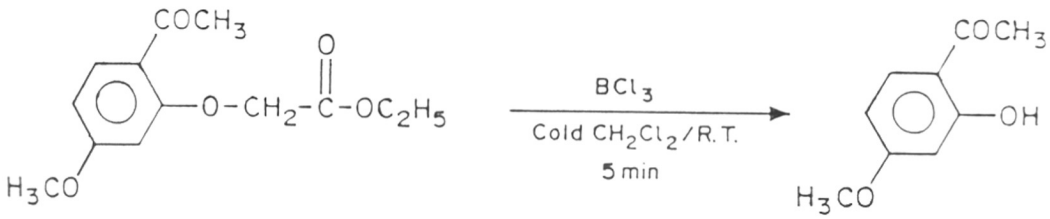
SCHEME - I



(1) (2) 77 %

Ref: Mc Omic etal ②

SCHEME - II



(3) (4)

Ref: Dean etal ③

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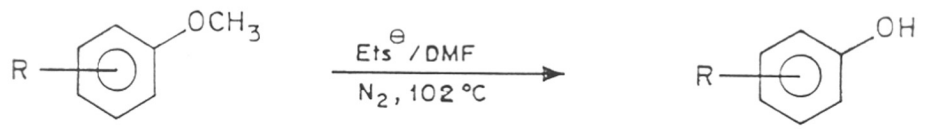


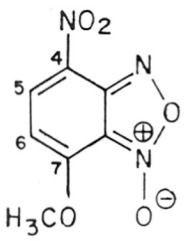
R = CH_3

94%

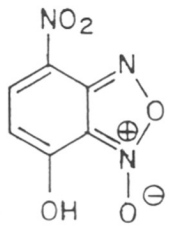
(5) (6)

Ref: Feutrill etal ④

SCHEME – IV



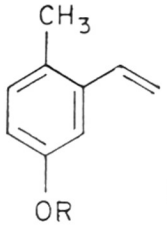
0·1N KOH
55 °C, 45 min.



(7) (8)

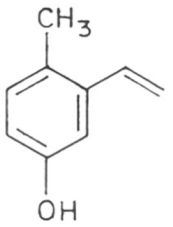
Ref: Buncel etal (5)

SCHEME – V



R = CH_3

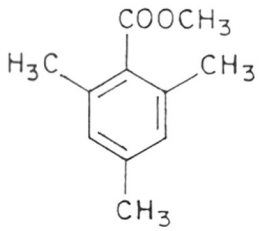
CH_3SLi
160 °C, 7 hrs



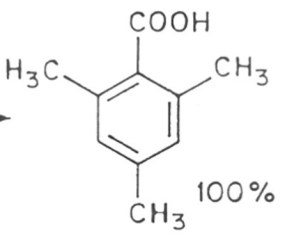
(9) (10)

Ref: Kelly etal (6)

SCHEME – VI



Li-n-Propyl mercaptide
HMP, R.T. 1·5 hr



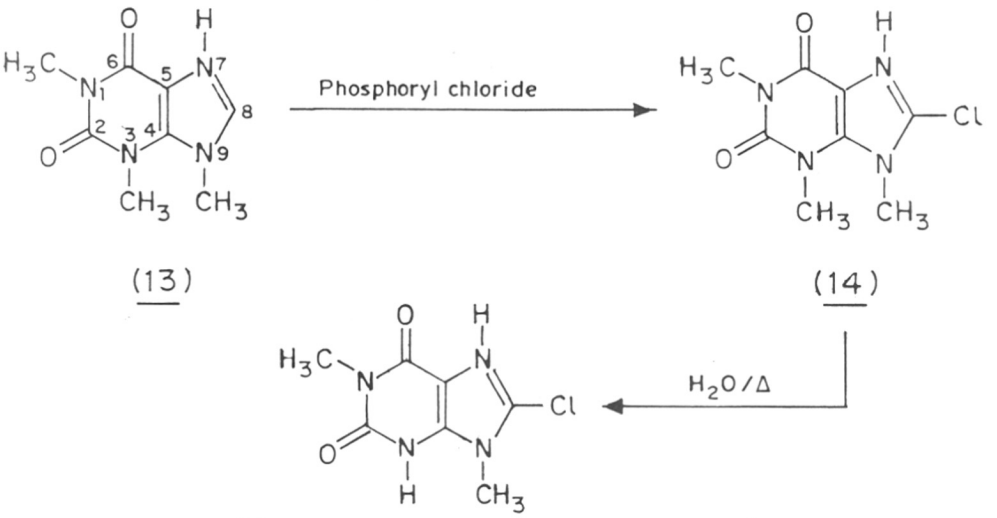
(11) (12)

Ref: Bartlett etal (7)

effective reagent for the cleavage of methyl esters under mild conditions. Methyl mesitoate (11) when treated with Lithium n-propyl mercaptide in HMP at room temperature for 1.5 hr. gave mesitoic acid (12) in 100% yield (Scheme-VI). All these are classic examples of O-demethylation.

We will now discuss about N-demethylation. 1,3,9-Trimethyl xanthine[8] (13) when treated with phosphoryl chloride, gave 8-chloro-1,3,9-trimethyl xanthine (14) which on hydrolysis gave 8-chloro-1,9-dimethyl xanthine (15) with elimination of methyl group from the nitrogen at 3 (Scheme-VII). Theophylline, caffeine, and theobromine are important drugs. Theophylline[9] can be prepared from caffeine in four steps by demethylation method. 1,3,7-Trimethyl xanthine (16), i.e. caffeine, when chlorinated in the presence of tetrachloroethane and nitrobenzene at 30°C gave (17) which on hydrolysis followed by heating for 22 hrs. gave 8-chloro-1,3-dimethyl xanthine (18). After reduction with zinc and hydrochloric acid it gave 1,3-dimethyl xanthine (19), i.e. theophylline (Scheme-VIII). During the literature survey, various references on isomerisation of xanthinium salts containing I^-, Cl^- and HSO_4^- respectively as anions were obtained. In the course of isomerisation, the methoxy group either migrates or is eliminated. Heating 7,9-dimethyl xanthinium[10] salt (20) in the presence of molecular iodine at 230°C for 30 minutes gave

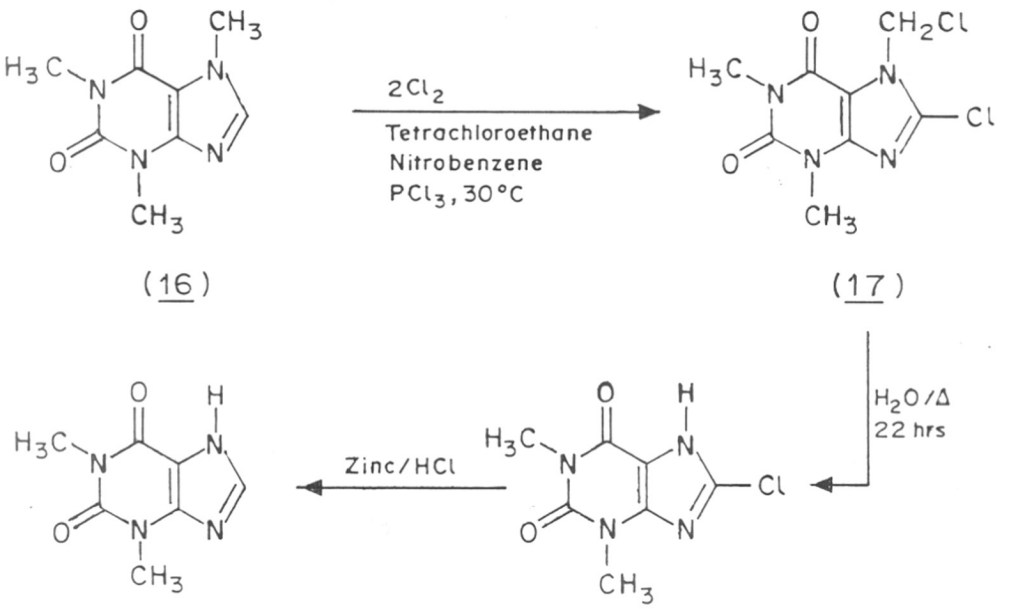
SCHEME - VII



(13) (14) (15)

Ref: Lister ⑧

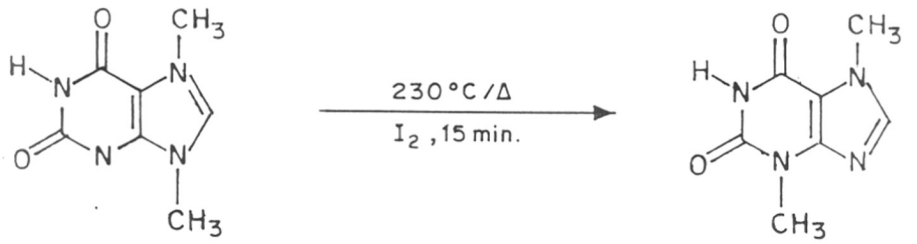
SCHEME - VIII



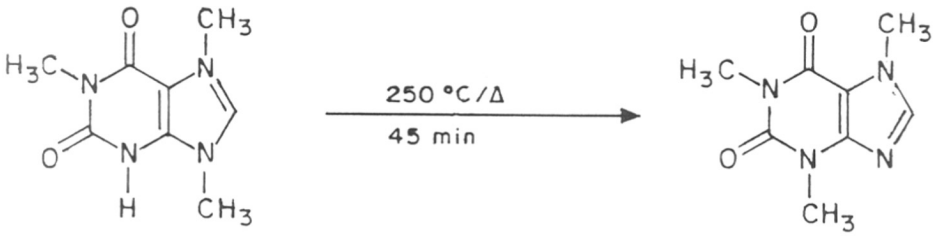
(16) (17) (18) (19)

Ref: Dewing etal ⑨

SCHEME - IX



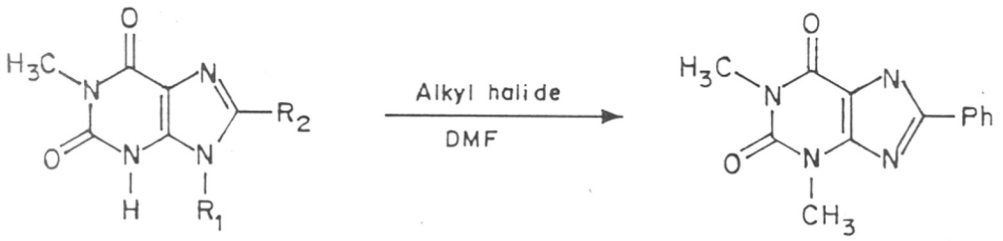
(20) (21)



(22) (16)

Ref: Muravich etal [10]

SCHEME - X



$R_1 = CH_3$

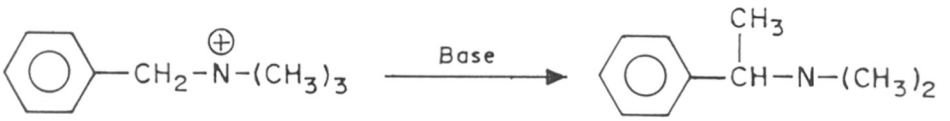
(23) $R_2 = Ph$ (24)

Ref : Yoneda etal [11]

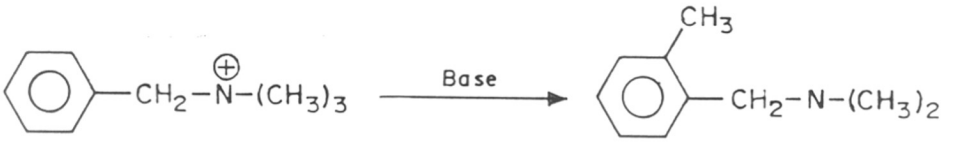
3,7-dimethyl xanthine (21), i.e. theobromine (Scheme-IX). During the fusion of 1,7,9-trimethyl xanthinium[10] salt (22) at 250°C for 45 minutes, it is converted to 1,3,7-trimethyl xanthine (16), i.e. caffeine, quantitatively (Scheme-IX). These facts demonstrate the ready migration of methyl group from N^9 to N^3 atom. Yoneda[11] et al have observed that alkylation of 9-substituted 1-methyl xanthine (23) with the excess of alkyl halide gave 3,7-dialkyl-1-methyl xanthine (24) with elimination of the 9-substituent (Scheme-X). The base promoted rearrangement of quaternary ammonium salts are well known. In Stevens rearrangement, one alkyl group migrates from the quaternary nitrogen atom to α-carbon of second alkyl group. The Sommelet Houser rearrangement involves the migration to the orthoposition of a benzyl quaternary ammonium salt. Both rearrangements may occur simultaneously although experimental conditions markedly affect the competing pathways (Scheme-XI). In general, rearrangement occur in those quaternary ammonium salts that do not contain β-hydrogen atom and thus are not capable of undergoing Hofmann elimination.

The problem of N-demethylation of quaternary ammonium salt is a difficult task. The classical method for demethylation involves pyrolysis of ammonium halides which may lead to extensive demethylation[12]. Refluxing ethanolamine has also been used for the purpose of demethylation[13], but this reagent can lead to

SCHEME-XI

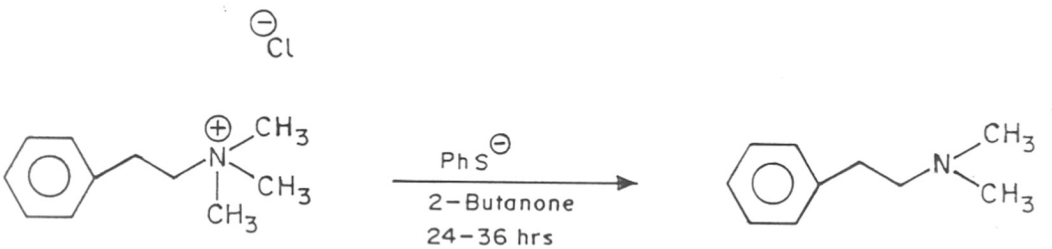


STEVENS REARRANGEMENT



SOMMELET HAUSER REARRANGEMENT

SCHEME - XII



(25) (26)

Ref : Shamma etal [14]

predominantly Hofmann elimination and when methoxy groups are present O-demethylation can also take place. Shama[14] et al have reported that N,N-dimethyl-β-phenethylamine methochloride (25) which is susceptible to Hofmann elimination[13], when treated with thiophenoxide anion in refluxing 2-butanone over a period of 24-36 hrs. gave N,N-dimethyl-β-phenethylamine (26) in 85% yield (Scheme-XII).

Present Work

Demethylation of N-methyls in cyclic amides by sodium thiophenolate has not been studied earlier. Therefore, we describe in this chapter a simple method of demethylation of N-methyl isocyanurates, N-methyl uracils and N-methyl xanthine derivatives by sodium thiophenolate. A possible mechanistic route involving the formation of quaternary ammonium salt intermediates such as (A), (B), (35), (37) during the reaction and their subsequent decomposition to thioanisole (30) and demethylated product is described in this chapter.

EXPERIMENTAL

All the compounds reported in this chapter are known earlier in the literature. The triazinetrione derivatives (27) and (29), 1,3-dimethyl-6-imino uracil (31) and thioanisole (30) were synthesized in our laboratory by following the known methods. Caffeine (16), theophylline (19), theobromine (21) and 3-methyl xanthine (38) were supplied by G.H. Boehringer shon. ingelhein Rhein (W. Germany) and Fluka Chemicals. These were used as authentic samples to identify and quantitatively estimate the reaction product by HPLC method. Earlier, the analysis of xanthine derivatives by HPLC was carried out by Voelter[15] et al. We have developed our own method of HPLC analysis. Following HPLC conditions were used:

Instrument	:	Waters Associates equipped with Data module integrator
Mobile phase	:	Methanol:Water (40:60) + Acetic acid (0.1 ml) pH 3.1-4
Column	:	μ bondapack C-18 cartridge (10 cm x 8mm I.D.)
Detector	:	UV λ -254 0.05 AUFS
Flow	:	3 ml/min.
Chart Speed	:	1 cm/min.

GLC was also employed whenever necessary.

General procedure used for quantitative estimation

Initially, the reaction mixture of all the experiments were analysed qualitatively. Quantitative estimation was done by external standard method. For this purpose, standard solutions of known concentration were prepared and by using serial dilution method peak matching was done. Based on these observations, quantitative estimation was done.

Preparation of standard compounds

1,3,5-Trimethyl-1,3,5-triazine-2,4,6 (1H,3H,5H)-trione[16] (MIC-Trimer) (27)

Methyl isocyanate (20g; 0.11 mol) was added dropwise to a stirred mixture containing 0.4g of anhydrous ferric chloride in 25 ml of anhydrous ethyl acetate at 70°C. The addition required about 40 minutes. After the addition, the reaction temperature was raised to 83°C over a period of 2 hrs. After cooling to room temperature, the reaction mixture was evaporated to dryness under reduced pressure to produce 16g of solid. The latter was dissolved in 80 ml of dichloromethane and was filtered through Hi-flow supercell to remove ferric chloride catalyst. The filterate upon evaporation to dryness under reduced pressure gave 15g (75%) of (27), m.p. 175-178°C (lit.[16] m.p. 175°C).

1,3-dimethyl-1,3,5-triazine-2,4,6 (1H,3H,5H) trione[17] (29)

A mixture of potassium cyanate (5.70g; 0.1 mol) in dimethyl formamide (100 ml) was allowed to react for 24 hr. at 75°C.

Dimethyl formamide was removed by distillation over steam bath to yield a solid mass as residue, which was stirred in water (50 ml) and filtered to remove MIC-Trimer (27). The filterate was acidified with concentrated hydrochloric acid. The precipitated compound was filtered and recrystallized from little charcoal and hot toluene to furnish pure colourless crystals of (29), yield 2.3g (40%), m.p. 218-220°C (lit.[17] 221-222°C).

Methyl-phenyl-sulfide (Thioanisole) (30)

A mixture of thiophenol (11.0g; 0.1 mol) sodium hydroxide solution (75 ml; 1.5 mol) and water (100 ml) in ethanol (200 ml) was stirred at room temperature for 30 minutes. Methyl iodide (29g; 0.2 mol) was added to the above mixture at room temperature and stirred for 1 hr. Ethanol was removed under reduced pressure and the resulting mixture was diluted with water (100 ml) and extracted with solvent ether. Ether layer was washed with water (150 ml). Brine and dried on sodium sulfate (Na_2SO_4). Evaporation of ether layer furnished crude product which was distilled at 186-188°C (lit.[18] 188°C), to get thioanisole (30), 11.3g (91%).

1,3-dimethyl 6-imino uracil[19] (31)

A reaction mixture consisting of 1,3-dimethyl urea (22.0g; 0.25 mol) of cyano acetic acid (23.4g; 0.275 mol) and 75 ml of acetic anhydride was heated to 75-85°C for 24 hrs.

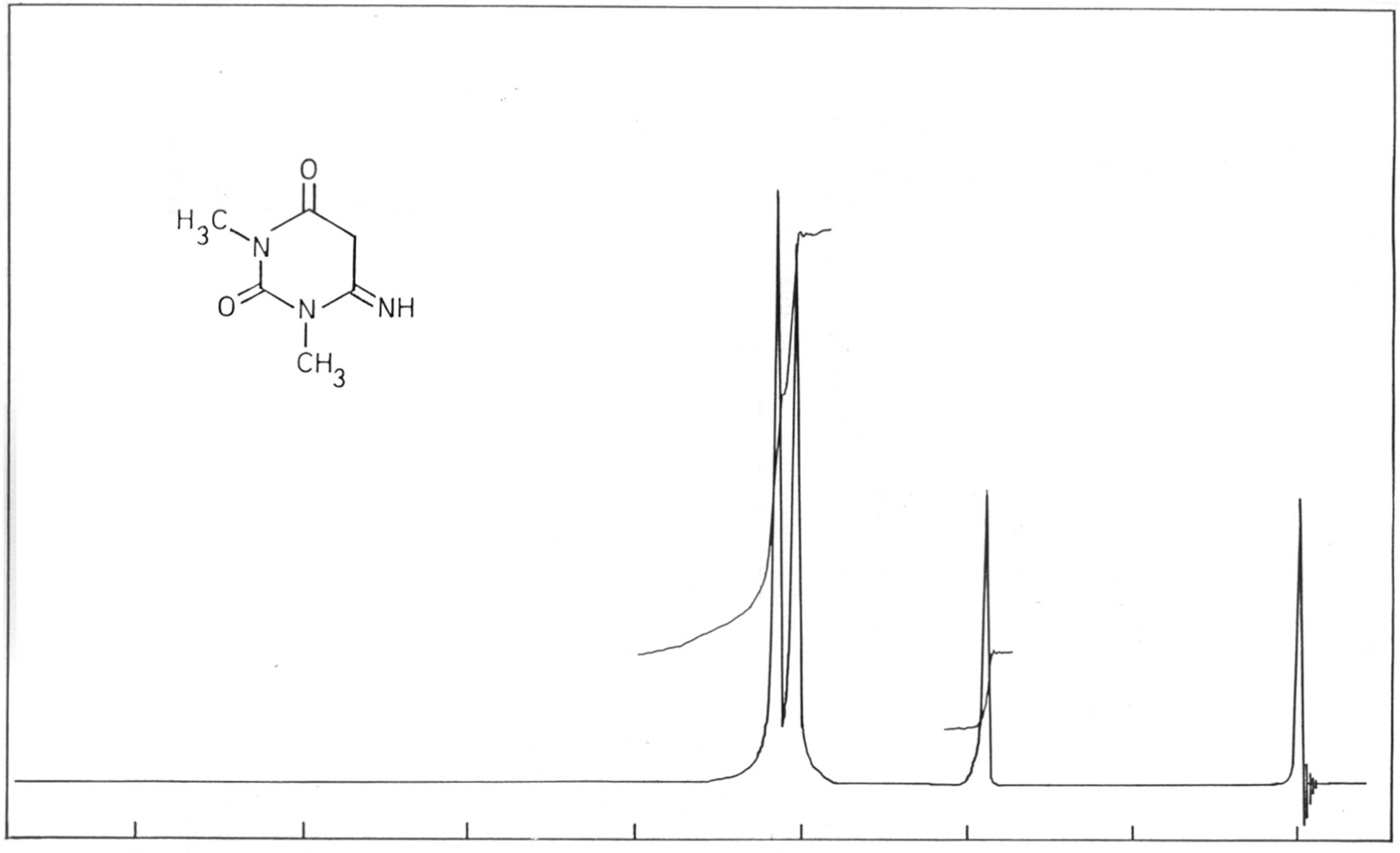


FIG: 1·1 NMR SPECTRUM OF 1,3-DIMETHYL-6-IMINO URACIL (31)

A mild exothermic reaction occurred during the first stages of heating, during which the reaction vessel was temporarily removed from the heating bath. The solvent was removed under reduced pressure, the external temperature being held at 80°C. Water (250 ml) was added. The resulting mixture was ring closed by adding water (75 ml), stirring and cooling at 10°C and then rapidly running in a solution of 75% (w/v) sodium hydroxide to a permanent alkaline reaction to phenolphthlein., A vigorous reaction took place, the temperature raising to 60-70°C and oil separated which solidified on cooling. The crystals were filtered off, washed with water and twice recrystallized from 20% aqueous ethanol. This product, the monohydrate of expected uracil, was dehydrated by heating at 80°C under vacuum for 24 hrs. to give 32g (82%) of (31), m.p. 302-304°C (lit.[19] m.p. 305-307°C).

^{1}H NMR (CF_3-COOH): (Fig.1.1), 1.8 (s, 2H, $C\underline{H}_2$), 3.01 (s, 3H, HN=C-N-$C\underline{H}_3$), 3.17(s, 3H, CO-N-CO)
$C\underline{H}_3$

Demethylation of 1,3,5-Trimethyl-1,3,5-triazine 2,4,6 (1H,3H,5H)-trione (MIC-Trimer) (27)

Sodium metal (0.086g; 0.0038 mol) was dissolved in anhydrous methanol (5 ml). Thiophenol (0.7g; 0.0063 mol) was added to the above sodium methoxide solution, stirred for 30 minutes under nitrogen atmosphere. Methanol was distilled off under reduced pressure to furnish dry sodium thiophenolate.

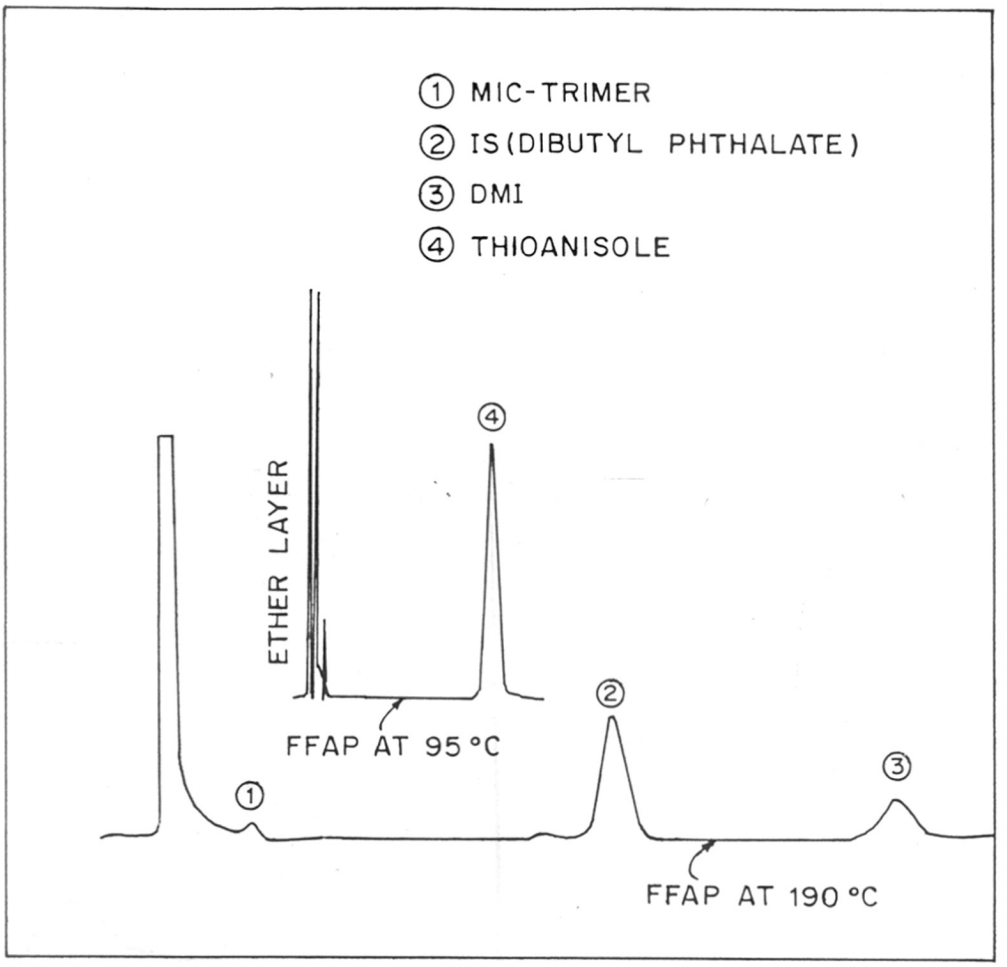


FIG: 1·2 GLC OF REACTION MIXTURE FROM MIC-TRIMER (27)

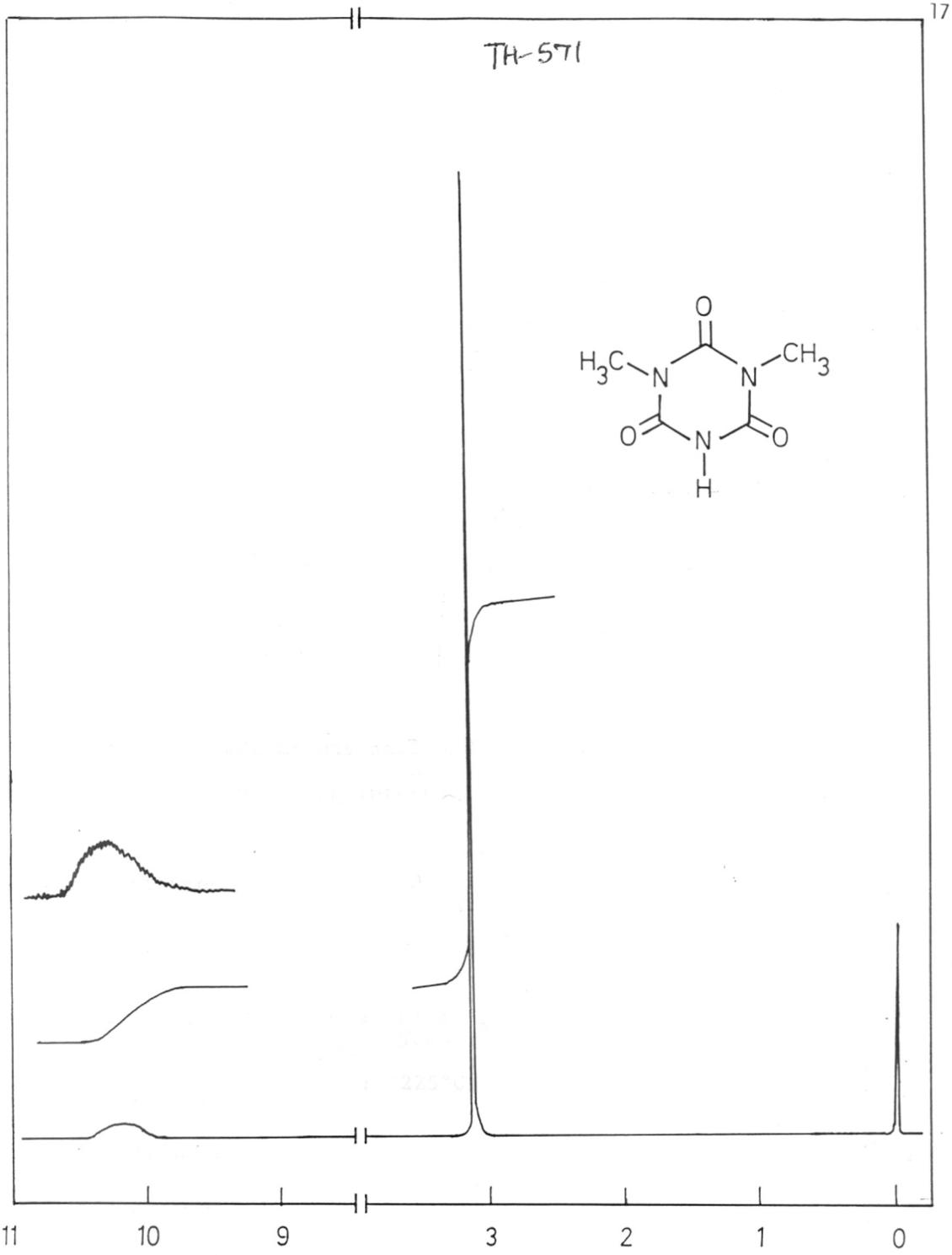


FIG: 1·3 NMR OF 1,3-DIMETHYL-1,3,5-TRIAZINE-2,4,6(1H,3H,5H)-TRIONE (29)

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GUM

This was added to MIC-Trimer (27) (0.65g; 0.0038 mol) taken in a stainless steel reactor. Nitrogen gas was bubbled through the reactor to replace air. The closed reactor was heated in a temperature controlled vertical muffle furnace at 300°C for 1.5 hr. The reactor was cooled to room temperature and the reaction mixture was dissolved in water (50 ml) and acidified with hydrochloric acid under cooling and immediately filtered. The residue was washed with minimum amount of water and dried at 100°C. The filterate was extracted with ether (50 ml). Ether extract was analysed at low temperature by GLC and the presence of thioanisole (30) was confirmed quantitatively and was found to contain 0.23g (55.8%). The solid obtained was weighed 0.32g (55%) of 1,3-Dimethyl-1,3,5-triazine-2,4,6 (1H,3H,5H) trione (29) m.p. 219-220°C (lit.[17] m.p. 221-222°C) was analysed by GLC at higher temperature (Fig.1.2) by using internal standard.

GLC Conditions -

Instrument	:	Hewlett Packard 5730A equipped with 3390A Integrator
Column	:	FFAP (3%) 6 ft. x 2mm I.D. Temperature - 95°C and 190°C
Detector	:	Flame ionisation detector Temperature - 250°C
Injection port temperature	:	225°C
Carrier gas flow	:	Nitrogen (35 ml/min)

^{1}H NMR [$(CD_3)_2CO$] (Fig.1.3), 3.1 (s, 6H, 2 N-C$\underline{H}_3$), 10.16 (s, 1H, N-$\underline{H}$)

Demethylation of 1,3-dimethyl-6-imino uracil ($\underline{31}$)

Sodium metal (0.25g; 0.01 mol) was dissolved in a solution of anhydrous methanol (5 ml). Thiophenol (1.1g; 0.01 mol) was added to the above mixture, stirred for 30 minutes under nitrogen atmosphere. Methanol was distilled off under reduced pressure to produce dry sodium thiophenolate. This was added to 1,3-dimethyl-6-imino uracil ($\underline{31}$) (1.5g; 0.01 mol) taken in a stainless steel reactor. Nitrogen gas was bubbled through the reactor to replace air. The closed reactor was heated in a temperature controlled vertical muffle furnace at 280-290°C for 1.5 hr. The reactor was cooled to room temperature, water (10 ml) was added to the reaction mixture. The solution was extracted with chloroform (60 ml). The aqueous layer was acidified with hydrochloric acid (2 ml) upto pH 5. The solution was cooled in a ice-salt mixture. Solid separated was filtered which weighed 0.23g (15%) of ($\underline{32}$), m.p. 305-307°C (lit.[19] m.p. 306-307°C). The chloroform solution was concentrated, dissolved in ether and was estimated by GLC for thioanisole ($\underline{30}$) and was found to contain 0.18g (13.2%) of ($\underline{30}$).

^{1}H NMR (CF_3-COOH) :(Fig.1.4), 1.8 (s, 2H, C$\underline{H}_2$), 3.01 (s, 3H, HN=C-N-C$\underline{H}_3$).

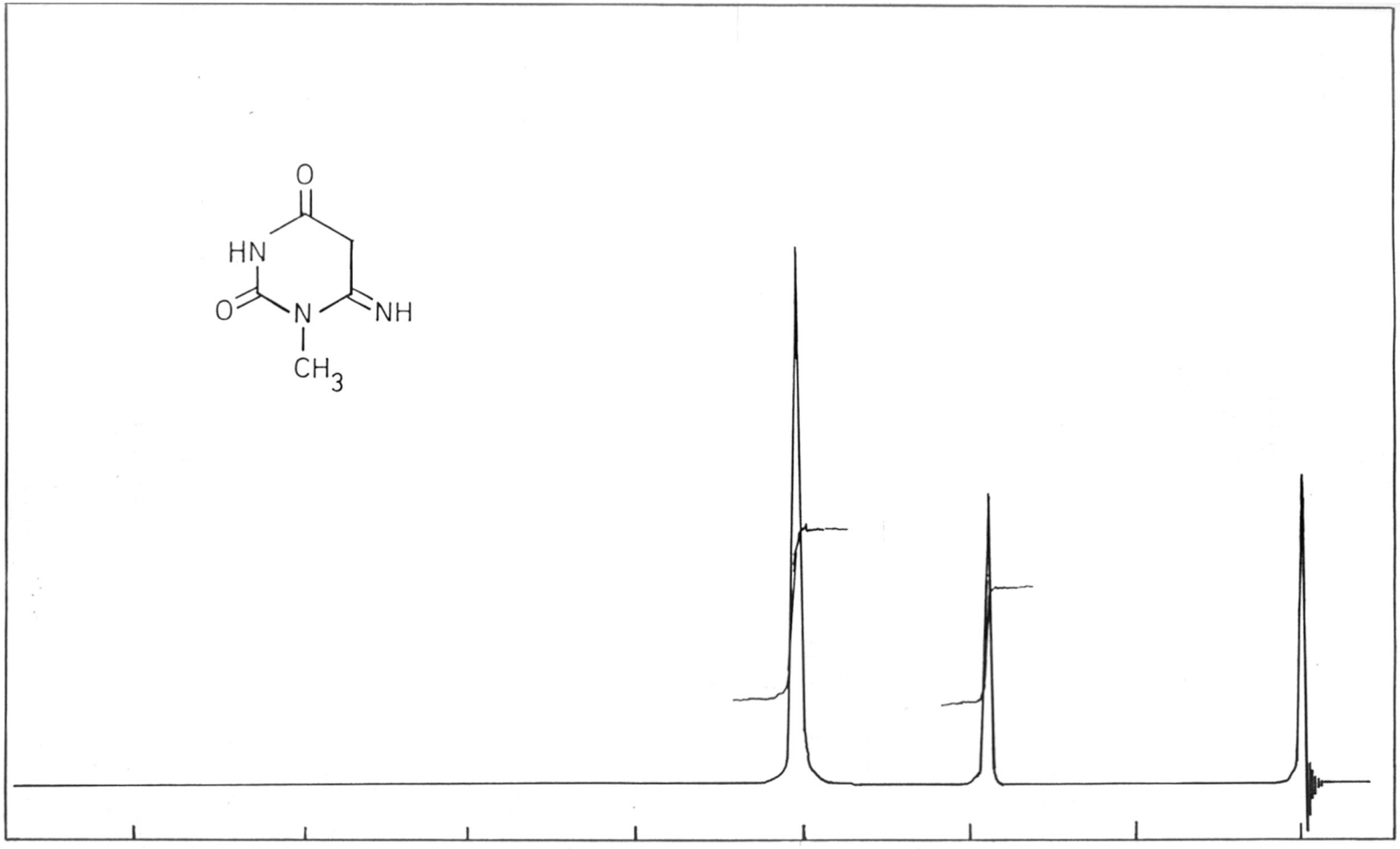


FIG: 1·4 NMR OF 1-METHYL-6-IMINO URACIL (32)

Demethylation of caffeine (1,3,7-Trimethyl xanthine) (16)

Sodium metal (0.23g; 0.010 mol) was dissolved in a solution of anhydrous methanol (5 ml). Thiophenol (0.97g; 0.0088 mol) was added to above sodium methoxide solution. Methanol was distilled off under reduced pressure to produce dry sodium thiophenolate. This was added to 1,3,7-trimethyl xanthine (16) (1.94g; 0.01 mol) taken in a stainless steel reactor. Nitrogen gas was bubbled through the reactor to replace air. The closed reactor was heated in a temperature controlled vertical muffle furnace at 250°C for 1.5 hr. The reactor was cooled to room temperature, the reaction mixture was acidified slightly with dilute hydrochloric acid, filtered. To the filterate, aqueous methanol (10 ml) was added to get a clear solution. The HPLC data showed 1,3-dimethyl xanthine (19), 0.72g (37%), 3,7-dimethyl xanthine (21), 0.408g (21%) and thioanisole (30), 0.582g (60%). (Fig.1.5).

Demethylation of Theophylline (1,3-dimethyl xanthine) (19)

Sodium metal (0.27g; 0.01 mol) was dissolved in anhydrous methanol (5 ml). Thiophenol (1.44g; 0.013 mol) was added to the above sodium methoxide solution. Methanol was distilled off under reduced pressure to produce dry sodium thiophenolate. This was added to 1,3-dimethyl xanthine (19) (1.24g; 0.0068 mol) taken in a stainless steel reactor. Nitrogen gas was bubbled through the reactor to replace air. The closed reactor was heated in a temperature controlled vertical muffle furnace at

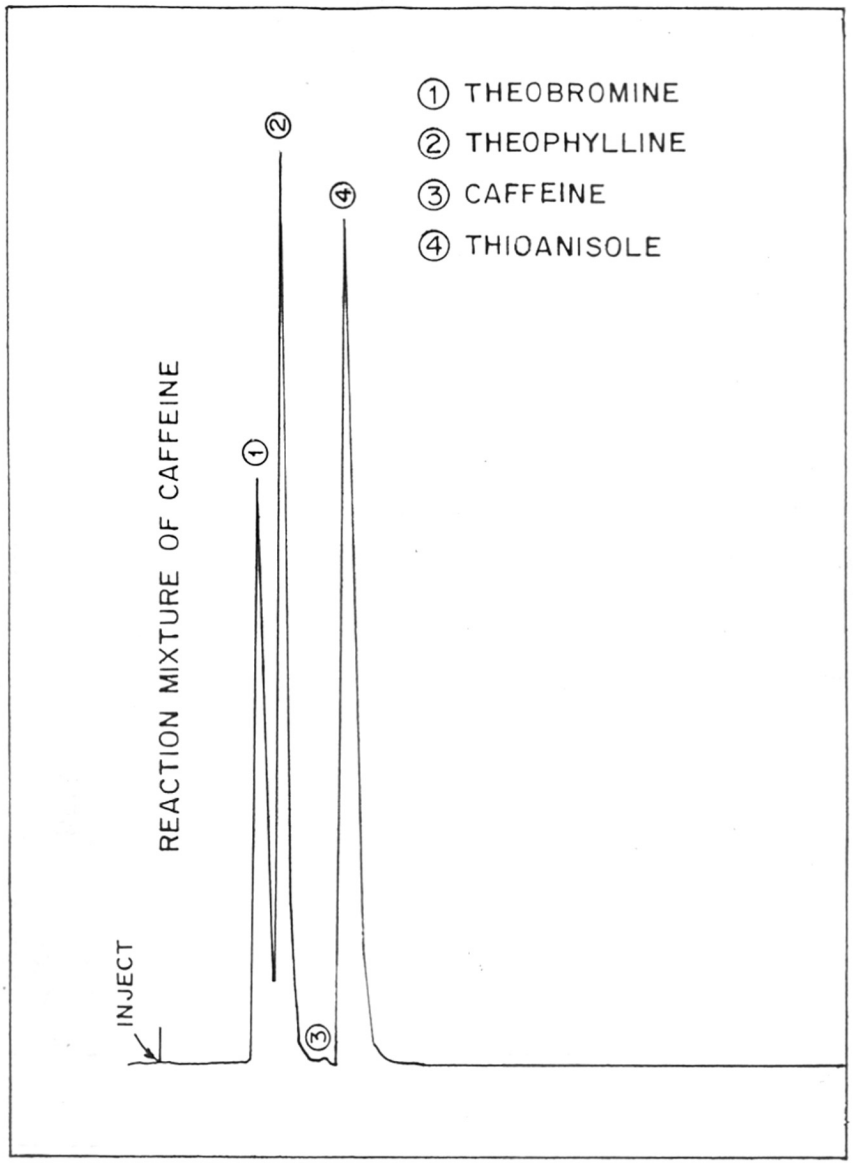


FIG: 1·5 HPLC OF REACTION MIXTURE FROM CAFFEINE (16)

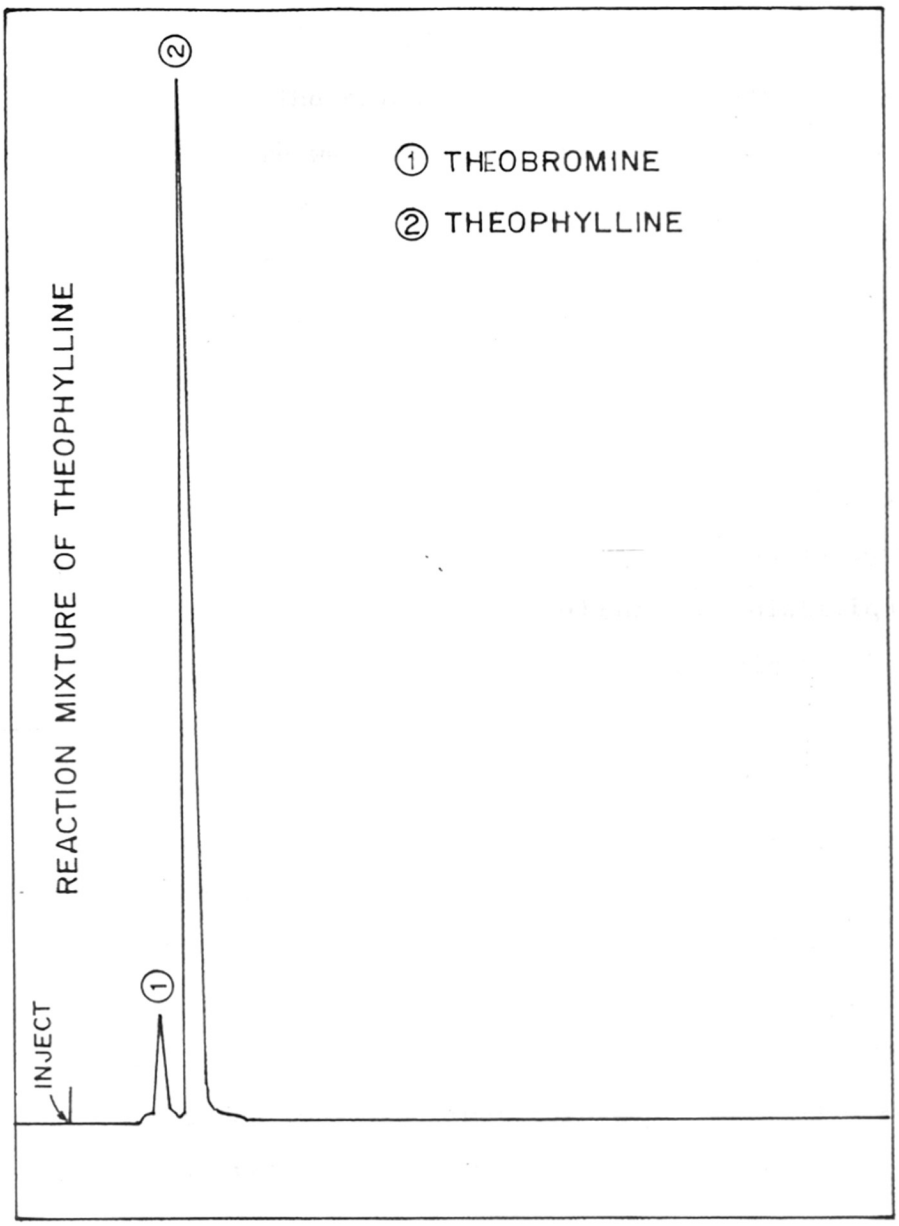


FIG: 1·6 HPLC OF REACTION MIXTURE FROM THEOPHYLLINE (19)

280°C for 1.5 hr. The reactor was cooled to room temperature. The reaction mixture was acidified with dilute hydrochloric acid and filtered. To the filterate aqueous methanol (10 ml) was added to get homogenous solution. It was analysed by HPLC and was found to contain 3,7-dimethyl xanthine (21) 0.127g (10.2%). (Fig.1.6).

Demethylation of Theobromine (3,7-dimethyl xanthine (21)

Sodium metal (0.23g; 0.010 mol) was dissolved in anhydrous methanol (5 ml). Thiophenol (1.1g; 0.01 mol) was added to the above sodium methoxide solution. Methanol was distilled off under reduced pressure to produce dry sodium thiophenolate. This was added to 3,7-dimethyl xanthine (21) (0.920g; 0.005 mol) taken in a stainless steel reactor. Nitrogen gas was bubbled through the reactor to replace air. The closed reactor was heated in a temperature controlled vertical muffle furnace at 280°C for 1.5 hr. The reactor was cooled to room temperature. The reaction mixture was slightly acidified with dilute hydrochloric acid and filtered. To the filterate, aqueous methanol (10 ml) was added to get a clear solution. HPLC data showed 3-methyl xanthine (38) 0.5g (58.9%), thioanisole (30), 0.308g (49%). (Fig.1.7).

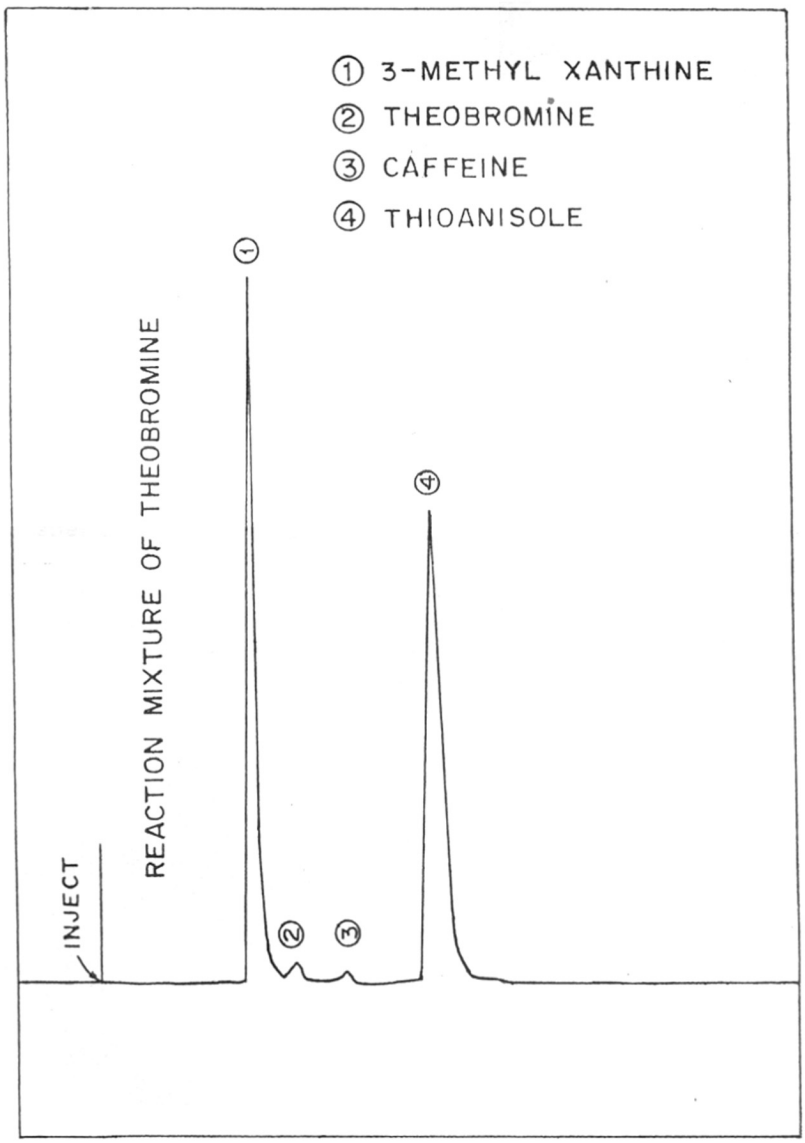


FIG: 1·7 HPLC OF REACTION MIXTURE FROM THEOBROMINE (21)

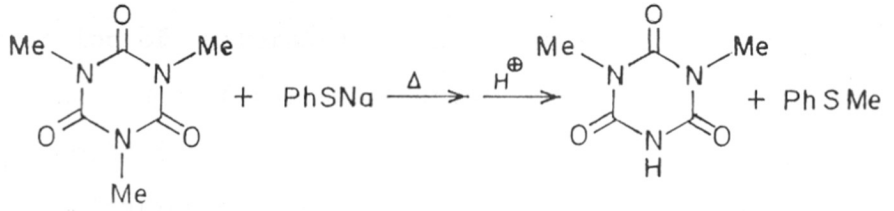
HPLC conditions

Instrument	:	Waters Associates equipped with Data module Integrator
Mobile phase	:	Methanol:Water (40:60) + Acetic acid (0.1 ml) pH 3.2
Column	:	μ-bondapack C-18 cartridge (10 cm x 8mm I.D.)
Detector	:	UV λ-254 0.05 AUFS
Flow	:	0.8 ml/min.
Chart speed	:	1 cm/min.

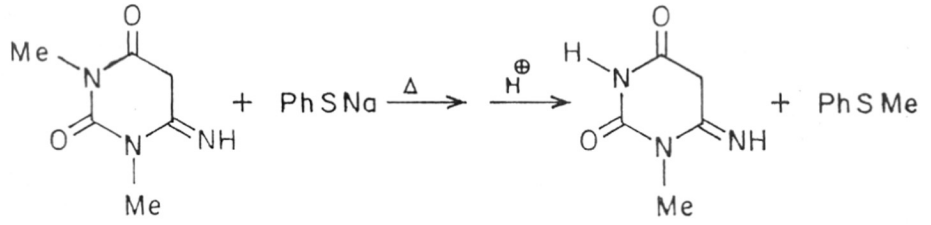
Results and Discussion

Demethylation of N-methyls in cyclic amides by sodium thiophenolate has not been studied earlier. We have described in this chapter a simple one step method of demethylation of N-methylisocyanurates, N-methyluracils and N-methylxanthines derivatives by sodium thiophenolate.

A mixture of 1,3,5-Trimethyl-1,3,5-triazine-2,4,6 (1H, 3H,5H)-trione[16] (27) and sodium thiophenolate (28) under nitrogen atmosphere when heated in a closed reactor at 300°C for 1.5 hr. gave mainly two products. 1,3-dimethyl-1,3,5-triazine-2,4,6 (1H,3H,5H)-trione (29) m.p. 221°C and thioanisole (30) in (55.0%) and (55.8%) yield respectively (Scheme-XIII). (Fig.1.2).



(27) (28) (29) (30)



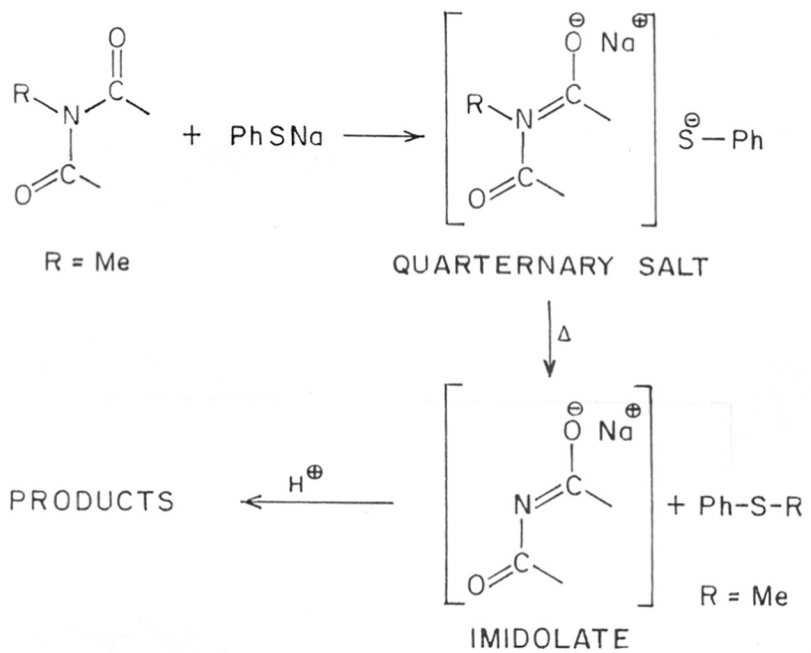
(31) (28) (32) (30)

SCHEME – XIII

A mixture of 1,3-dimethyl-6-iminouracil[19] (30) and sodium thiophenolate (28) when heated in a stainless steel reactor at 280-290°C under nitrogen atmosphere furnished 1-methyl-6-iminouracil (32) m.p. 306-307°C, (Fig.1.4) and thioanisole (30) in about (15%) and (13.2%) yield respectively (Scheme-XIII). Demethylation reaction did not take place when above reactions were carried out in solvents like dimethylformamide, dimethylsulfoxide and xylene mixture under refluxing conditions. Heating triazine trione derivative (27) alone in stainless steel reactor at 300°C gave demethylated product (29) in only (3%) yield. The 1,3-dimethyl-6-iminouracil (31) was unchanged when heated alone at 290°C, indicating sodium thiophenolate was necessary for demethylation.

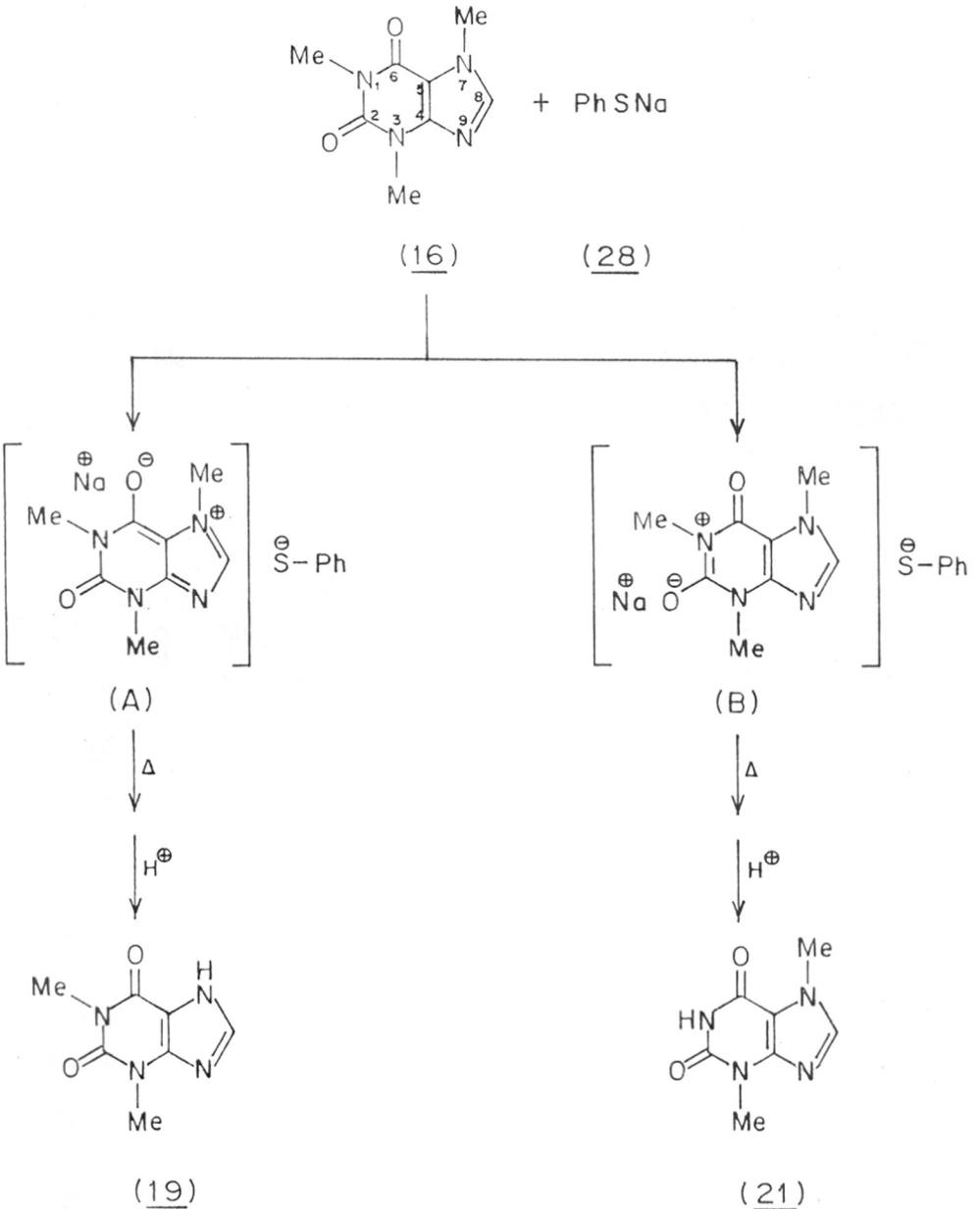
A plausible mechanism of the reaction appears to be formation of quaternary ammonium ionic intermediates at the melting range of the substrates. Na^+ from sodium thiophenolate (28) could form an ionic bond with carbonyl oxygen resulting in quaternization of nitrogen atom of the substrate. The quaternary ammonium thiophenolate salts thus formed could decompose into sodium imidolate and thioanisole (30) at higher temperature as shown in the general mechanism given below. Acidification furnished demethylated products.

General Mechanism



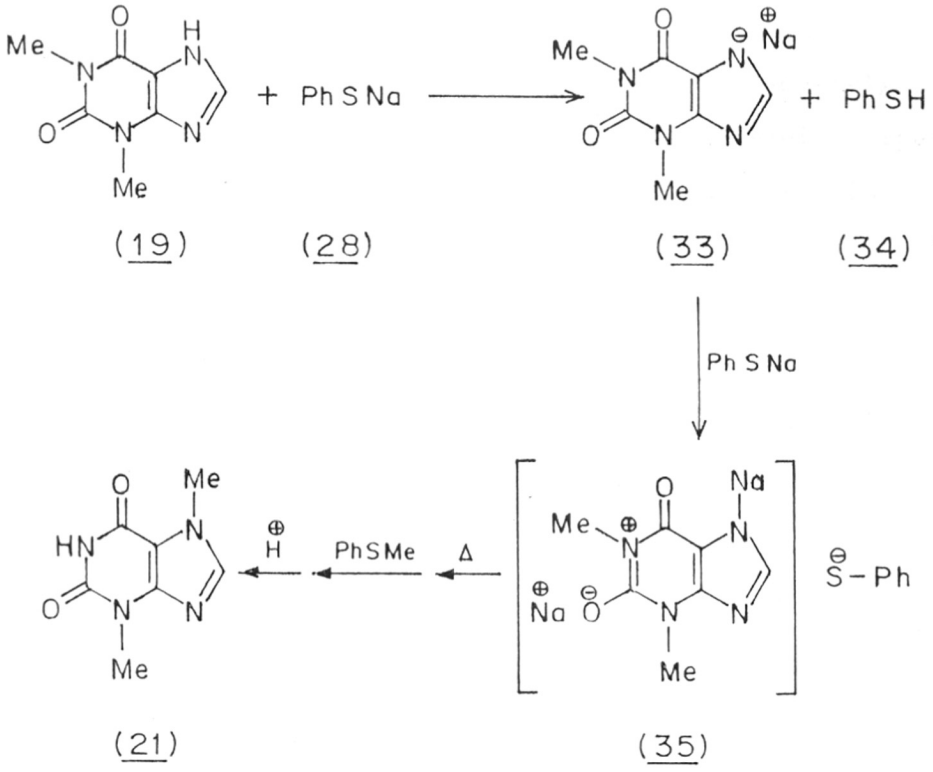
Extension of this type of demethylation reaction to N-methyl-xanthines gave some useful and interesting results. Heating a mixture of caffeine (1,3,7-Trimethylxanthine) (16) and sodium thiophenolate (28) under nitrogen atmosphere at 250°C furnished theophylline (1,3-dimethylxanthine) (19) and theobromine (3,7-dimethylxanthine) (21) in (37%) and (21%) yield respectively. (Fig.1.5),apart from thioanisole (30) in (60%) (Scheme-XIV). As expected, quaternary salt intermediates [A], [B] formation during the reaction could be responsible for giving rise to the demethylated products (19), (21).

N^7 quaternisation with extended conjugation appears to be more favoured when compared to N^1 quaternisation as reflected in the yield of the demethylated products formed.



SCHEME – XIV

Reaction of theophylline (1,3-dimethylxanthine) (19) and sodium thiophenolate (28) in 1:1 molar ratio at 280°C gave only thiophenol (34) and sodium salt of theophylline (33). Repeating the reaction with two molar equivalents of sodium thiophenolate (28) produced theobromine (3,7-dimethylxanthine) (21) in only (10.2%) yield (Scheme-XV), (Fig.1.6).

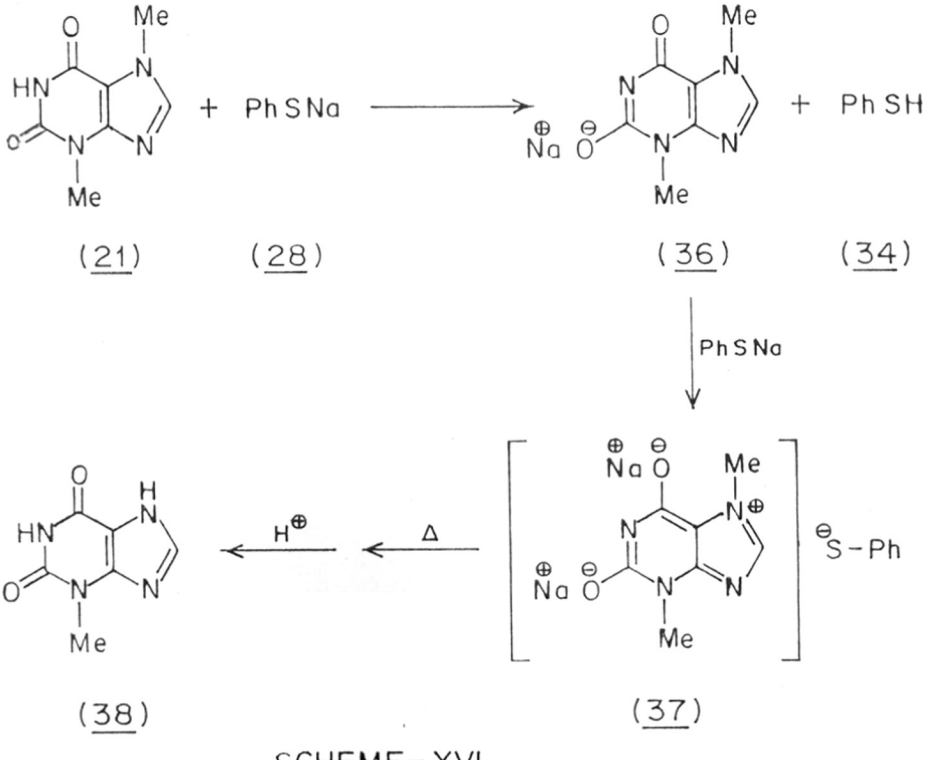


SCHEME - XV

Presumably the demethylated product (38) got methylated by thioanisole (30) at more basic N^7 position to give theobromine (3,7-dimethylxanthine) (21). This was confirmed by reacting

anhydrous sodio theophylline (33) and thioanisole (30) at 280°C in a stainless steel reactor which gave N^7 methylated product caffeine (1,3,7-trimethylxanthine) (16) and N^1 demethylated product (3-methylxanthine) (38) as expected, however, in poor yields (< 15%).

A 1:2 molar ratio mixture of theobromine (3,7-dimethylxanthine) (21) and sodium thiophenolate (28) respectively when heated at 280°C under nitrogen atmosphere gave 3-methylxanthine (38) and thioanisole (30) in (58.9%) and (49%) yield respectively (Scheme-XVI), (Fig.1.7). The reaction mixture also contained trace amount of caffeine (1,3,7-trimethylxanthine) (16) (< 1%), which must have formed by progressive methylation of 3-methylxanthine (38) by thioanisole (30).



(21) (28) (36) (34)

(38) (37)

SCHEME-XVI

Demethylation of N^3 methyls in caffeine (16), theophylline (19) and theobromine (21) was not observed in the above mentioned reactions. Apparently, positive charge cannot be stabilized at N^3 position as its electron pair is in conjugation with double bond on one side and carbonyl on the other side.

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CHAPTER - II

INTRODUCTION

Recent investigations have revealed that alkyl substituted ureas and other related products are of immense importance from physiological and biological point of view. It is imperative to have qualitative as well as quantitative estimation of these compounds. Although alkyl ureas have been reported long back, their uses and estimation methods have been reported only recently.

Alkyl substituted ureas may be classified as follows:

i) Those in which the substituent is attached to nitrogen (N-alkyl ureas) and

ii) Those in which the substituent is attached to oxygen (O-alkyl ureas).

The N-alkyl ureas are generally crystalline solids. They melt at temperatures lower than urea itself. Some tetra-substituted compounds are oils. The N-alkyl ureas decompose on heating giving polymers of cyanic acids and primary amines. However, more highly substituted ureas are stable and may be distilled unchanged. They are monoacid bases and except for tetrasubstituted compounds, give crystalline salts. All are hydrolysed by alkali to carbondioxide and amine.

Alkyl ureas are very important from biochemical, medicinal and polymer chemistry point of view. In recent literature, there are several references quoting the uses of alkyl ureas in these fields. Some of the uses are given below:

I) Polymer chemistry: Takagi[1] et al have reported 1,1-dimethyl urea (3) as crosslinking agent in epoxy resin adhesives. Polyepoxides were mixed with (3) as hardners to give compositions at relatively low temperatures. Sato[2] et al employed 1,3-dimethyl urea (2) as a catalyst for condensation of phenol with formaldehyde. A German Patent[3] reports the use of alkyl substituted urea for dyeing of polyester fibres.

1,1,3,3-Tetramethyl urea (5) is used in the removal of polyvinal chloride deposits from polymer reactors. In Belgium Patent[4], it has been reported that deposits of polyvinal chloride on the interior walls of bulk or suspension polymerisation reactors were removed rapidly by treating the reactors with hot alkyl substituted amide solvents. It is also used as aprotic dipolar solvent in the manufacture of Bis phenol A-decachlorodiphenyl co-polymer. 1,3-dimethyl 1,3,5-triazine 2,4,6 (1H,3H,5H)-trione i.e. Dimethyl isocyanuric acid DMI (8) is used as fire proofing agent for plastics[5].

II) Medicinal chemistry: Alkyl ureas are used for the solubalization of pharmaceutical products. The effect of urea and urea derivatives on water solubility of certain drugs has been studied by Rohedewald[6] and others. The effect of urea, methyl urea, ethyl urea and thiourea on water solubility of aminophenozone, caffeine, sulfanilamide and N-acetyl sulfanilamide were studied. In all the cases, thiourea increased the solubility of drugs more than urea did. For all the drugs except caffeine, the increase in water solubility produced by urea derivative increased with increase in the degree of N-methylation. In recent years, number of reports have been appeared in the literature which have been concerned with the presence of methyl urea in blood fluid. Physiological abnormalities such as hepatic diseases or renal failures may affect blood urea concentrations[7,8]. Schuster[9] et al have reported that monomethyl urea (1) has antiphytoviral activity. A series of substituted ureas showed antiphytoviral activity when used in combination with plant hormones, growth regulators or antiviral heterocyclic compounds, a synergestic activity was observed.

General uses: Darlack[10] et al have reported that 1,3-dimethyl urea (2) is used in photographic emulsion for removal of aldehyde during colour processing. Lawton[11] has reported that (2) is also used as a stabilizer for photothermographic copying material.

Present Work:

From the literature survey, it was found that complete estimation of alkyl substituted ureas and other related products has not been reported. So we have taken up this work.

In the Bhopal accident involving methyl isocyanate (MIC), numerous products were formed. An examination of samples of residues showed presence of different chemical entities such as 1,1,3-Trimethylurea (4), MIC-Trimer (9), 1,3-Dimethylurea (2), Dihydro-1,3,5-trimethyl-1,3,5-triazine-2,4 (1H,3H)-dione (7), 1,3,5-Trimethylbiuret (6) and 1,3-Dimethyl-1,3,5-triazine-2,4,6 (1H,3H,5H)-trione (8) etc. In order to determine the conditions of formation of these chemical entities found in the residues, a large number of experiments were carried out. Analytical study, GLC in particular, was carried out in order to estimate the compounds qualitatively as well as quantitatively. Flame ionisation detector was used throughout the course of investigation. Element specific detectors were not employed. A number of stationary phases having wide differences in their polarity were used for the first time to separate these compounds from a mixture. Retention time behaviour of these compounds is discussed under the light of "Solute-Solvent" interaction.

D'Silva[12] et al reported Gas Chromatographic analysis of alkyl ureas and other related products. However, GLC study

was carried out on 25m x 0.32mm. I.D., 1.0 μm film thickness, OV-1701 fused silica capillary column.

Taking into consideration the above experimental work, simple Gas Liquid Chromatographic method was developed wherein usual open tubular columns of 6 ft. x 2mm I.D. have been employed. Efforts were also made to reduce the length of the column. The synthesis and quantitative estimation of alkyl ureas and related products has been discussed in the following part of the thesis.

Introduction to Gas Chromatography

Chromatography is a physical separation of two or more compounds, based on their differential distribution between two phases; one of which is stationary and the other fluid. In case of gas chromatography, the fluid is a gas.

Gas chromatography is one of the most widely employed analytical technique today. It is used in all the branches of chemical science and in many industries. The wide acceptance and success of this technique have been due to features, such as rapidity of the analysis, high efficiency and use of very small amount of sample. Presently, gas chromatography is used in finding the concentration of impurities in parts per million (ppm) and parts per billion (ppb) range. Thousands of publications connected with theory and applications were published since the beginning of this technique.

Historical

Chromatography had its beginning about 1850 in the separation of dyes by F.F. Runge[13]. This process utilized filter paper and a solvent for the separation of various dye colours. Runge made use of the dye-paper affinity and the differences in molecular weight to achieve a separation. The technique, still in wide use today, is known as paper chromatography.

In 1906, Tswett[14] described the use of glass columns packed with a suitable absorbant for separation of coloured plant pigments. In 1941, Martin and Synge[15] first suggested the possibility of using gas as the mobile phase in a chromatographic apparatus; the suggestion was a theoretical one and was not put into practice. In the development of gas chromatography, the first apparatus was described by Martin and James[16] in 1952. It employed an automatic burette for detection and determination of acids and bases. The first working gas chromatograph was suitable only for these two functional groups.

In about 1955, the first commercial instrument became available.

The instrument

The gas chromatograph employs a carrier gas (mobile phase) under pressure to move a vapour sample from the injection port through a stationary phase (column) where separation takes place, to a detector where the sample is converted to an electrical signal which is then measured, usually by a recorder/integrator.

Equipment of Gas Chromatograph

1. Carrier gas system
2. Injection port
3. Columns
4. Detector

1. Carrier gas

The most common carrier gases are hydrogen, nitrogen and argon. The most important consideration in selection of carrier gas is the nature of the detector being used. An electron capture detector for instance, requires argon-methane mixture. A thermal conductivity detector works best with helium or hydrogen. Selection of nitrogen for use in a thermal conductivity detector would generally not be good as the sensitivity of the detector is much reduced. The carrier gas selected must be inert, dry and pure. The use of impure carrier gas will produce some problems such as baseline drift and noise. Commercial grade gases should be dried by means of molecular sieve trap between the cylinder and chromatograph[17].

2. Injection port

The injection port provides a means of introducing the sample to the flowing carrier gas stream and subsequently to the column.

A heated injection port vapourises non-gaseous samples; the temperature, therefore, must be variable and controlled. The port is also designed to permit use of various sampling device, e.g. syringe, solid sampler, pyrolyzer, etc. The most frequently used technique for sample introduction is by means of a microliter syringe through a self sealing rubber septum.

3. Columns

The column is the most important single part of the gas chromatograph. It is composed of three elements:

i) The container for the packing, usually metal or glass tubing

ii) The solid support

iii) The stationary phase

The stationary phase should be the only active portion of the column; separation takes place between carrier gas and this material. The column is generally called as "heart" of the gas chromatograph. So we shall discuss in detail about the column technology, particularly the stationary phase.

The choice of proper stationary phase for an effective separation is of great importance. In gas chromatography, the stationary phase may be solid adsorbant, porous polymer or liquid phase. Adsorbants are generally used for gases. Porous polymers are used for very difficult separations. The liquid phase-solid support systems are more difficult to prepare and suffer from column bleed and other problems, but they offer enormous versatality in separating ability.

The principle factors in selecting appropriate liquid phase are summarised below:

a) Low vapour pressure at operating temperature

b) Chemical stability and low viscocity at operating temperature

c) Reasonable solubility in some common solvents.

d) Selectivity for the components to be separated.

According to Littlewood[18], stationary phases can be classified into four groups:

Group-I: Non-polar stationary phase

Non-polar materials (Squalane, Silicones, etc.) separate essentially by boiling point. The hydrocarbons are much more soluble in these stationary phases than any other polar solutes with a similar boiling point. As non-polar stationary phases do not interact specifically with the solutes to be separated, they can be used as reference phases in GLC.

Liquid paraffin was used as a stationary phase to separate C_3-C_4 hydrocarbon[19]. Squalane is used to separate C_5-C_8 hydrocarbons[20,21] and some mercaptans[22]. n-hexadecane, n-tetracosane etc. are the stationary phases among saturated hydrocarbons.

Apiezon greases are obtained by heating lubricating oil to a high temperature. Among different apiezon greases, Apiezon-L is the most commonly used stationary phase for the analysis of methyl esters of fatty acids[23].

Non-polar boiling point columns are extremely useful and generally the first thing to try when dealing with totally unknown sample.

Group-II: Medium polar stationary phase

These phases are universal in gas chromatography because

they readily dissolve the polar solutes as well as those that are non-polar.

Phenyl silicones

These phases can be obtained by substituting phenyl group into methyl silicone. Substitution of phenyl group increases the solubility parameter and lubricating property. Different phenyl silicones can be prepared by changing proportion of groups such as phenyl, vinyl, cyanopropyl, trifluoropropyl, etc. Phenyl silicones have been used for the analysis of pesticides[24] and higher aromatic hydrocarbons[25].

Group-III: Polar stationary phase

Many compounds contain atoms other than carbon and hydrogen such as oxygen in alcohols. Other common "hetero" atoms are nitrogen, chlorine, sulfur and phosphorous. These atoms differ from carbon in their affinity for bonding electrons, with the result that the electron distribution in molecules of which they are a part is not quite symmetric. This means that one part of the molecule appears to be slightly positively charged while some other part has slightly negative character, meaning that the molecule is polar. Such polar molecules will be retained on the liquid phases which are also polar, and this provides a second mechanism for separation in addition to simple boiling point. These phases are mainly used for the analysis of polar solutes.

Examples

C'wax 20M is widely used polar stationary phase for the analysis of alcohols, ethers, esters, etc. Other stationary phases most used in GLC are polymeric compounds of ethylene oxide. The principle factors determining the retention characteristics of these phases is the concentration of the hydroxyl end group. Some of the polymeric stationary phases are Poly (ethylene glycol), Poly (vinyl formyl propionitrile) etc.

The linear polyester stationary phases can be easily synthesised from number of dibasic acids and glycols. They are stable upto 200-250°C. Analysis of fatty acid esters on Apiezon-L or Silicone grease was not satisfactory. Orr and Callen[26] used polyester phases Reoplex 400 and found to give some excellent separation. Some polyester stationary phases are -

Poly (ethylene glycol succinate)[26]

Poly (propylene glycol adipate)[27]

Poly (ethylene glycol phthlate)

Group-IV: Specific stationary phase

In this group, as the name indicates, stationary phases are included with particular class of solute. Bradford et al reported high selectivity of silver nitrate-ethylene glycol as a stationary phase for the separation of butanes[28].

Recently, Wasik and Tsang[29] used aqueous solutions of silver nitrate as a stationary phase. Separation of O,m- and p-xylenes is obtained on a very selective stationary phase - Bentone-34.

Stationary phases of liquid crystals are termed as specific phases. These phases separate molecules according to their size and shape.

There is no effective method for selecting the stationary phase for a particular mixture. When more than three or four compounds are to be separated and particularly, if a variety of chemical species is involved, one should refer Kovats retention index.

The basic idea of retention index is to treat all the compounds regardless of their chemical nature, as though they were members of a single series. Some standard is also necessary if the system is to be applied to more than one liquid phase. Generally, normal hydrocarbons are used as standards because they are readily available, cover a wide range of molecular weight and boiling point and are separated on all columns. A semilog plot of corrected retention times against carbon number is usually used. Unknown sample is analysed under the same conditions and retention data obtained is used for further diagnosis.

The Rohrschneider[30] and McReynolds constants are two closely related systems for classifying liquid phase in terms of their separating power. This is done by using a set of reference compounds to determine how much longer the reference compound is retained by the liquid phase being tested than by some "standard" liquid phase.

4. Detector

The chromatographic detector is a device which indicates and measures the amount of separated compounds in the carrier gas. There are numerous types of detectors used in gas chromatography. However, only four types are in common usage viz.

A) Thermal Conductivity Detector (TCD)

B) Flame Ionization Detector (FID)

C) Electron Capture Detector (ECD)

D) Flame Photometric Detector (FPD)

The flame ionization detector was used throughout the course of investigation. So we shall discuss mainly about flame ionization detector, its working principle and limitations as well.

B) Flame Ionization Detector

a. Operating principle

Fig.(2.1) shows typical FID set up. A tiny flame of hydrogen is maintained at a capillary jet made up of quartz, stainless steel or platinum; air or oxygen is introduced

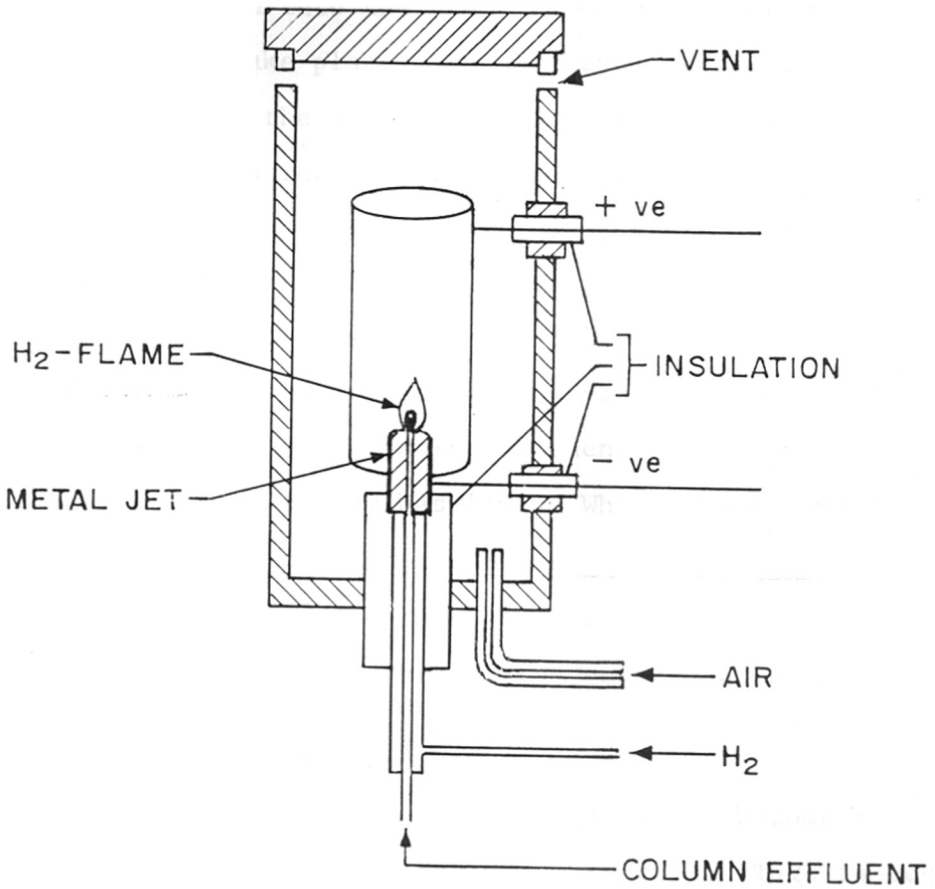


FIG: 2·1 TYPICAL FLAME IONISATION DETECTOR

through a side by inlet for supporting combustion. Column effluents are led into the flame wherein ionization of the components may take place. An electrode system located closely picks up the ionization current which is then amplified and suitably fed into the recorder. When only carrier gas, which is in most cases, nitrogen, argon, helium, passes through the flame there is no or very feeble and constant ionization current flowing across the electrodes; this background current is suppressed by applying opposing "bucking voltage" and thus when sample component is eluting, the recorder traces a steady baseline. When sample component elutes and passes through the flame, its molecules are ionized and resulting ionization current after amplification is fed to a suitable recorder that traces the corresponding curve.

b. Detector sensitivity

The flame ionization detector (FID) has become a most commonly used detector in Gas Chromatograph. This is because it possesses several outstanding features -

i) It responds to virtually all organic compounds with roughly same high sensitivity.

ii) It does not respond to common carrier gas impurities such as water and carbondisulfide.

iii) In the absence of the sample, it has virtually no response. This gives a stable base line.

iv) The response of FID is independent of the detector temperature.

v) The lack of response to air and water makes the FID especially suitable for the analysis of air pollutants or aqueous samples such as alcoholic beverages, biological materials etc. Similarly, the absence of "solvent peak" makes carbondisulfide a convenient solvent for the use with the FID detector.

c. Flow rate Vs. detector response

The FID performance depends on the proper choice of gas flow rate. In general, good sensitivity and stability are obtained with a carrier gas flow of 30 ml/min., hydrogen flow of 30 ml/min. and air flow at 300 ml/min.

d. Linear range

The FID has widest linear range of any detector in common use. Linear range is between 10^6 and 10^7. The combination of high sensitivity and wide linear range makes the FID the choice in the trace analysis.

However, FID has certain limitations. It does not give any response to the following compounds:
Noble gases, oxygen, nitrogen, carbonmonoxide, carbondioxide, water, nitrogen oxides, ammonia, hydrogen sulfide, carbon-disulfide, $SiCl_4$ and SiF_4 etc.

e. FID Response

The response of a detector is the quantity of a signal generated by a given amount of the sample. The response for any compound given by flame ionization detector is governed by many factors such as structure and the elements present in the compound.

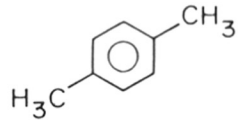
We have to consider flame chemistry of FID detector. Since FID uses a diffusion flame, the mechanism of giving response to the compound begins at the tip of the flame jet. In general, we can assume the following reaction takes place:

$$CH+O \longrightarrow CHO^{+} + e^{-}$$

These charged species are responsible for giving response[31]. During the analysis of the compounds having amino group etc. the magnitude of the response for hydrocarbons, amines and hydroxyl compounds with equally long carbon chains were compared and it was found that the response for hydrocarbon is definitely greater than that for other substances. The same reason holds good for compounds with oxygen atom also. Thus, we can predict effective number of carbon atoms which can undergo above mentioned reaction and hence we can predict at least semiqualitative and semiquantitative picture of the response given by a particular compound.

As an illustrative example, see Table-IA.

TABLE - I A

S.No.	COMPOUND	STRUCTURE	RELATIVE RESPONCE FACTOR
1	PARA XYLENE		1·0
2	BUTANE	$CH_3-CH_2-CH_2-CH_3$	1·09
3	n-BUTANOL	$CH_3-CH_2-CH_2-CH_2OH$	0·66
4	n-BUTYRALDEHYDE	$CH_3-CH_2-CH_2-\overset{O}{\overset{\|\|}{C}}-H$	0·62
5	n-BUTYNIC ACID	$CH_3-CH_2-CH_2-\overset{O}{\overset{\|\|}{C}}-OH$	0·48
6	t-BUTYL AMINE	$CH_3-\overset{CH_3}{\overset{\|}{\underset{CH_3}{\underset{\|}{C}}}}-NH_2$	0·54
7	MYTHYL ETHYL KETONE	$CH_3-\overset{O}{\overset{\|\|}{C}}-C_2H_5$	0·61

From this table, we can easily conclude that compounds 2-7 have the same number of carbon atoms, but there is lot of difference in their FID response. These theoretical aspects will be discussed in more details in the results and discussion part of the present work.

EXPERIMENTAL

Synthesis of alkyl ureas and related products

Chart-I gives the structures, numbers and names of the compounds used in the present investigation. Shortforms for these compounds are also given.

Monomethyl urea (1)

Procedure:- 5.7g of MIC in methylene chloride (50 ml) was treated with ammonia (2g) in (25 ml) of methylene chloride at 0-5°C. Reaction mixture was stirred for 2 hrs. and precipitated monomethyl urea was filtered. Yield - 7.0g, m.p. 101-102°C (lit.[33a] 102°C)

1,3-Dimethyl urea (Symmetrical) (2)

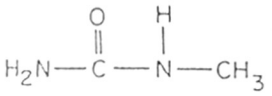
Obtained from Aldrich Chemical Company Inc. USA.

1,1-Dimethyl urea (Asymmetrical)[32] (3)

Procedure:- 13 ml of 40% dimethylamine solution was diluted with 10 ml of water and 10g of nitrourea was added to it with stirring. Temperature rises to 35-40°C. It was then raised to 50-60°C when nitrous oxide (N_2O) coloured brown fumes started to evolve. It was then cooled a little to stop the reaction. It was warmed upto 70°C for 30 minutes, then at 80°C for 5-7 minutes and then finally at 90-100°C for 10 minutes, when evolution of gas ceases. Filter crystallised from 90% ethanol. Yield 3.5, m.p. 182°C (lit.[32] 182-184°C).

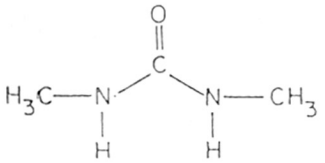
CHART - I

Compound (1)
Mono Methyl Urea



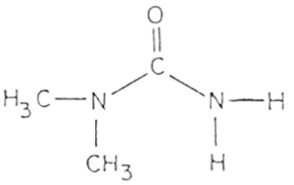
(MMU)

Compound (2)
Dimethyl Urea
(Symmetrical)



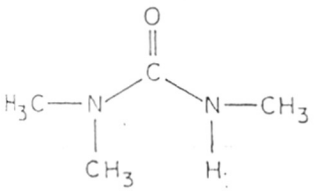
(DMU - S)

Compound (3)
Dimethyl urea
(Asymmetrical)



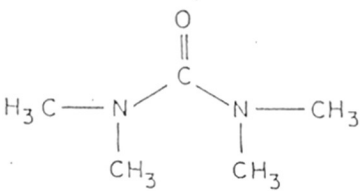
(DMU - A)

Compound (4)
Trimethyl Urea



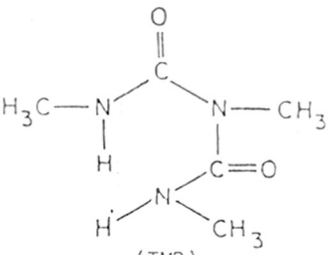
(TMU)

Compound (5)
Tetra methyl Urea



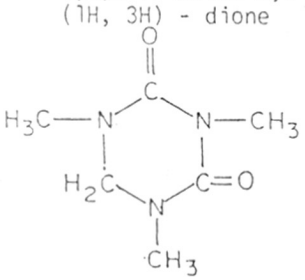
(Tr. MU)

Compound (6)
Trimethyl biuret



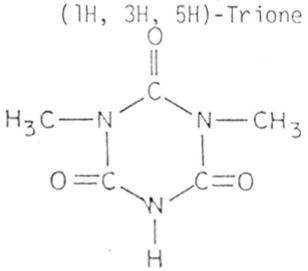
(TMB)

Compound (7)
Dihydro-1,3,5-Trimethyl
1,3,5-Triazine-2,4
(1H, 3H) - dione



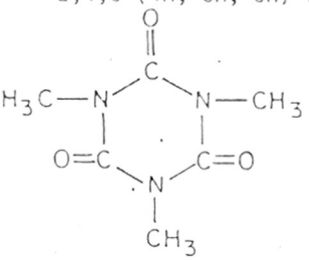
(Dione)

Compound (8)
1,3 Dimethyl-1,3,5
Triazine-2,4,6
(1H, 3H, 5H)-Trione



(DMI)

Compound (9)
1,3,5-Trimethyl -
1,3,5-Triazine-
2,4,6-(1H, 3H, 5H)-Trione



(MIC - Trimer)

1,1,3-Trimethylurea[33b] (4)

Procedure:- To a solution of pet ether (125 ml) and dimethylamine (4.5g), methyl isocyanate (5.7g) was added at 0-5° in 30 minutes. A colourless solid separated immediately. The reaction mixture was stirred for 5 hrs. Afterwards, excess of dimethylamine in pet ether (10ml, 0.8N) was added to the reaction mixture and stirred for 30 minutes. The solution was found to be alkaline (pH 8). The crystalline trimethyl urea (4) was filtered, washed with pet ether and dried under vacuum at room temperature. Yield - 9.5g, m.p. 74°C (lit.[33] 74-75°C).

1,1,3,3-Tetramethyl urea (5)

Obtained from Aldrich Chemical Company Inc. USA.

1,3,5-Trimethyl biuret[34] (6)

Procedure:- A mixture of 1,3-dimethyl urea (2) (3g) and methyl isocyanate (3g) was heated in stainless steel bomb reactor at 100°C for 2 hrs. Afterwards the unreacted methyl isocyanate was evaporated and the residue was recrystallised from hot benzene. Yield - 1.5g, m.p. 122-124°C (lit.[34] 125-126°C).

Dihydro-1,3,5-trimethyl-1,3,5-triazine-2,4 (1H,3H)-dione[35] (7)

Procedure:- To a solution of 1,3,5-Trimethyl biuret (6) (2g) in carbon tetrachloride (5 ml), methylal (2.4g) and concentrated sulfuric acid (6g) was added. The reaction mixture

was stirred at room temperature for 24 hrs. Next day, the solvent was evaporated and the residue was diluted with water (20 ml). The reaction mixture was extracted with chloroform (50 ml). The chloroform layer was dried and distilled. The residue was crystallized from benzene and pet ether (60-80°C) gave colourless crystals. Yield - 1.2g, m.p. 93°C (lit.[35] m.p. 95°C).

1,3-Dimethyl-1,3,5-triazine-2,4,6 (1H,3H,5H)-trione[36] (8)

Procedure:- A mixture of potassium isocyanate (2.0g) and methyl isocyanate (5.7g) in dimethylformamide (100 ml) was allowed to react for 24 hr. at 75°C. The dimethylformamide was removed by distillation over steam bath to yield a solid mass as a residue. It was stirred in water (50 ml) and filtered to remove MIC-Trimer (9). The filtrate was acidified with concentrated hydrochloric acid. The precipitated solid was filtered and was recrystallized from little charcoal and hot toluene to furnish pure colourless crystals of (8). Yield - 2.2g, m.p. 218-220°C (lit.[36] m.p. 221-222°C).

1,3,5-Trimethyl-1,3,5-triazine-2,4,6 (1H,3H,5H)-trione (MIC-Trimer)[37] (9)

Procedure:- To a solution of dichloromethane (100 ml) and stannic chloride (0.5g), methyl isocyanate (22g) was added at 0-5°C in 30 minutes. The reaction mixture was stirred

under ice-cold condition for 5 hrs. The precipitated MIC-Trimer (9) was filtered and was recrystallized from hot benzene. Yield - 17g, m.p. 175-178°C (lit.[37] m.p. 175°C).

Gas Chromatographic conditions

A] Instrumentation

Two instruments were used for gas chromatographic analysis -

I] A Hewlett-Packard Model-Serial No.5730A, equipped with flame ionization detector and 3380A Integrator

II] A Carlo-Erba Model Fracto Vap 2450, equipped with flame ionization detector and 3390A Integrator. Spectra Physics Integrator SP-4100 was also used whenever necessary.

B] GLC operating conditions

Column	:	Various columns were employed See Table-IIA
Detector	:	Flame ionization detector
Carrier gas	:	Nitrogen (35 ml/min)
Column oven temperature	:	Refer Table-IIA
Injection port temperature	:	225°C
Detector temperature	:	250°C
Injection volume	:	2 µl

Table-IIA

S.No.	Name of the Column	Amount of stationary phase (wt %)	Dimension of the column	Oven temp.
1.	OV-101	3%	6ft x 2mm ID	155°C
2.	OV-25	3%	6ft x 2mm ID	155°C
3.	OV-17 (stainless steel)	10%	6ft x ¼" OD	180°C
4.	QF_1	5%	6ft x 2mm ID	180°C
5.	OV-17+OV-210	OV-17 (1.7%) OV-210(2.1%)	6ft x 2mm ID	155°C
6.	OV-225	3%	6ft x 2mm ID	155°C
7.	FFAP	3%	3ft x 2mm ID	190°C
8.	Carbowax 20M	7%	3ft x 4mm ID	190°C

N.B. Chromosorb W-HP (80/100) was used as a supporting material for the preparation of the above columns.

C] Preparation of total representative sample

A total representative sample was prepared by mixing samples drawn from various windows of the tank. The organic compounds were determined by GLC. All the organic compounds could be well resolved on FFAP column (Fig.2.2). Acetone was used as a solvent to prepare the solution.

D] Standard solutions

The standard solution of each compound was prepared by using purified compounds, with a concentration to match the quantity of that compound actually present in the sample of

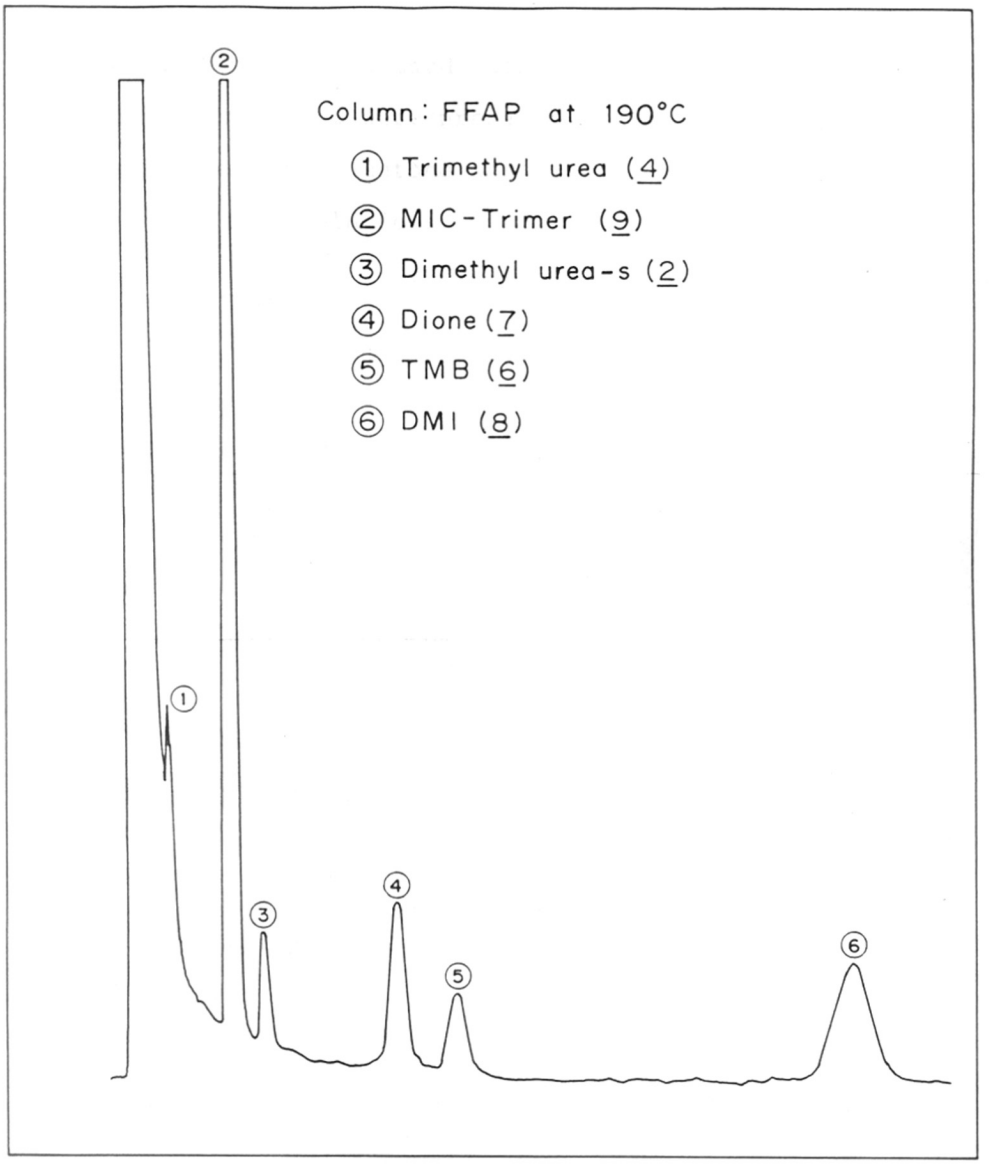


FIG: 2·2 GLC OF TOTAL REPRESENTATIVE SAMPLE

the residues. Standard solutions of various concentrations of each compound were prepared to match the peaks of the sample matrix. Acetone was used as a solvent for preparing the standard solutions.

E] GLC analysis

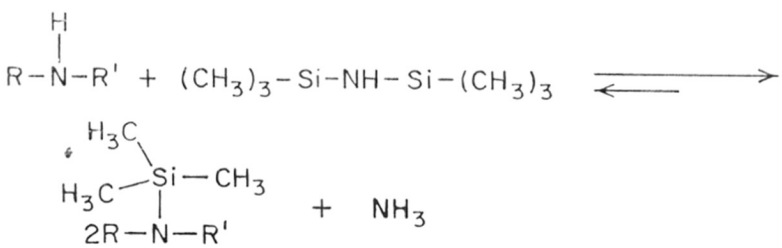
Gas Liquid Chromatographic analysis of total representative sample was carried out on FFAP column under the conditions mentioned in Table-IIA. Results of the analysis of different samples are tabulated in Table-IIIA.

Table-IIIA

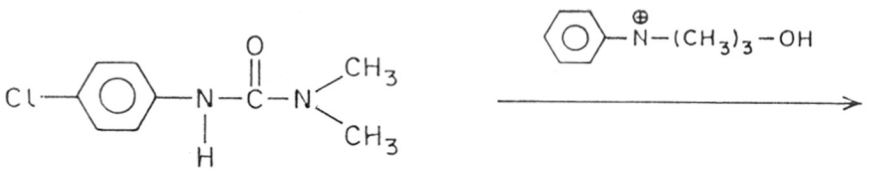
S.No.	Name of the compound	% Composition
1	TMU (4)	2 - 4%
2	DMU (2)	1 - 2%
3	MIC-Trimer (9)	40 - 55%
4	TMB (6)	4 - 8%
5	DIONE (7)	5 - 7%
6	DMI (8)	13 - 20%

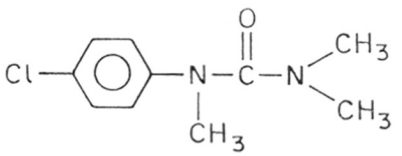
Results and Discussion

Reiser[38] in 1964 was first to apply the Gas Liquid Chromatographic technique for the separation of substituted ureas. He employed thermal conductivity detector for the separation of substituted ureas and found that carbowax 20M was the best stationary phase. While going through the literature survey, we found that plenty of work has been done on the analysis of substituted phenyl ureas, as compared to alkyl ureas and related products. This is obvious because substituted phenyl ureas are used as herbicides on large scale. However, it was pointed out by previous workers, that analysis of substituted phenyl ureas as such was difficult. Several approaches were studied and it was found that silylated derivatives[39] could be analysed without decomposition by GLC using SE-30 and carbowax 20M columns.



Another approach was replacement of active hydrogen atom from substituted phenyl urea to convert it to a fairly volatile and stable methylated derivative by using trimethylanilinium hydroxide[40]. This provides a means for stabilization of phenyl ureas for GLC analysis.





A very useful technique was developed by Kirkland[41] for the analysis of substituted phenyl ureas. In this method, the alkaline hydrolysis of phenyl ureas were carried out and the resulting substituted aniline derivative was extracted by a suitable solvent and was concentrated to the known volume. This extract was used for GLC analysis using TCD or FID detector.

Tsutomu Mommose[42] studied the analysis of substituted ureas using TLC technique. The author has given systematic study of many alkyl ureas as well as aryl ureas. However, he has mentioned that some of the compounds do interfere in the method developed by him.

Analysis of Alkyl Ureas and Related Products

Gas chromatographic analysis of alkyl ureas and other related products faces a special problem. Generally, these compounds are somewhat thermolabile and they have some properties of adsorption on any active surface. For this purpose, one has to be very careful regarding the selection of parameters of gas chromatographic analysis.

i) The supporting material used in GC column should be fairly deactivated so that the sites of adsorption are to a minimum level.

ii) To avoid decomposition, the temperature of the detector and injector port should be kept at minimum level.

iii) The stationary phase which plays a vital role in the resolution must be properly selected.

Monomethyl urea has received some attention for the obvious reason that it has some biological significance. Gas chromatographic technique has been used to study monomethyl urea, however, the investigation was carried out by the technique of derivatization[8]. The author pointed out that trifluoroacetyl derivative of monomethyl urea when kept in ethylacetate solution slowly undergoes process of decomposition.

At this stage, we wish to point out that no derivatization attempts were made for the analysis of alkyl ureas and other related products. All the compounds were analysed as such.

There is always some risk in derivatization reaction, because all the compounds of a typical reaction mixture mixture may not attain same degree of derivatization and, therefore, quantitative estimation may give erraneous results. Some such difficulties are frequently found in the analysis of derivatized amino acids[43].

Now we consider the structural features of the compounds under investigation. We have divided the compounds under two categories:

i) Acyclic compounds

ii) Cyclic compounds

In both the categories, number of active hydrogen atoms, number of combustible carbon atoms and molecular weight has a strong impact on retention times. After studying these structural features, we have employed a range of stationary phases from non-polar (OV-101) to highly polar stationary phase like FFAP and carbowax 20M.

Detector response and structure of the compound

The performance and response given by the flame ionization detector, is a well established topic[44]. In general, one can say that the number of ionizable or combustible carbon atoms governs the detector response.

So, as described in the experimental part, we have analysed all the compounds (see Chart-I) at various concentrations and recorded the response given by a properly tuned flame ionization detector. Initially, we consider the compounds Monomethyl urea (1), Dimethyl urea symmetrical (2), Dimethyl urea asymmetrical (3), Trimethyl urea (4) and Tetramethyl urea (5). When the response of these compounds (1-5) was normalised to equal weights, it gave a very clear inequality as shown below:

Tetramethyl urea (5) > Trimethyl urea (4) > Dimethyl urea symmetrical (2) and Dimethyl urea asymmetrical (3) > Monomethyl urea (1).

Due to slow evaporation of stationary phase and generation of naked active sites on the column, it is a must that these response factors have to be checked from time to time for quantitative estimation.

These observations are in exact agreement with the fact that tetramethyl urea (5) has four ionizable carbon atoms, trimethyl urea (4) has three such carbon atoms, dimethyl urea (2) and (3) has two such carbon atoms and monomethyl urea (1) has just one. Extremely feable response given by monomethyl urea (1) may have two reasons:

i) It has only one ionizable carbon atom

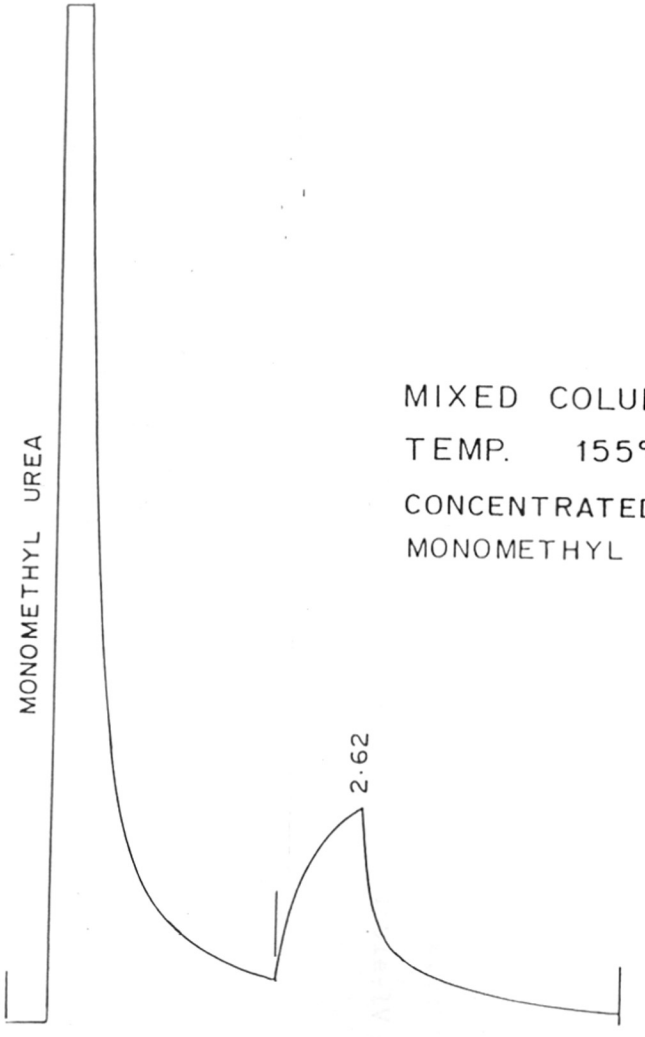


FIG: 2·3 GLC OF MONOMETHYL UREA (1)

ii) It has three active hydrogen atoms, therefore, it may have some tendency to adsorb irreversibly on the supporting material of a column. We tried to analyse highly concentrated solution of monomethyl urea (1), but it resulted in a heavily distorted peak (see Fig.2.3). Thermal conductivity detector can be used under such conditions[38].

Retention time behaviour of all the compounds given in Chart-I

We have recorded retention time, relative retention time for all the compounds given in Chart-I. See Table-IV A and Table-V A.

Retention time behaviour of substituted ureas

Tetramethyl urea (5) has no active hydrogen atom, while trimethyl urea (4) has one, dimethyl urea (2) and (3) has two, and monomethyl urea (1) has as many as three active hydrogen atoms. These typical structural features do reflect in the retention times of these compounds and "solute-solvent" interactions.

On OV-101 column, which is a typical non-polar column, dimethyl urea (2) emerges well before MIC-Trimer (9). But on OV-225 column, the nitrile group in the stationary phase, starts playing its role and retention times of dimethyl urea (2) and MIC-Trimer (9) are increased but they do not overlap.

TABLE-IV A

S.No.	Compound (Short Form)	OV-101 (3%) t_R	RRT*	OV-25 (3%) t_R	RRT*	OV-17 (10%) t_R	RRT*	QF-1 (5%) t_R	RRT*
1.	MMU (1)	-	-	2.14	0.33	2.07	0.33	1.74	0.59
2.	DMU-S (2)	1.39	0.40	2.02	0.31	1.54	0.30	1.52	0.52
3.	DMU-A (3)	1.04	0.30	1.64	0.25	2.83	0.46	1.42	0.48
4.	TMU (4)	1.07	0.31	1.55	0.24	1.51	0.24	1.23	0.42
5.	Tr.MU (5)	0.88	0.25	0.90	0.14	0.98	0.16	0.77	0.26
6.	TMB (6)	3.98	1.15	9.79	1.50	7.79	1.26	3.95	1.35
7.	Dione (7)	4.97	1.43	13.07	2.00	10.35	1.67	6.58	2.25
8.	DMI (8)	-	-	9.40	1.44	8.06	1.30	4.09	1.40
9.	MIC-T (9)	3.47	1.00	6.62	1.00	6.19	1.00	2.93	1.00

t_R - Retention time (in minutes)

*Relative retention time w.r.t. MIC - Trimer (9)

TABLE-V A

S.No.	Compound (Short Form)	OV-17 + OV-210 t_R	RRT*	OV-225 (3%) t_R	RRT*	FFAP (3%) t_R	RRT*	Carbowax 20M(7%) t_R	RRT*
1.	MMU (1)	2.20	0.44	6.73	0.75	-	-	-	-
2.	DMU-S (2)	1.87	0.38	5.39	0.60	2.33	1.28	5.42	1.12
3.	DMU-A (3)	1.52	0.31	3.16	0.35	1.35	0.73	-	-
4.	TMU (4)	1.38	0.28	2.71	0.30	1.08	0.59	2.04	0.42
5.	Tr.MU (5)	0.83	0.17	0.90	0.10	0.82	0.44	-	-
6.	TMB (6)	6.37	1.28	22.68	2.53	5.40	2.95	13.30	2.76
7.	Dione (7)	10.06	2.02	23.68	2.64	4.39	2.39	11.31	2.34
8.	DMI (8)	7.56	1.52	27.84	3.11	11.42	6.24	-	-
9.	MIC-T (9)	4.98	1.00	8.96	1.00	1.83	1.00	4.82	1.00

t_R - Retention time (in minutes)

*Relative retention time w.r.t. MIC - Trimer (9)

When we compare the retention times of this pair on FFAP column, order of elution is reversed i.e. MIC-Trimer (9) elutes first and then dimethyl urea (2). These facts can be explained very easily when we consider the structures of these two compounds. MIC-Trimer (9) has no active hydrogen, therefore, it does not have any appreciable interaction with the stationary phase FFAP. But dimethyl urea has two such active hydrogen atoms, therefore, it faces quite strong interaction with the stationary phase and it is retained on the column for a longer time. This pair of compound behaves more or less same on carbowax 20M column.

Now we consider another pair of compound namely tetramethyl urea (5) and trimethyl urea (4). On OV-101, OV-17, QF_1 columns, the retention time of trimethyl urea (4) is more than the retention time of tetramethyl urea (5). But on OV-225 column, the nitrile functional group plays its vital role and suddenly there is a wide gap between the retention time of these two compounds i.e. retention time of tetramethyl urea (5) is just (0.91 min), while the retention time of trimethyl urea (4) is (2.71 min) - almost a three fold rise.

Retention time behaviour of compound Dihydro-1,3,5-trimethyl-1,3,5-triazine-2,4(1H,3H)-dione (7) and 1,3-Dimethyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (8)

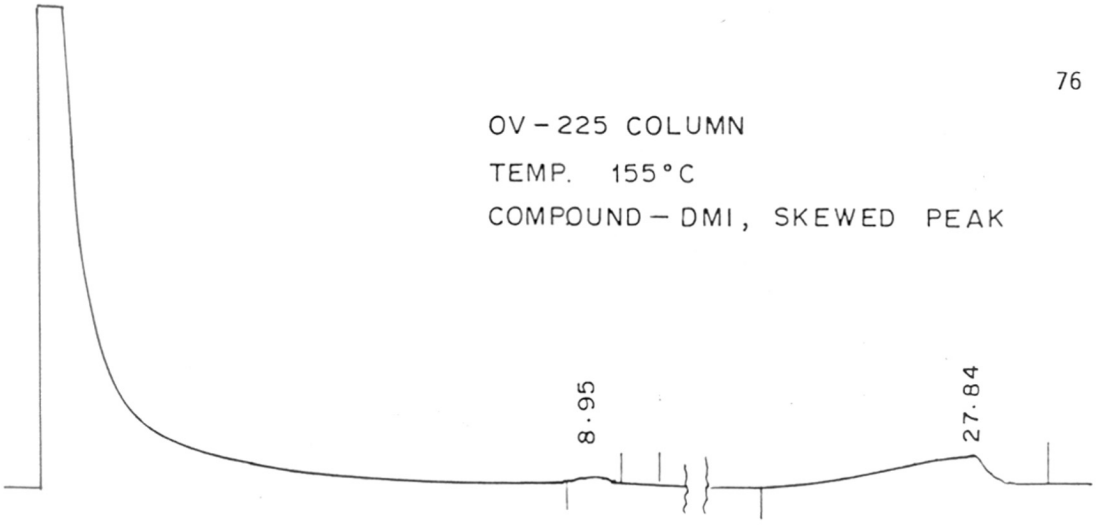
Compound (8) has one hydrogen atom which is strongly

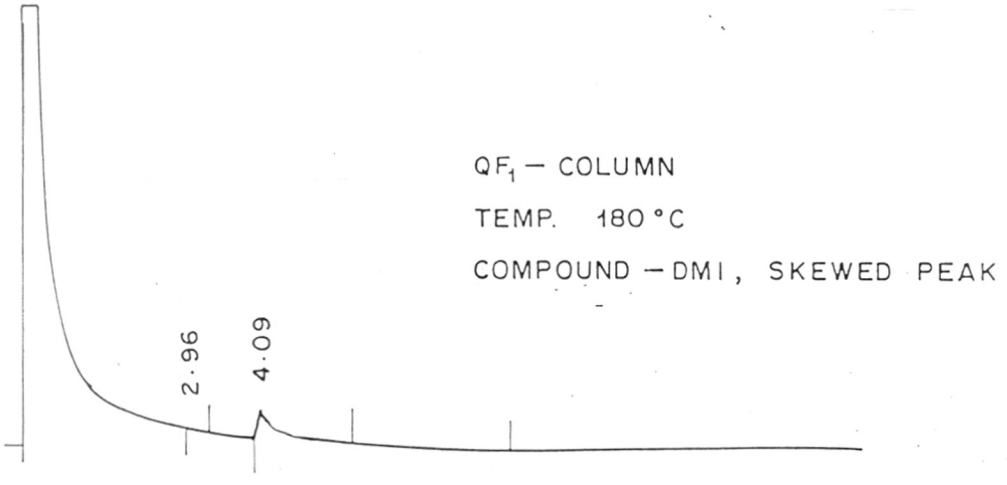
activated. But there is no such structural feature in the case of compound (7). These facts do reflect in their retention time behaviour. On medium polar column like QF_1, the compound (7) elutes well after the compound (8). But on FFAP column, complete reversal of retention time takes place. Compound (8) has very high retention time on OV-225 column. Moreover, the peak is extremely distorted. See (Fig.2.4). Ultimately, the desired symmetrical peak was obtained on FFAP column. The mixture of all the compounds was injected on FFAP column. See (Fig.2.5). The compound having retention time 7.38 is dibutyl phthalate, an internal standard. For identification of other compounds, see Table-V A.

Retention time behaviour of compound 1,3,5-trimethyl biuret (6) and Dihydro-1,3,5-trimethyl-1,3,5-triazine-2,4 (1H,3H)-dione (7)

Structural features of these two compounds also reflects on their retention time behaviour. Compound (7) has higher retention time on non-polar column as recorded in Table-IV A, while reversal of retention time has taken place on FFAP column.

After studying the retention time data of all these compounds, we prepared a blend of two stationary phases namely OV-17 and OV-210 in a definite proportion and retention times were recorded. This column resolved all the compounds as shown





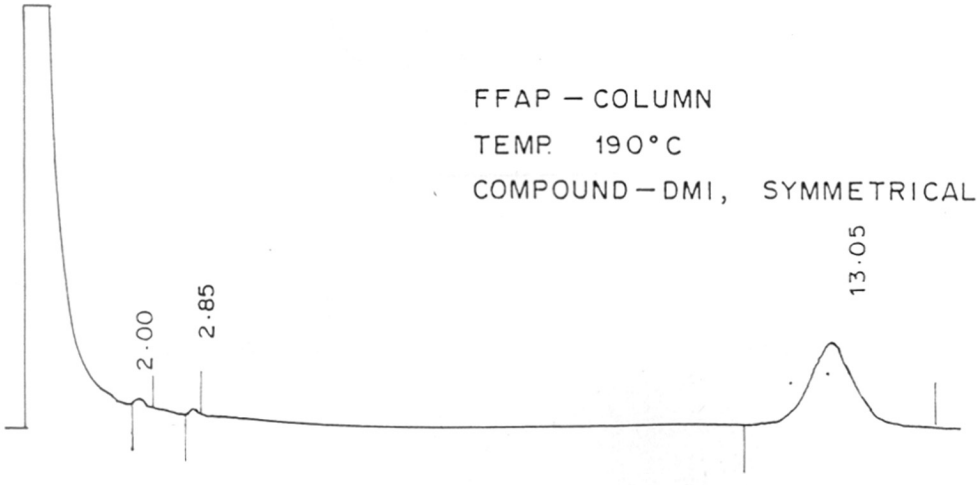


FIG: 2·4 GLC OF **DMI** (8) ON DIFFERENT COLUMNS

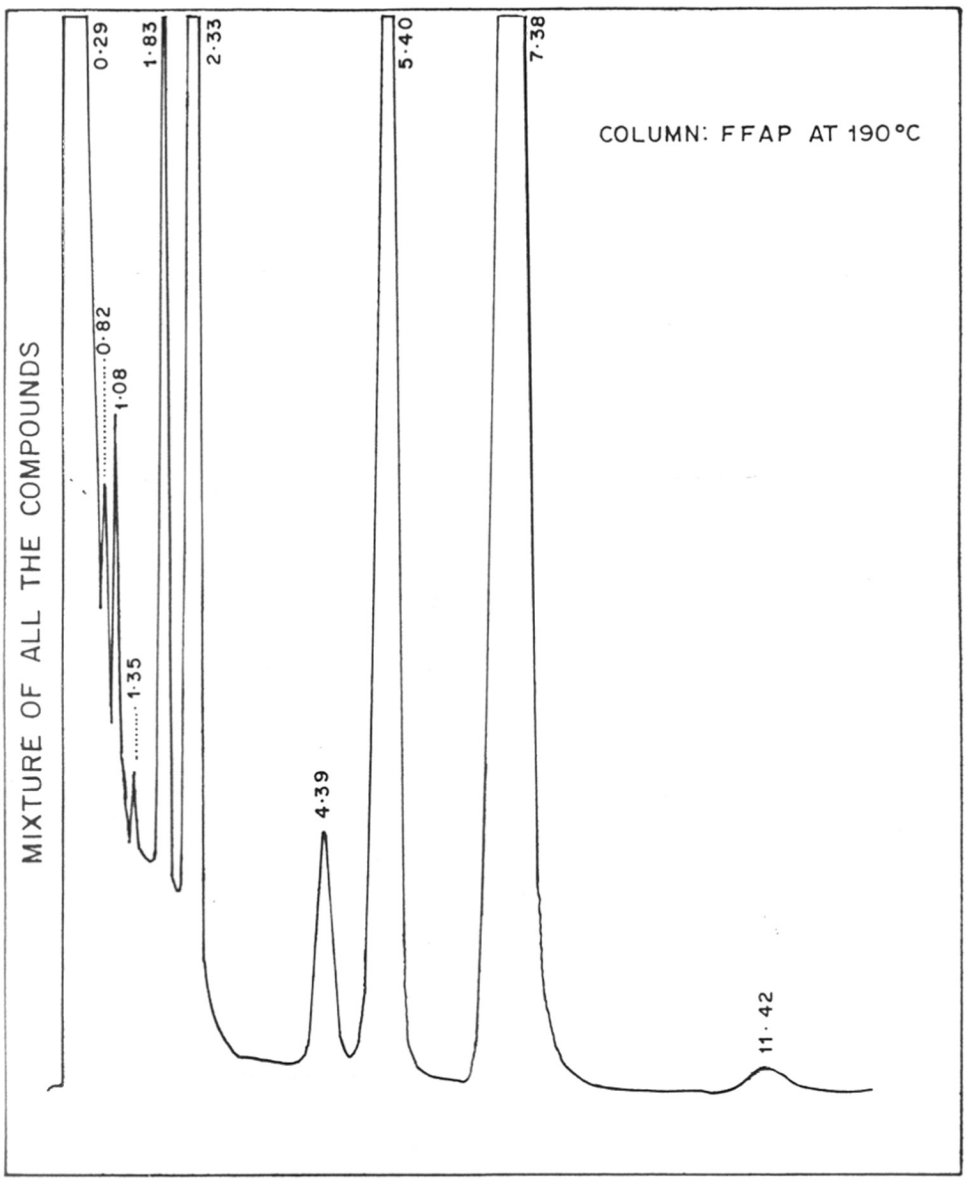
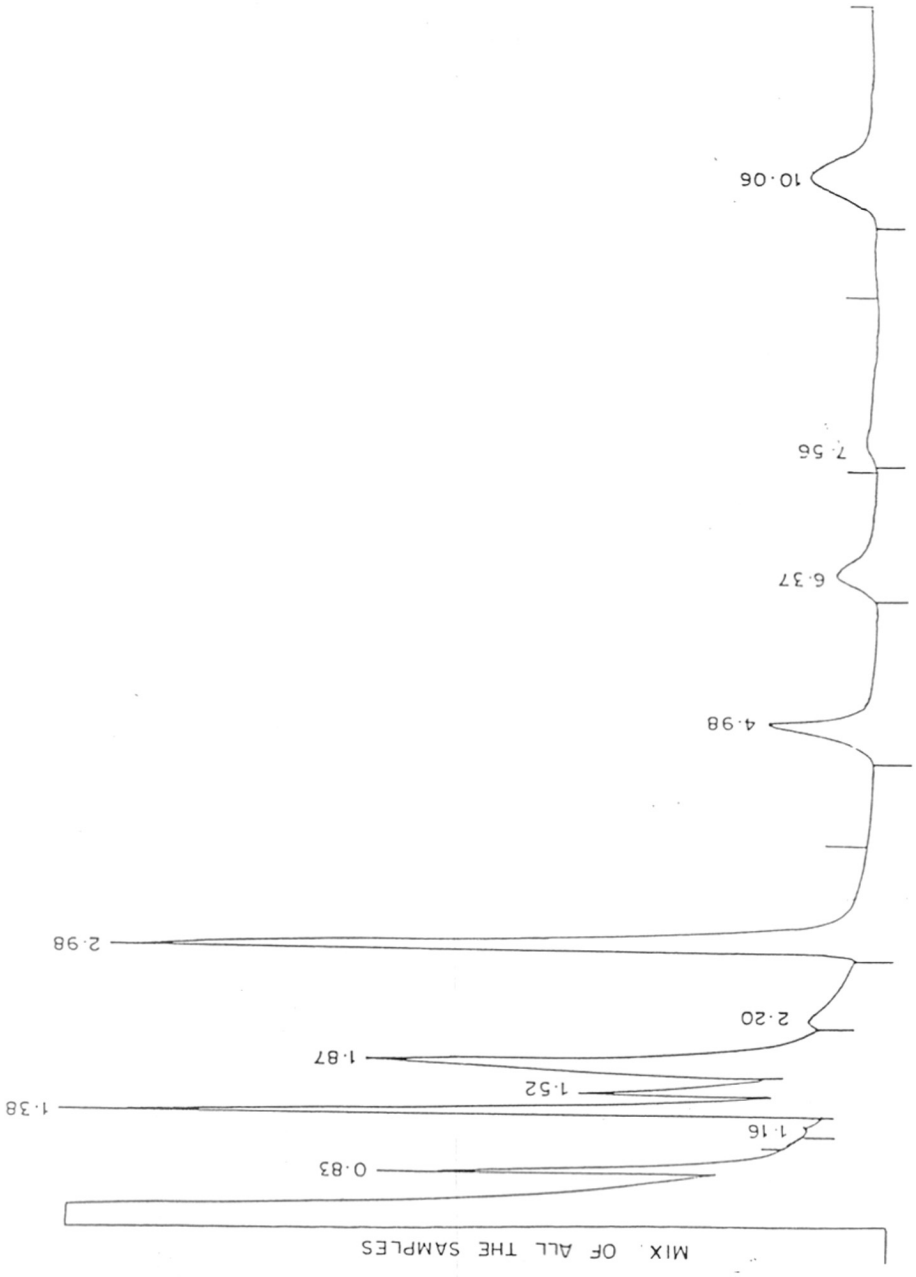


FIG: 2·5 GLC OF MIXTURE OF ALL THE COMPOUNDS



MIXED COLUMN (OV-17 + OV-210)
TEMP. 155°C

FIG. 2.6 GLC OF MIXTURE OF ALL THE COMPOUNDS

in (Fig.2.6). For identification of the compounds, see (Table-V A). Compound having retention time (2.98) is 2,6-dimethyl naphthalene, an internal standard.

Utility of McReynolds retention indices

McReynolds retention indices are well documented in the literature. From these indices, one can easily predict the retention time behaviour of the compounds we have studied. Compound having fairly active hydrogen atoms will be retained for a longer time on polar columns, such as FFAP and OV-225 columns. These predictions are in good agreement with the order of elution of the compounds we have studied on various columns. For example, see (Table-VI A).

TABLE-VI

Stationary phase	McReynolds constants				
	X' Benzene	Y' n-Butanol	Z' 2-Pentanone	U' Nitropropane	S' Pyridine
1. FFAP	340	580	397	602	627
2. OV-225	228	369	338	492	386
3. OV-101	017	057	045	067	043

These constants clearly indicate that compound having strongly activated hydrogen atom e.g. Nitropropane should have fairly high retention time on OV-225 and FFAP columns. We have

also observed same elution pattern for the compounds we have studied. For e.g. compound (8) elutes last on FFAP and OV-225 columns, because it has highly activated hydrogen atom. The retention time behaviour of other compounds has been already discussed.

Quantitative analysis

Standard compounds and standard solutions were prepared as described in the Experimental part. The graph of detector response in the arbitrary units Vs. concentration was plotted for most of the compounds analysed. See graph 1, 2 & 3.

These graphs give clear indication that detector response is quite linear over a sufficiently broad range and can be used as a guideline for quantitative estimation. The slopes of these straight line graphs are the values of detector response for the respective compound.

Whenever an unknown sample is to be analysed for quantitative estimation in a mixture, the sample is dissolved in a suitable solvent and a solution of known concentration is prepared. This solution is analysed and rough idea about the concentration of the sample component in the mixture is judged. Then a solution of known and nearest possible concentration to that of unknown is analysed. Based on these two observations, we could estimate the unknown compound with 2-3% error.

Table-VII A gives the actual and obtained weights.

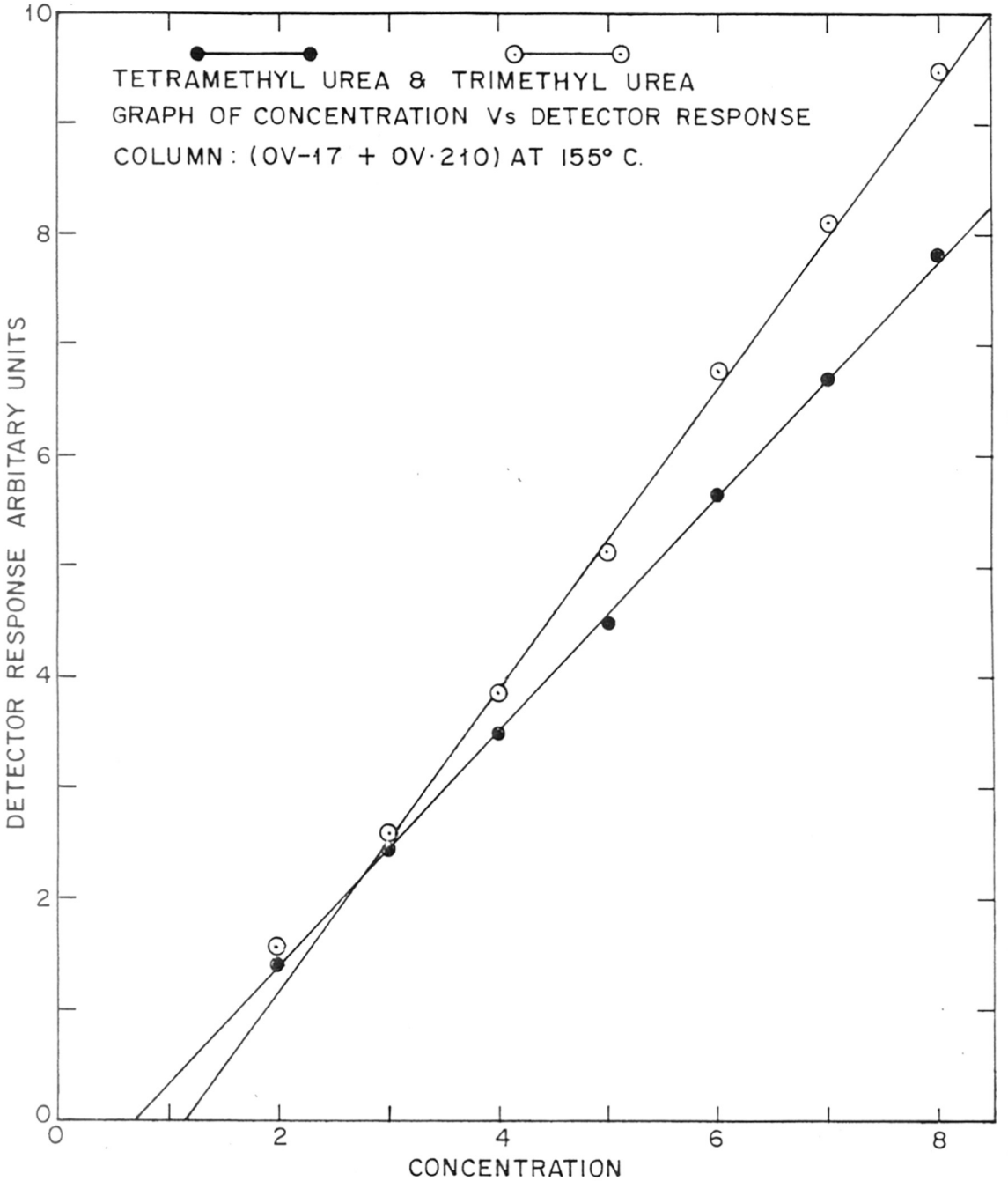
TABLE-VII A

FFAP column

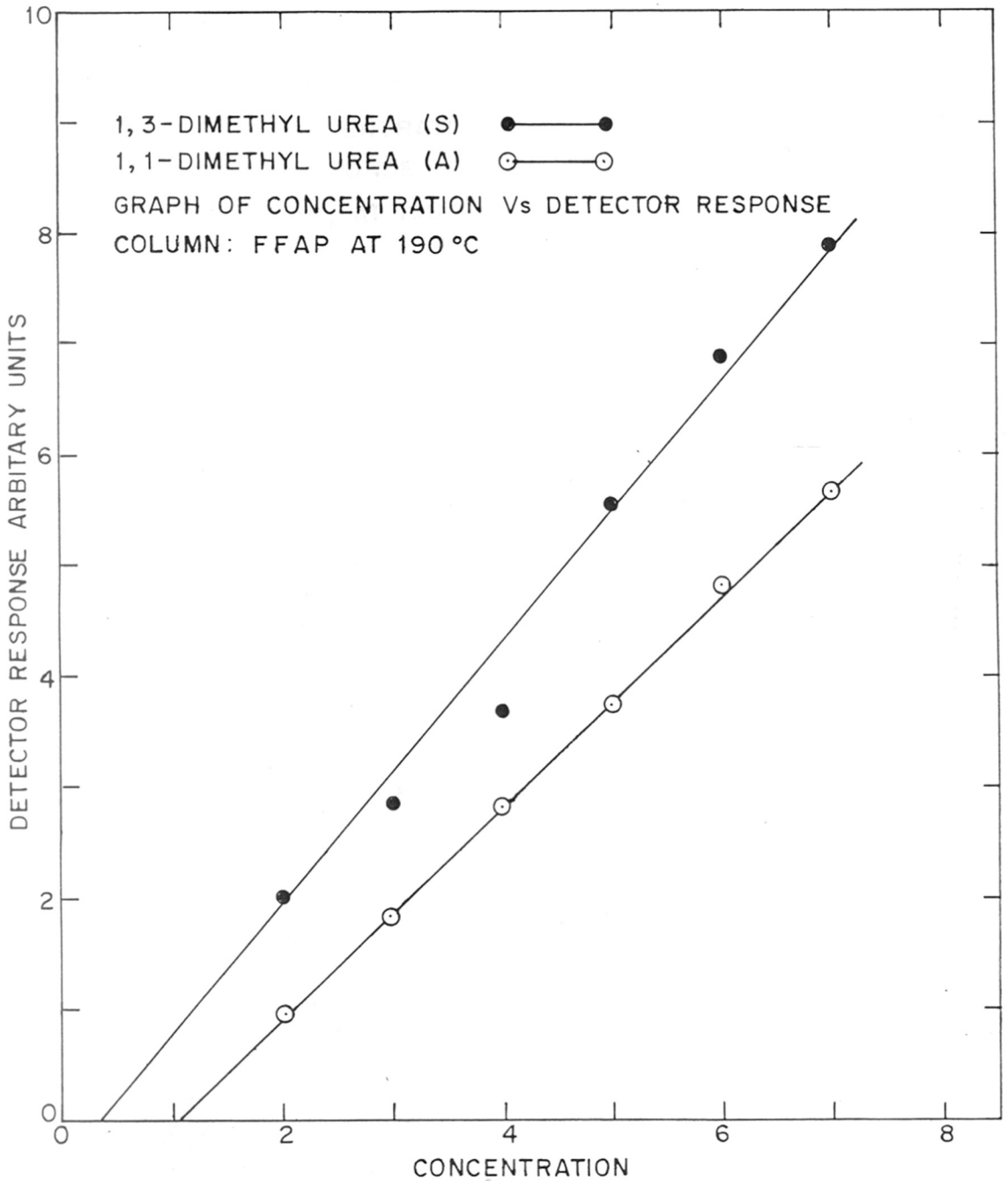
S.No.	Compound	Actual wt. in mg.	Obtained	% error
1.	Tetramethyl urea (5)	42.7 mg	41.3 mg	3.2%
2.	Trimethyl urea (4)	43.10 mg	42.0 mg	2.55%
3.	MIC-Trimer (9)	24.0 mg	23.3 mg	2.9%
4.	1,3,5-Trimethyl biuret (6)	45.3 mg	44.1 mg	2.6%

A keen observation of the graphs 1-3 shows that the straight lines do not pass through zero origin. This effect is due to the fact that because of the typical nature of the compounds that leads to certain degree of adsorption on the supporting material of the column. Such type of observation has been reported by Evans[7]. He converted monomethyl urea into its trifluoroacetyl derivative and analysed the derivatized product by GLC. In the case of derivatized product also, it was observed that the straight line graph does not pass through the zero origin!

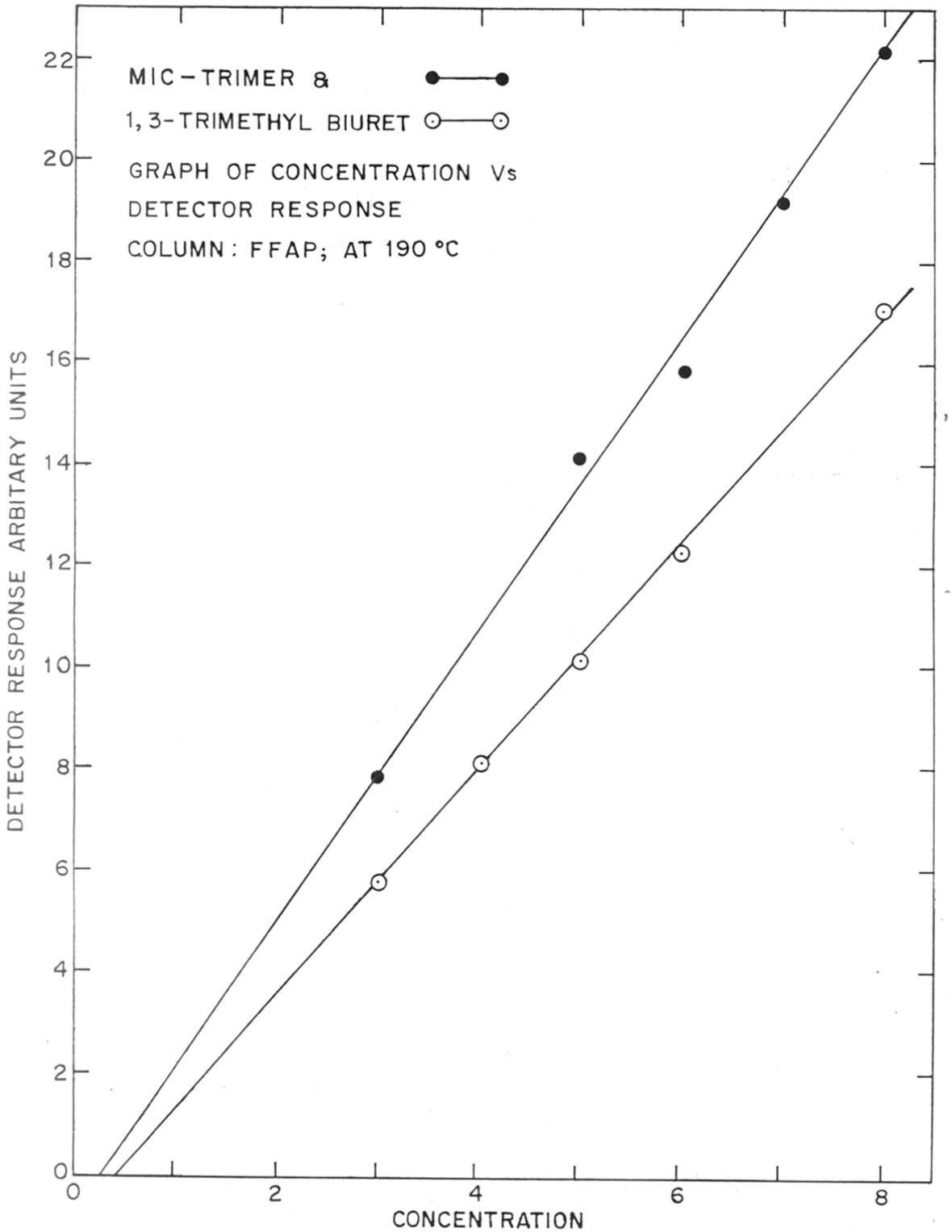
After thorough investigation, it was established that the FFAP and a blend of (OV-17 + OV-210) are the good columns to


TETRAMETHYL UREA & TRIMETHYL UREA
GRAPH OF CONCENTRATION Vs DETECTOR RESPONSE
COLUMN : (OV-17 + OV-210) AT 155° C.
DETECTOR RESPONSE ARBITARY UNITS
CONCENTRATION
0
2
4
6
8
10

GRAPH-1


1, 3-DIMETHYL UREA (S)
1, 1-DIMETHYL UREA (A)
GRAPH OF CONCENTRATION Vs DETECTOR RESPONSE
COLUMN: FFAP AT 190 °C
DETECTOR RESPONSE ARBITARY UNITS
CONCENTRATION
0
2
4
6
8
10

GRAPH-2


MIC-TRIMER &
1,3-TRIMETHYL BIURET
GRAPH OF CONCENTRATION Vs
DETECTOR RESPONSE
COLUMN: FFAP; AT 190 °C
DETECTOR RESPONSE ARBITARY UNITS
CONCENTRATION
0
2
4
6
8
10
12
14
16
18
20
22

GRAPH-3

resolve all the compounds under investigation without derivatization. We took all the precautionary measures reported in the literature[45] and found that both the above mentioned columns give good results for quantitative estimation.

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1. DEMETHYLATION OF N-METHYLISOCYANURATES, N-METHYL URACILS AND N-METHYLXANTHINES BY THIOPHENOLATE ANIONS
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