Reactions of *p*-Dimethylaminocinnamaldehyde with Urea, Thiourea and Their N-Alkyl/Aryl Derivatives

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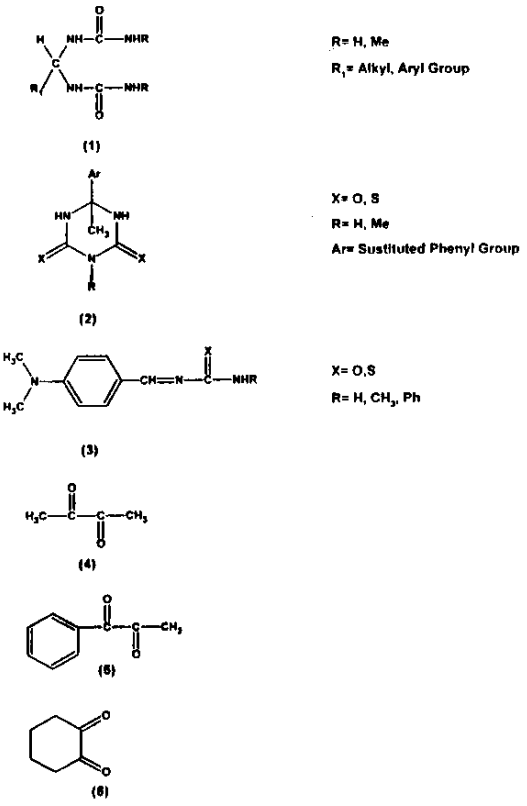
Summary: The reaction of p-dimethylaminocinnamaldehyde with urea, thiourea and their N-alkyl/aryl derivatives in acid media yields colored products. The structures of the coloured products are illustrated with chemical and spectroscopic means. They are found to be shift-bases 4(a-f).the pinkish orange color developed in case of urea is used for the preparation of calibration curves for the estimation of urea present in biological as well as non-biological fluids. The optimum amounts of p-dimethylaminocinnamaldehyde and H_2SO_4 (36 N) are 150 mg /100 ml and 0.2 to 0.3 ml in 80 ml CH_3OH. These are quite suitable quantities for the reaction to proceed favourably. Moreover, the fluctuation of the pinkish orange color absorbance depends upon the strength of acid. The graphs are drawn using absorbances against urea concentration before and after heating solutions at 50°C.

Introduction

The importance of assay of urea present in the biological as well as non-biological fluids has been reported [1]. Several workers [1] make use of *p*-dimethylaminobenzaldehyde as a diagnostic reagent for the estimation of urea and compared results with diacetylmono-oxime and Berthelot methods. They could not generalised analytical procedure. In the present work we have replaced *p*-dimethylamino-benzaldehyde with p-dimethylaminocinnamaldehyde in order to make the analytical procedure more sensitive and specific. In this case products resulting from the reaction of *p*-dimethylaminocinnamal-dehyde with ureas and their alkyl/aryl derivatives are isolated and identified. The calibration curves are prepared in case of urea before testing this analytical method in hospital laboratories.



Results And Discussion

The condensation of urea with aliphatic aldehydes had been reported [2-3]. The products of the reactions were alklidine diureas, although other products were also possible, depending on degree of polymerization. The reaction of urea with benzaldehyde was first reported by Schiff [4], who suggested an empirical formula for the products of $C_9H_{12}N_4O_2$ and structure (1).

Recently, Bulter and Hussain [5] reported the reactions of benzaldehyde and substituted benzaldehydes with urea, thiourea and their alkyl/aryl derivatives in acid media. They reported the cyclic structures of the products (2) resulting from the reaction of ureas with substituted benzaldehyde. They also found that benzaldehydes substituted with electron drawing groups reacted faster with ureas than unsubstituted benzaldehydes. The behaviour of

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p-dimethylaminobenzaldehyde was surprising, it did not follow the same reaction path as reported for other aldehydes [5].

Hussain [6] reported that the products resulting from the reaction of *p*-dimethylamino-benzaldehyde with urea, thiourea and their alkyl/aryl derivatives were Schiff bases (3). They gave yellow-blue colouration in aqueous media. The yellow colour obtained from the reaction of urea with *p*-dimethylaminobenzaldehyde was used for the assay of urea present in biological fluids. We thought that the increase in the conjugation of p-dimethylamino-benzaldehyde might enhance the sensitivity of analytical procedure for the estimation of urea. So we selected *p*-dimethylaminocinnamaldehyde as a colouring agent. It gave pinkish orange colour with urea in acid media. The colour absorbed at λ_{max} 514 nm, while *p*-dimethylaminocinnamal-dehyde itself absorbed at 387 nm and in acid media it reflected maximum absorbance at λ_{max} 232 nm. The absorbance shift from λ_{max} 387 to 232 nm (red shift) was ascribed due to protonation of the *p*-dimethylaminocinnamaldehyde.

However, here is useless to comment on pinkish orange colour unless its nature is not known. Hence, we decided first to do reactions of *p*-dimethylaminocinnamaldehyde with ureas in order to identify their end products.

Reactions of P-Dimethylaminocinnamaldehyde with Urea

Equimolar quantities of urea and *p*-methylaminocinnamaldehyde were suspended in anhydrous benzene containing a few drops of TFA. The mixture was stirred for 2 hours at room temperature. During stirring, dark red to violet coloured material appeared. After isolation and purification the product had pinkish red colour. It melted sharply at 165°C. Its mass spectrum and elemental analysis yielded the molecular formula $C_{12}H_{15}N_3O$. We tentatively suggested the structure (4a). The compound was found to be very sensitive towards acidic and basic hydrolysis. It decolourized the solutions of $KMnO_4$ and Br_2. In UV/visible spectra it absorbed at λ_{max} 514 nm and its methanolic solution was very stable in ultra violet light. The pinkish orange colour indicated the formation of >C = N- in compound. (4a) Moreover, its infrared spectra in KBr confirmed the presence of -NH_2, carbonyl and -C=N groups present in compound (4a).

Similarly, the *p*-dimethylaminocinnamal-dehyde with methyl urea yielded a yellow solid which melted at 155°C. Its elemental analysis and molecular weight determination corresponded to the empirical formula $C_{13}H_{17}N_3O$. We assigned the structure (4b). Its other behaviour was found to be similar to compound (4a). Its infrared spectra in KBr indicated the stretching vibration of NH, Carbonyl and C = N groups present in compound (4b).

Likewise, phenylurea with *p*-dimethylamino-cinnamaldehyde yielded a dark violet solid which had m.p. 165°C. We assigned the structure (4c) on the basis of its molecular weight determination and elemental analysis. Its empirical formula was found to be $C_{18}H_{19}N_3O$. The decolourization of aqueous solutions of Br_2 and $KMnO_4$ indicated the presence of -C=N- in the compound (4c). In addition, its infrared spectra also confirm the presence of -C=N and C=O groups present in compound (4c).

Similarly, thiourea, methyl thiourea and phenylthiourea reacted with p-dimethylamino-cinnamaldehyde and yielded compounds $C_{12}H_{15}N_3S$, $C_{13}H_{17}N_3S$ and $C_{18}H_{19}N_3S$ respectively. On the basis of spectroscopic analysis we assigned structures 4 (d-f) to them, respectively. Other physical and chemical characters were very similar to those compounds reported earlier.

Estimation of Urea with P-Dimethylaminoinnamal dehyde

As stated earlier, the reaction of urea with *p*-dimethylaminocinnamaldehyde yielded pinkish orange colour. We would like to make use of this colour in the assay of urea in the same manners as with *p*-dimethylaminobenzaldehyde [1]. However, an extensive work has been done in this connection but no one is able to find the accurate method for the determination of urea present in biological fluids. It is reported [7] that ∝-diketones containing at least one methyl group adjacent to carbonyl group react readily with urea and its alkyl derivatives in acid solution to give intensely coloured solutions. These colours have been used by Ormsby [8], Dickeman [9] and Siest [10] for the estimation of urea concentration present in biological fluids.

Of the three diketones, namely butane-2,3-dione (5) 1-phenylpropane-1,2-dione (6) and cyclohexane-1,2-dione (7), the first one has been extensively used while the last two have never been widely used in hospital laboratories

After thorough studies of the products resulting from the reactions of ∝-diketones with urea we come to know that for an accurate estimation of the urea concentration present in biological fluid, we need another diagnostic reagent. It should be accurate, sensitive and should not give any side product. We think that *p*-dimethylaminocinnamaldehyde can fulfil these conditions. That is why, in the present work *p*-dimethylaminobenzaldehyde is replaced with *p*-dimethylaminocinnamaldehyde in order to make this procedure more sensitive and accurate. It has reacted with urea and its alkyl or aryl derivatives with the formation of > C = N - bond. The dimethylamino group present at para position of phenyl group is considered as an oxo group and has enhanced the colour intensity which has developed due to the formation of C = N. Here, we are trying to find out optimum parameters of this reaction where the pinkish orange colour should remain stable, sensitive and specific. We have discovered that this colour is highly sensitive and fluctuate with the strength of acid. We think probably the degree of protonation of the chromogen is the cause of fluctuation of the absorbance. Hence, we have focused our intention to study the exact pH of the reaction media where the pinkish orange colour obtained from the reaction of urea with p-dimethylaminocinnamaldehyde remains stable and help in shifting equilibria from left to right. We believe that the actual chromogen which is responsible for the colour is Schiff base (4a). The formation of Schiff-base in acidic media depends upon the acid strength. We suggest a reaction mechanism as shown in Scheme-1.

It is quite clear that the Schiff base with quinoide resonating structure has light absorbing property and it absorbed at λ_{max}514 nm. The increase and decrease in the absorption intensity depend upon the quantity of the compound, greater the formation of this compound, greater will be the absorption. We find that the formation of this compound is controlled by the strength of acid.

In this connection we have performed a series of experiments using CH_3OH and H_2SO_4 of various strengths as reaction media. Other factors like optimum amount of *p*-dimethylaminocinnamaldehyde, minimum and maximum amounts of urea present in samples and effect of acid strength on λ_{max} of the reaction product are also studied.

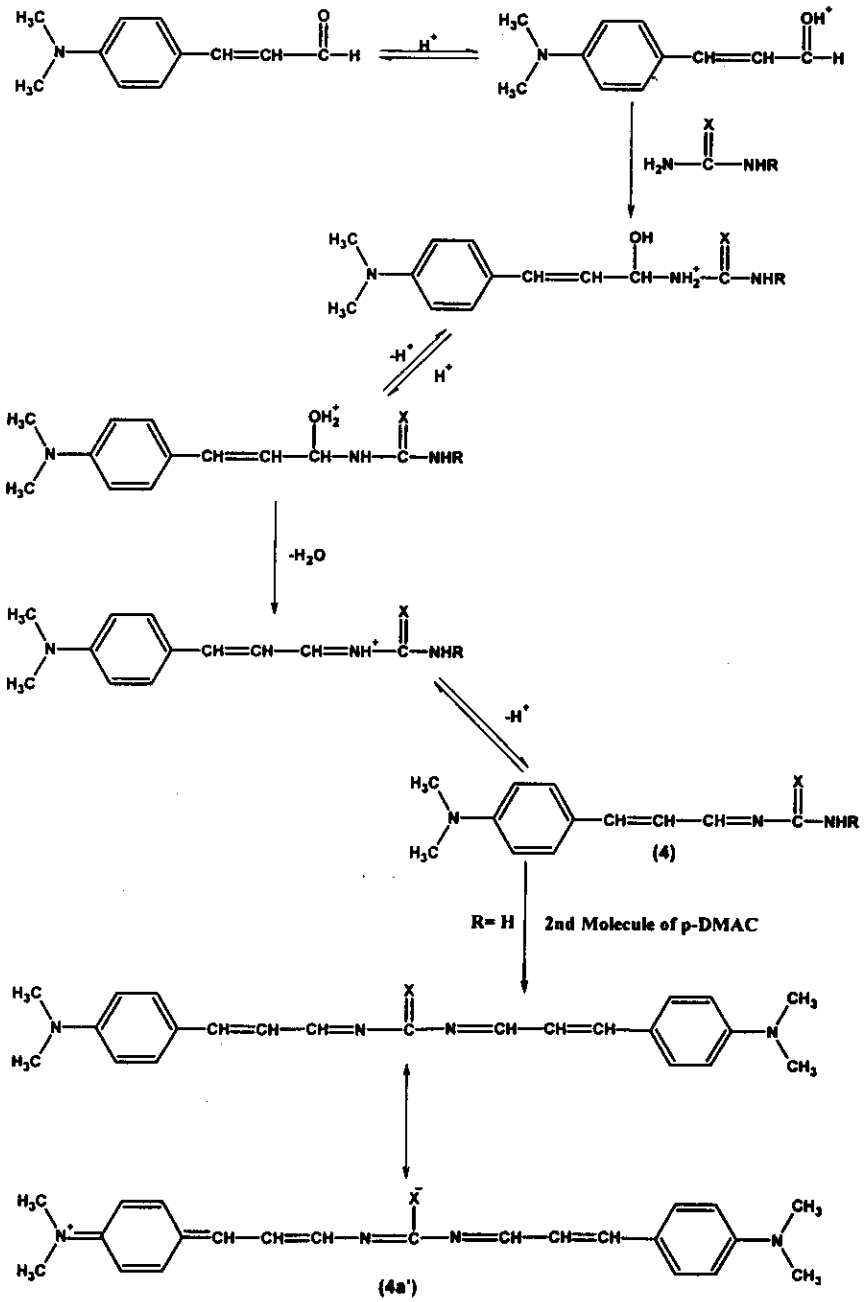
The absorbances of methanol, protonated methanol, urea in CH_3OH - H_2SO_4 mixture, *p*-dimethylaminocinnamaldehyde in methanol and CH_3OH - H_2SO_4 mixtures using distilled water, methanol and protonated methanol, as reference solvents, respectively, were studied and they show λ_{max} at 196 (1.95 abs), 243 (0.263), 263 (2.673), 387 (1.694), and 232 (3.396) nm, respectively.

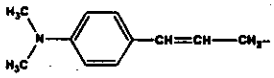
In addition, when aqueous as well as methanolic solutions of urea are made to react with *p*-dimethylaminocinnamaldehyde a new peak at λ_{max} 514 nm is appeared. Spectral studies clearly indicate that this is the "product of the reaction peak" which is quite different from others. But, this peak varies from 510 to 553 nm. The change in λ_{max} is probably, due to the degree of protonation of reactants and products. However, after a series of experimentations, the optimum amount of *p*-dimethylaminocinnamal dehyde and H_2SO_4 (36N) are found to be 150mg/100ml, 0.2 - 0.3-ml/80 ml in CH_3OH. They are quite suitable quantities for the reaction to proceed favourably. It is worthwhile to point out here that in case of an aqueous solution of urea the maximum limit of detectable urea is 12.5 mg/100ml. On the other hand if the methanolic solution of urea is used, the maximum limit is 50 mg/ 100 ml present in sample. Beyond this limit, the adsorbances of the coloured solutions become out of the spectrophotometer range. Surprisingly, a slight addition of water in the form of aqueous solution of urea, makes the analytical procedure more sensitive as compared to that where pure methanol has been used. The cause in this connection has already been explained{1}.

In urea molecule two amino groups are flank on either side of the carbonyl group. It has been reported{11-18} that the oxygen of urea is protonated first and then amino group depending on the strength of acid. Theoretically, two products are possible from the reaction of urea with *p*-dimethylaminocinnamaldehyde (4a) and (4a′).

The product (4a) is isolated and identified while we fail to recover product (4a′) from the reaction mixture. Contrarily, it could be possible that heavily protonated second NH_2 group of urea fails to condense with the second molecule of *p*-dimethylaminocinnamaldehyde and negates the presence of product (4a′).

However, in the UV/visible spectral studies of pinkish orange colour, the evidence for the formation of this product (4a′) is realized. When 2:1 molar ratio of *p*-dimethylaminocinnamaldehyde and urea are used, the absorbances of pinkish orange solution are



(4)	a	R= H	X= O
	a'	R= 	X= O
	b	R= CH_3	X= O
	c	R= Ph	X= O
	d	R= H	X= S
	e	R= CH_3	X= S
	f	R= Ph	X= S

SCHEME- I

found to be double than the absorbances where 1:1 molar ratio quantities are used.

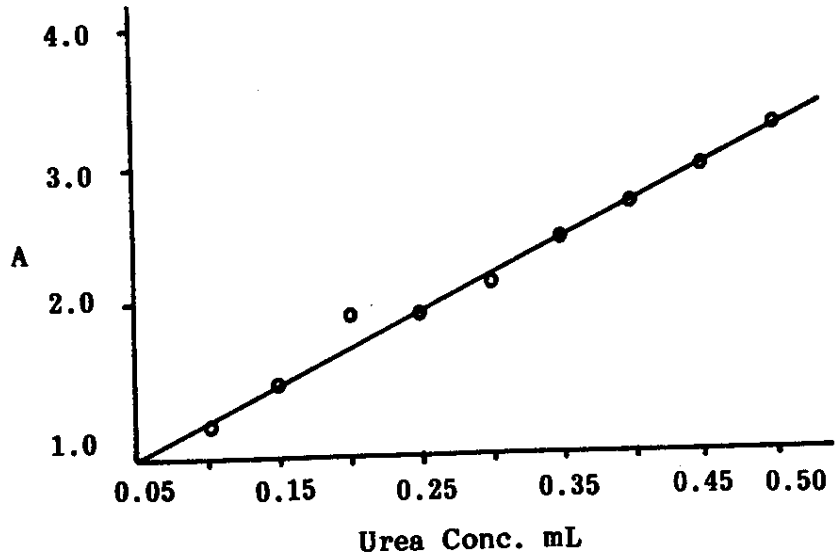
In both cases no changes in λ_{max} is seen. This is probably due to the fact that two identical chromogenic groups exist on either side of >C=O group of urea product (4a′). At one time only one group is involved in the formation of quinoide structures while the other remains as such. The carbonyl group in the mid of the two chromogenic groups of product (4a′) probably acts as insulator and stop the extensive conjugation from one to the last end. This is clear from resonating structure of compound (4a′). That is why λ_{max} remains fixed and the additive effects of both groups contribute in the enhancement of absorbances pertaining to pinkish orange colour developed in urea-p-dimethylamino-cinnamaldehyde reaction. We have prepared standard graphs (1A, 1B, IIA, IIB, and IIIA) after determining all the facts and figures of this reaction. The graphs (1A, 1B, IIA, IIB, and IIIA) can be utilized in the determination of urea concentration present in biological samples.

The limitation of this analytical procedure are quite clear that below and above the quantities of chemicals used in the preparation of graphs (1A, 1B, IIA, IIB, and IIIA) can not follow the "Beer's Law". Hence, we think that this could be very sensitive and accurate procedure for the determination of very minimum amount of urea concentration present in samples.

Table –I:Absorbances using CH_3OH - H_2SO_4 (80:0.2 ml v/v) Soln. at 514 nm

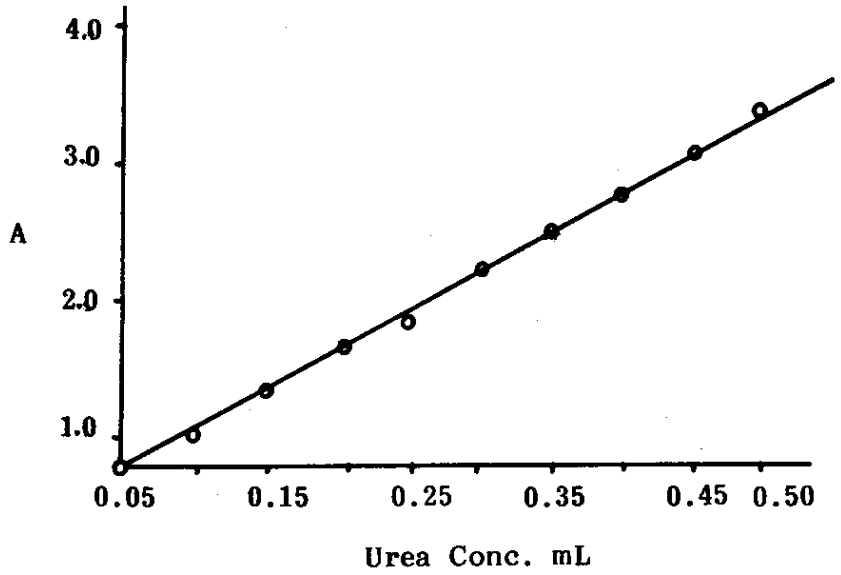
Sr. No.	Volume of urea Solution 1 ml=10 mg ml	Volume of p-DMAC Solution 1 ml=10 mg ml	Volume of CH_3OH-H_2SO_4 (80:0:2 v/v) ml	Total Volume ml	pH	ABSORBANCES Before heating	After heating for 20 min at 50 C^0
1.	0.05	1.5	8.45	10.0	0.18	0.859	0.880
2.	0.10	1.5	8.40	10.0	0.63	1.061	1.075
3.	0.15	1.5	8.35	10.0	0.73	1.359	1.388
4.	0.20	1.5	8.30	10.0	0.86	1.956	1.983
5.	0.25	1.5	8.25	10.0	0.89	1.812	1.834
6.	0.30	1.5	8.20	10.0	0.92	2.122	2.174
7.	0.35	1.5	8.15	10.0	0.99	2.440	2.489
8.	0.40	1.5	8.10	10.0	1.25	2.723	2.779
9.	0.45	1.5	8.05	10.0	1.55	2.993	3.061
10.	0.50	1.5	8.00	10.0	1.59	3.256	3.369

p-DMAC= p-dimethylaminocinnamaldehyde.



GRAPH 1-A

Absorbances using CH_3OH - H_2SO_4 (80:0.2 v/v) Soln. At 514 nm after heating Reference solvent CH_3OH-H_2SO_4



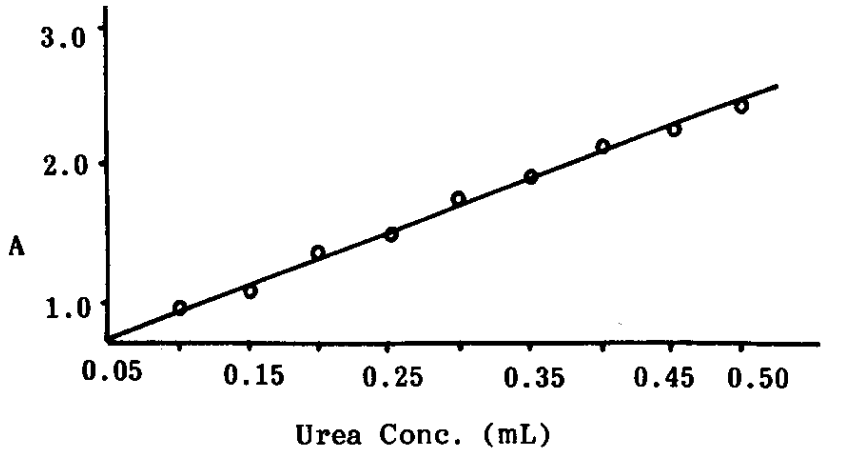
GRAPH I-B

Absorbances using CH_3OH - H_2SO_4 (80:0.3 v/v) Soln. At 514 nm before heating Reference solvent CH_3OH-H_2SO_4

TABLE –II: Absorbances using CH_3OH - H_2SO_4 (80:0.3 ml v/v) Soln. at 514 nm

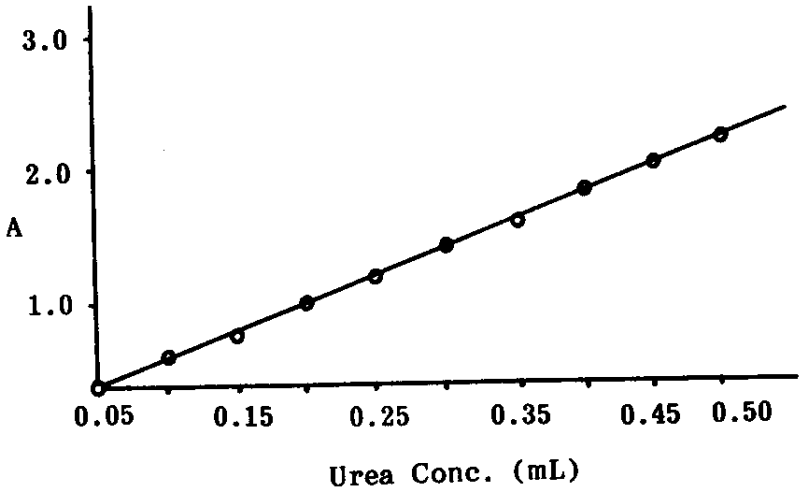
Sr. No.	Volume of urea Solution 1 ml=10 mg ml	Volume of p-DMAC Solution 1 ml=10 mg ml	Volume of CH_3OH-H_2SO_4 (80:0.3 v/v) ml	Total Volume ml	pH	ABSORBANCES	
						Before heating	After heating, for 20 min at 50 C°
1.	0.05	1.5	8.45	10.0	0.18	0.674	0.672
2.	0.10	1.5	8.40	10.0	0.23	0.902	0.867
3.	0.15	1.5	8.35	10.0	0.52	1.070	1.031
4.	0.20	1.5	8.30	10.0	0.59	1.328	1.283
5.	0.25	1.5	8.25	10.0	0.61	1.431	1.380
6.	0.30	1.5	8.20	10.0	0.69	1.699	1.668
7.	0.35	1.5	8.15	10.0	0.72	1.894	1.863
8.	0.40	1.5	8.10	10.0	0.78	2.129	2.120
9.	0.45	1.5	8.05	10.0	0.83	2.316	2.320
10.	0.50	1.5	8.00	10.0	1.05	2.411	2.439

p-DMAC= p-dimethylaminocinnamaldehyde.



GRAPH II-A

Absorbances using CH_3OH - H_2SO_4 (80:0.3 v/v) Soln. At 514 nm before heating Reference solvent CH_3OH-H_2SO_4



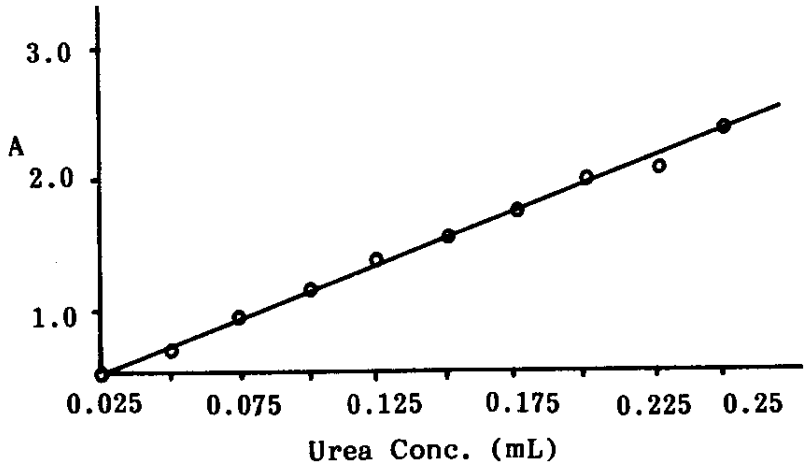
GRAPH II-B

Absorbances using CH_3OH - H_2SO_4 (80:0.3 v/v) Soln. At 514 nm after heating Reference solvent CH_3OH-H_2SO_4

TABLE –III: Absorbances using CH_3OH - H_2SO_4 (80:0.3 ml v/v) Soln. at 514 nm

Sr. No.	Volume of Urea Solution 1 ml=05 mg ml	Volume of p-DMAC Solution 1 ml=10 mg ml	Volume of CH_3OH-H_2SO_4 (80:0.3 v/v) ml	Total Volume ml	ABSORBANCES Before heating
1.	0.025	1.5	8.475	10.0	0.597
2.	0.050	1.5	8.450	10.0	0.735
3.	0.075	1.5	8.425	10.0	0.959
4.	0.100	1.5	8.400	10.0	1.151
5.	0.125	1.5	8.375	10.0	1.371
6.	0.150	1.5	8.350	10.0	1.541
7.	0.175	1.5	8.325	10.0	1.730
8.	0.200	1.5	8.300	10.0	1.955
9.	0.225	1.5	8.275	10.0	2.023
10.	0.250	1.5	8.250	10.0	2.297

p-DMAC= p-dimethylaminocinnamaldehyde.
0.5 % aq. solution of Urea is used.



GRAPH III-A

Absorbances using CH_3OH - H_2SO_4 (80:0.3 v/v) Soln. At 514 nm before heating using an aqueous solution of urea (0.5%). Reference solvent CH_3OH-H_2SO_4

However, we can not say any thing at this time unless it will be applied in Hospital Laboratories.

Experimental

1. Reaction of p-Dimethylaminocinnamaldehyde With Urea

p-Dimethylaminocinnamadehyde (1.8g) and and urea (0.6g) were added in a conical flask containing benzene (20 ml) and TFA (1.0 ml). It was stirred at room temperature for 2 hours. Dark red to violet colour appeared. During the stirring a solid material settled down. It was isolated, washed with benzene and recrystallized in ether.When dried, it had m.p. 165°C(4a). It is pinkish red in color. When it is treated with dilute acid or base, its red color gets discharged. It is soluble in methanol, ethanol, water, acetone, DMF, DMA, DMSO, partially soluble in chloroform and insoluble in ethylacetate,ether and benzene. m/z 217 (M^+) (Found: C, 66.35;H, 6.69;N, 19.36%. $C_{12}H_{15}N_3O$ requires; C, 66.34; H,6.96; N, 19.33%.) IR (KBr) ν_{max} 3740, 3350 (NH_2), 1730 (C=O) and 1660(C=N) cm^{-1}.

2. Methylurea

In this case *p*-dimethylaminocinnamaldehyde-(1.8g) and methylurea (0.74g) were taken. The rest of the procedure was same as had described in experiment no.1.

The reaction product (4b) was recrystallized in chloroform. When dried, it had m.p. 155°C. It is yellow in colour. When it is treated with dilute acid or base, its colour gets discharged. It is soluble in methanol, ethanol, acetone, chloroform, DMSO, DMF, and DMA partially soluble in ethylacetate and insoluble in ether, pet. ether and benzene. m/z 231 (M^+), (Found: C, 67.60; H; 7.41; N,18.15%. $C_{13}H_{17}N_3O$ requires; C, 67.51; H, 7.41; N, 18.17%). IR (KBr) ν_{max} 3210 (NH), 1732 (C=O) and 1672 (C=N) cm^{-1}.

3. Phenylurea

The experiment no.1 was repeated with *p*-dimethylaminocinnamaldehyde (1.8g) and phenyl-urea (1.3g). The product was worked out as had explained previously.

The solid product (4c) was obtained. It was recrystallised in chloroform. When dried it had m.p. 165°C. It is dark violet in colour. When it is treated with dilute acid or base, its colour gets discharged. It is soluble in acetone, DMSO, DMF, DMA partially soluble in methanol, ethanol and in H_2O. It is insoluble in ether, pet. ether and benzene. m/z 293(M^+) (Found; C, 73.70, H, 6.53; N,14.34%. $C_{18}H_{19}N_3O$ requires; C, 73.69; H, 6.53; N, 14.32%). IR (KBr) ν_{max} 3150 (NH), 1730 (C=O) and 1660(C=N) cm^{-1}.

4. Thiourea

The experiment No. 1 was repeated using *p*-dimethylaminocinnamaldehyde (1.8g) and thiourea (0.76g). The reaction product (4) was worked out as had described previously and recrystallized in chloroform. When dried, it had m.p. 151°C. It is red violet in colour. When it is treated with dilute acid or base its colour gets discharged. It is soluble in water, methanol, ethanol, acetone, DMF, DMA, DMSO and insoluble in ether, pet ether and benzene.m/z 233 (M^+) (Found: C, 61, 82; H, 6.85; N, 13.1; S, 13.69%. $C_{12}H_{15}N_3S$ requires., C, 61.77; H, 6.48; N, 18.10; S, 13.74%). IR (K Br) ν_{max} 3270 (NH_2), 1680 (C=N) and 1600 (C=S) cm^{-1}.

5. Methyl Thiourea

Experiment no. 1 was repeated with *p*-dimethylaminocinnamal dehyde (1.8g) and methyl thiourea (0.9g). The reaction product (4e) was isolated in the same manner as had discussed previously. It was recrystallized in chloroform, m.p. 95±2°C. It is dark pink in color. Dilute acid and base decolourize its aqueous solution. It is soluble in water, methanol, ethanol, acetone, DMSO, DMF and DMA. m/z 247 (M^+) (Found:C, 63.15; H, 6.95; S 12.92% $C_{13}H_{17}N_3S$ requires; C, 63.13; H, 6.9; N, 16.99; S, 12.96%). IR (KBr) ν_{max} 3260 (NH) 1690 (C=N) and 1609 (C=S) cm^{-1}.

6. Phenylthiourea

A mixture of *p*-dimethylaminocinnamal-dehyde (1.8g), phenylthiourea (1.5g), benzene (20 ml) and TFA (10 ml) was taken in a conical flask. It was stirred for 4 hours at room temperature. Two layers were separated, one settled down and the other was benzene. The lower layer was separated and washed with benzene. It was treated with excess amount of benzene. On standing, blue shinning crystals settled down. They were separated and washed with ether. Dried product (4f) had m.p. 102°C. It is violet in colour. When it is treated with dilue acid or base its colour gets discharged. It is soluble in methanol, ethanol, acetone, chloroform,

DMF, DMA and DMSO, partially soluble in pet. ether, benzene and insoluble in water. m/z 309 (M^+)(Found: C,69.9; H,6.59; N,13.77; S,10.56%. $C_{18}H_{19}N_3S$ requires; C, 69.87; H, 6.19; N, 13.57; S, 10.35%) IR(KBr) ν_{max} 3270 (NH), 1680 (C=N) and 1610 (C=S) cm^{-1}.

General Procedure:

Ten measuring flasks of each 10 ml capacity were taken. The variable quantities of urea solution (1%) and constant quantities of *p*-dimethylamino-cinnamaldehyde solution (1%) were added in each flask. The volume of each flask was made upto the mark by adding CH_3OH - H_2SO_4 mixture. The way of mixing chemicals was shown at their respective places,.(Tables I , II, and III). The pinkish orange color developed in each case. The pH of the reaction mixture in each case was noted. The absorbances of coloured solutions were recorded scanned at λ_{max} 514 before and after heating at 50°C for 20 minutes using blank solution (without urea) as a reference solvent. Graphs were drawn using absorbances against urea concentration.

Preparation of Stock Solutions:

a) Urea:

Anhydrous urea (1.0g) was dissolved in distilled methanol and made up the volume 100 ml

1.0--ml of soln. = 10 mg urea.

b) p-*Dimethylaminocinnamaldehyde (DMAC):*

One gram was dissolved in methanol and diluted to 100 ml

ml of p. DMAC = 10.0 mg.

c) CH_3OH-H_2SO_4

Methanol (80 ml) was taken in a beaker and different volumes of acid (H_2SO_4 36 N) ranging 0.05 to 10 ml were added. The whole mixture was thoroughly stirred and pH of the solution in each case was recorded. For the preparation of calibration curves 0.2 to 0.3 ml sulphurc acid was used in 80ml methanol

d) Blank Solution:

In a 10 ml measuring flask, 1.5 ml *p*-dimethylamino-cinnamaldehyde solution (1%) was added. The volume was made up to the mark with CH_3OH-H_2SO_4 solution.

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