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THE SYNTHESIS OF 2-AMINO FURAN FROM A NITRILE BEARING ACTIVE METHYLENE AND α–HYDROXYKETONE AND INVESTIGATION OF ITS PROPERTIES

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ABSTRACT

In this study substituted heteroaromatic amines were synthesized by a cyclisation reaction achieved by means a special base catalysed cyclisation reaction, using α-hydroxy ketone and active methylene compounds. The effect of substituent in both the product and the Schiff's base obtained by the condensation of the product with salicylaldehyde or β-hydroxy-α naphthaldehyde was investigated by determining their UV, IR, HNMR characteristics and PKa values.

INTRODUCTION

There are many studies about the synthesis of heteroaromatic amines from nitriles bearing active methylene in the literature. The hetero aromatic amines such as substituted 2 amino pyrrole Gewald, 1961 substituted 2-amino thiophene Gewald, 1961 and 2-aminofurane Gewald, 1961 synthesized by Karl Gewald et al. are some of those compounds mentioned above. The compound in which we are interested in our study is the last one mentioned above.

RESULTS AND DISCUSSION

The purpose of this study was to synthesise substituted 2-aminofurane by placing furyl groups to the 4-and 5-positions of the substituted heteroaromatic ring, using a special Knoevenagel 1898, conden-

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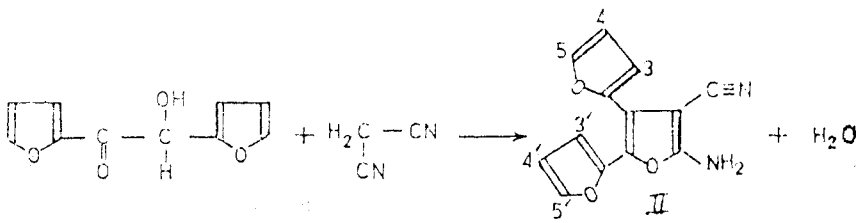
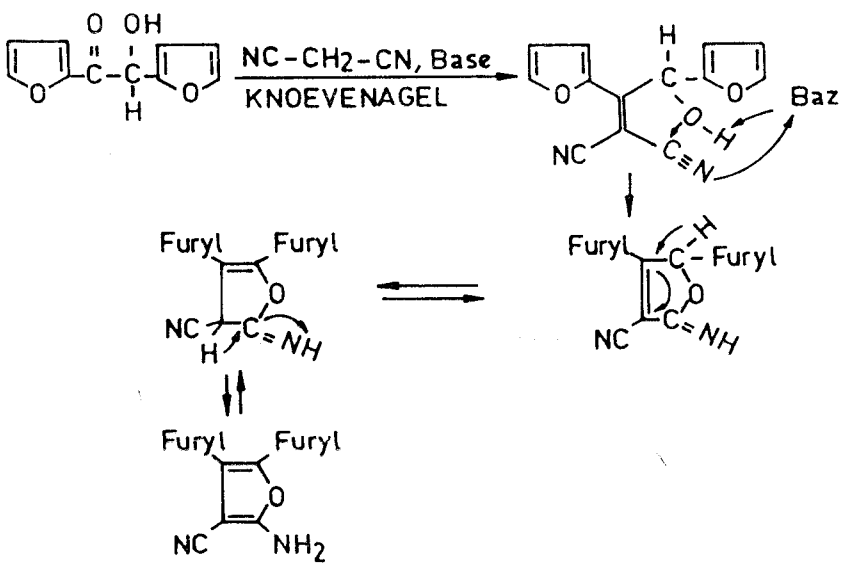
sation reaction; investigate the effect of substituent upon the basicity and the UV, IR, HNMR characteristics of the compound; find their structure by means of instrumental techniques, and determine how these effects and charecteristics vary in the Schiff's bases obtained by the condensation of this compound with salicylaldehyde and β-hydroxy- α-naphtaldehyde. The heteroaromatic compound synthesized in this study was 2-amino-4,5-difuryl-3-cyanofuran (II). Malonic acid dinitrile, furoin and diethylamine were used as active methylene compound, α-hydroxy ketone and base catalyst respectively (Eq. 1).



Equation 1

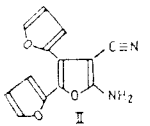
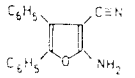
Mechanism of the reaction:



In order to investigate the effect of substituents in this sybstituted heteroaromatic amine mentioned above, 2-amino-4,5 di phenyl 3 cyanofuran (I) (GEWALD, 1966) which has electron withdrawing phenyl proups at its 4-and 5-positions, was used in our synthesis-2-amino-4,5-difuryl-3-cyanofuran (II) was obtained by inserting phenyl groups to the 4,5 positions of the heteroaromatic ring. When the UV spectrum of this compound is examined, one can see that the bonds correspondings to absorbtion of -NH, -C ≡ N and -NH_2 groups are higher than the ones observed for 2-amino-4,5diphenyl-3-cyano furan (I) (Table 1). This can be explained by the inductive effects of oxygen atoms in the furyl groups. The characteristics IR bands pectrum of the compound was found to be in accordance with those in the literature. This shows that the compound (II) fits the proposed structure. The results of elementary analysis are also in agreement with this structure. The HNMR spectrum of compound II taken in DMSO gives a more detailed information about the structure of the compound: The spectrum shows a complicated structure having the peaks belonging to different groups at various chemical shift values. The peak at δ = 7.80 ppm obviously belongs to NH_2protons which have the highest chemical shift δ or the lowest field value due to inductive effect of N atom. This peak does not appear alone but merges with a broad signal which appears near to H_5, H'_5 protons integration shows, the large signal at δ = 7.80 ppm corresponding two protons, belonging to NH_2protons. The doublet observed at δ = 6,85 ppm was formed by the coupling of H'_3 proton with H'_4 proton. The doublet observed at δ = 6.75 ppm is the result of the coupling of H_3 proton with H_4 proton. The H'_3 proton is expected to give higher chemical shift due its inductive effect. H'_4 proton gives a doublet of doublet (dd) at δ = 6.59 by coupling with H'_3 and H'_5 protons. H_4 proton also gives a (dd) at δ = 6.55 ppm, since it couples with H'_3 and H_4 protons. The doublet observed at δ = 7.75 ppm is due to coupling of H'_5 proton with H'_4 proton. The doublet observed for H_5 proton at δ = 7.70 ppm forms by the coupling of H_5 proton with H_4 proton. The detailed analysis of HNMR peaks confirms the structure of the compound II.

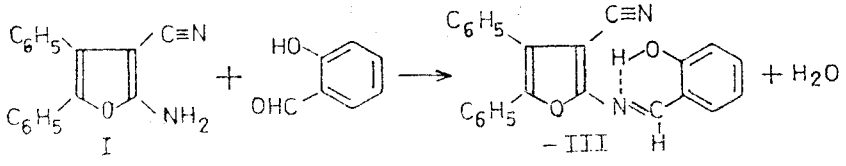
The pKa' values were found to be 18.0 after titration of compound II with tetrabutylamonium hydroxyde in anhydrous pyridine, (Table 1) The pKa' value of compound II was determined as 18.6. These pKa' values belonging to compound (I) and (II) shows that although

Table 1: The UV, IR, HNMR and pKa Values of Substituted heteroaromatic amines

Compound	pK'_a	UV λ_{max} nm(log ε)	IR(KBr)			HNMR($CDCl_3$)	
		CH_3OH	C≡N	NH	NH_2	NH_2	Heteroarom.
 II	18,0	C_2H_5OH 230,5,00), 261(5,05),335(5,02	2200	3440-3315	1650	(DMSO) 7,8(2H), 6,85(d)H_3' 6,75(d)H_3 , 6,59(dd)H_4' 6,55(dd)H_4 , 7,75(d)H_5', 7,70(d)H_5	
 I	18,6	228(4,13), 270(4,00) 320(4,09)	2210	3490-3400	1650	4,9(2H), 7,90-7,17 (m) fenil. 3,78(H)	

the compounds have the same heteroatoms the difference in the resonance and inductive effects of phenyl and furyl substituents slightly change the basic power of the compounds (0.6 pKa unit). One can easily see that the inductive effects in II are found at lower value (Handbook Chem. Physis, 1973) This shows that furyl groups have much more electron withdrawing effect than phenyl groups.

In this study we emphasized the changes in the substituent effects and the UV, IR, and HNMR characteristics, after the formation of Schiff's bases. For this purpose four Schiff's bases, the condensation products of amines I and II with salicylaldehyde and β-hydroxy α naphthaldehyde, were prepared and the changes in these effects were investigated. The condensation product of 2-Amino-4,5-diphenyl-3-cyano furan (I) with salicylaldehyde is 2-salicylidine-amino-4,5-diphenyl-3-cyano furan (III). (Eq. 2)

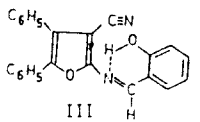
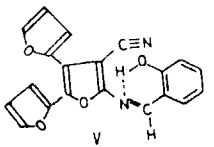


Equation 2

The batochromic effects of salicylaldehyde and furan ring carying two aromatic substituent in this schff's base causes the conjugation of aromatic groups and shifts the absorbtion to higher wavelengths There are π-π*transition and oxochromic effects in this compound. These observations show that the substituent effect increases the batochromic effect and deepends the conjugation. When the IR spectrum is examined, the NH_2 band observed at 1650 cm^{-1} for compound I (Table 1) shifts to 1640-1550 cm^{-1} by the formation of a Schiff's base (look Table II). These results also confirm that the conjugation gets deeper. When the HNMR (in $CDCl_3$) spectrum is examined there appear multiplets belonging to phenyl group at δ = 7,38-9,68 ppm.

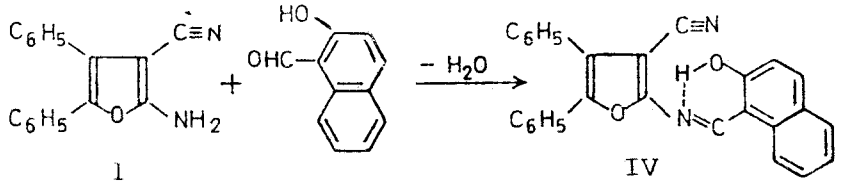
The azomethine proton gives a singlet peak at δ = 8.76 ppm. The carbon atom to which proton of this group is attached, neighbours the nitrogen atom. The appearance of this peak at high chemical shift values is expected, since this proton is not subjected to shielding

Table 2: The UV, IR, HNMR and pKa' Values of Salicylaldehyde Schiff's bases

Compound	pK'_a	UV($CH_3COOC_2H_5$)	IR(KBr)	HNMR($CDCl_3$)
		λ_{max}nm (log∈)	OH |-C≡N-|, C=N-	OH |H-C=N-|Arom. ve Hetero arom. halka
 III	14,2	404(4,55) 281(3,31)	3500-3300 2225 1600-1550	11,13(s) 8,76(s) 7,38-6,68(m) fenil
 V	14,3	430(4,27) 299(4,46)	3500-3300 2200 1560-1540	11,60(s) 8,70(s) fenil, furan

due to inductive effect of nitrogen atom. The integration shows only 1 proton. This confirms the singlet peak which appear at δ = 8.76 ppm belongs to azomethine group. The singlet peak corresponding to 1 proton at δ = 11.13 ppm belogs to OH proton. The azomethine group is ortho to OH and these causes the formation of an intra molecular hydrogen bond between the hydrogen and the nitrogen (Friedman, 1961) The peak at δ = 11.13 ppm disappears in the HNMR spectrum, after the trteament of this sample with D_2O. This confirms that this peak definitely belongs to OH proton. The pKa′ for the Schiffs base 2-salicylidene-amino 4,5 diphenyl-3-cyano furan III was found to be 14.2 after the potentiometric tiration of this Schiff's base with tetrabutylammuniumhydroxide in pyridine. The pKa′ values for salicylaldehyte and amine (I) (2-amino 4,5 diphenyl 3-cyano furan) were determined as 14.2 and 15.0 respectively. The same value for salicylaldehyde was 15.0 and 18.6 for amine I (2-amino 4,5 diphenyl-3-cyano furan) (Table 1 and 2). This observations indicate that the basicity of amine nitrogen decreases (due to decrease in the electron density on the nitrogen atom) and the acidity of aldehyde increases. All the electrons on the compound are withdrawing by the inductive and resonance effects. Therefore substituents increase the acidity of aldehyde and decrease the the basicity of nitrogen group during the formation of Schiff's bases.

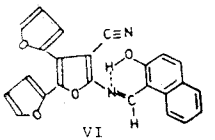
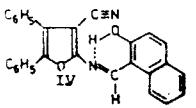
The substituents deepen the conjugation (Table 3) and the inductive and reasonance effects of the substituent decrease the electron density on the nitrogen atom in the schiffs base [2- (β-hydroxy-α-naphtylidene)-amino-4,5 diphenyl-3- cyano furan] (IV) formed by the condensation of the same amine (I) with β-hydroxy-α-naphthaldehyde (Eq. 3).



I IV

Equation 3

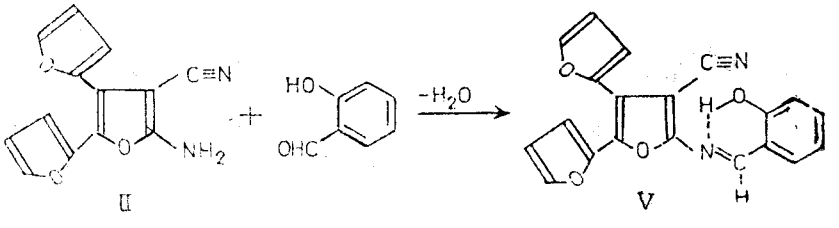
Table 3: The UV, IR, HNMR and pKa' Values of β-Hydroxy-α-naphthaldehyde Schiff's Bases

Compound	pK'_a	UV($CH_3COOC_2H_5$)		IR(KBr)			HNMR($CDCl_3$)	
		λ_{max} nm	(log∈)	OH	-C≡N-	-C=N-	OH δ ppm	H-C=N-
 VI	12,3	468 nm 458	4,26 4,27	3500-3300	2220	1600-1450	12,5(s) 6,58H_3,H'_3 8,20-6,85(m)	8,53(s) 7,4(m)H_5,H'_5 7,5(m) naftalin halkası
 IV	12,5	455 252	4,29 4,28	3500-3300	2225	1610-1540	11,73(s) 8,25-7,30(m) naftil ve fenil	9,80(s)

When the IR spectrum of this compound is examined same characteristic bands observed in compound III are seen. The difference between the compound IV and compound III is the presence of a naphthalene ring. The bands belonging to aromatic, nafthalalene and furan rings merged together in IR spectrum. The HNMR spectrum of compound IV in $CDCl_3$ gives multiplets belonging protons of naphthyl and phenyl groups, which are not observed in the spectrum of compound III. The singlets observed at $\delta = 9.80$ ppm and $\delta = 11.73$ ppm belong to azomethine and OH protons.

Therefore the spectrum observed for compound III fits the structure proposed for this compound. The pKa′ value for 2-(β-hydroxy-α naphtylidene) -amino-4,5-diphenyl 3-cyano furan (IV) was found to be 12.5. If one takes the account that the pKa′ value β-hydroxy-α naphthaldelyde is 13.4 one concludes that aldehyde group increases the acidity. This results is in agreement with the case that naphtyl groups are much more acidic. Therefore it becomes clear that the electron density on nitrogen is decreased by the substituents on the aromatic amine ring and the ring effect of the aldehyde group after the formation of a Schiff's base from compounds III and IV.

In the Schiffs base 2-salicylidene-amino-4,5-difuryl 3-cyanofuran (V) formed by the condensation reaction of 2 amino-4,5-difuryl-3-cyano furan (II) in which the ring is substituted with two furyl rings at 4 and 5 positions and salicvlaldehyde (Eq. 4), the absorption

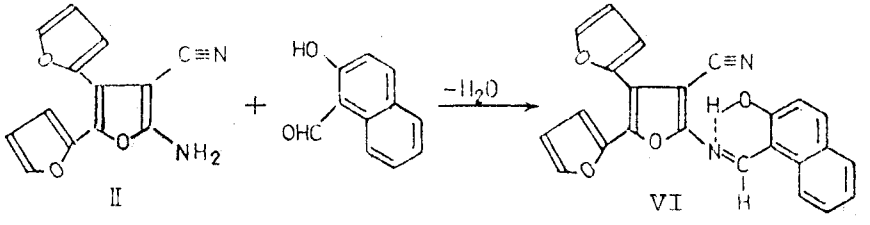


Equation 4

shifts to maximum wavelength of the chromophore, (i.e. the higher wavelength). In the compound (V) where 4,5-diphenyl groups in compound III are replaced with difuryl groups, the conjugation gets even deeper (Table 2). The effect of this deep conjugation is clearly seen in IR spectrum. The band observed at 2225 cm^{-1}belonging to -C ≡ N at the 4-position of 2 aminofuran ring of compound III, appears at 2200 $cm^{-1}$for compound V. The singlet peak of azomethine

groups in HNMR spectrum at $\delta = 8.70$ ppm is seen at highly different chemical shift values compared seen at highlt different chemical shift values compared with the Schiff's base substituted with phenyl groups (Table 2). The singlet peak observed for OH proton of compound III at $\delta = 11.14$ ppm. shifts to lower field or higher chemical shift value ($\delta = 11.60$ ppm) for compound V. This observation indicate that the inductive effect of oxygen atoms in the furyl rings suppresses the resonance effect of phenyl rings in compound III. The pKa' value for Schiff's base V was found to be 14.3 by titrating it with tetrabutylammonium hydroxide. This value indicates that the acidity of salicylaldehiyde is increased by the formation of Schiff's bases. But the acidity of 2 salicylidene-amino 4,5-diphenyl-3-cyano furan (III) Schiff's base increases and its basicity decreases (pKa' = 14.2) compared with compound V. The reason for that can be explained by the suppression of inductive effect of oxygen atoms in furan rings in compound V and by the resonance effects of phenyl groups in compound III.

The condensation of amine II and β-hydroxy naphthaldehyde gives 2- (β-hydroxy-α-naphtylidene amino 4,5-difuryl-3-cyano furan (VI) Schiff's base (Eq. 5).



Equation 5

The effects of substituent upon the characteristics mentioned before, during the formation of this Schiff's base are not different to those observed for Schiff's base IV. The acidifying effects of naphthyl ring is clearly observed in 2- (β-hydroxy-α-naphthylidene-amino 4,5-difuryl-3-cyano-furan (VI). While pKa' value for compound IV was 12.5 the same value was found to be 14.3 for compound (V) and 12.3 for compound (IV). Therefore there is 0.2 pKa' difference compared with the phenyl substituted compound.

EXPERIMENTAL

2-Amino-4,5 Difuryl-3-Cyano-furan (II)

19.2 g (0.10 mol) of furoin, 8.5. g (0.13 mol) malonic acid dinitride and 30 ml of purified dimethyl formamide are mixed with a magnetic stirrer in a three necked 250 ml flask. Then 5 ml of diethylamine is added into this dropwise at room temperature. The temperature of the mikture increased to 40°C after this addition then it is cooled down to room temperature in a cold water bath and kept at room temperature for 24 hours without stirring. The dark red-brown reaction mixture is poured into water which has the twice the volume of the original mixture by stirring constantly with a magnetic stirrer. The resulting precipitate is kept for a while for the completion of the precipitation and filtered by suction, it is then washed with water, dried in oven and recrystallized twice from methanol. The product obtained was 19.93 g (0.083 mol) and has a m. p of 190°C. The yield was 83 %. It is insoluble in water, alcohol and ether but soluble in chloroform and acetone.

Elemental Analysis:

Calculated (%) C 65.00 H 3.33 N 11.66

for $C_{13}H_8N_2O_3$

Found (%) C 64.83 H 3.48 N 11.15

UV $(C_2H_5OH)\lambda_{max}$(nm) / loge 230 (5.00), 2.61 (5.05), 335 (5.02)

IR (KBr) $\upsilon_{max}(cm^{-1})$ 3440–3315 (N-H), 1650 (NH_2), 2210 (C ≡ N)

HNMR (DMSO) (ppm) δ 7.80 (2H), 6.85 d (H'_3), 6.75 d(H_3) 6.59 dd (H'_4), 6.55 dd (H_4) 7.75 d (H'_5) 7.70 d (H_5)

pKa' 18.0

(Table 1)

PREPARATION OF NEW 2-HYDROXY HETEROAROMATIC SCHIFF'S BASES

GENERAL PROCEDURE

0.01 mol of substituted heteroaromatic amine is dissolved in absolute alcohol in a 250 ml round bottom flask in hot condition.

Then 0.01 mol of soap solutions of salicylaldehyde of β-hydoxy α-naphthaldehyde in absolute alcohol is added to this mixture and the resulting mixture is refluxed for two hours. The crystals seperated after cooling down the solution are filtered out, dried in oven and recrystallized from absolute ethanol.

The four Schiff's bases investigated in this study were prepared by the method described above. The properties and the experimental results obtained for each Schiff's base are given under its name.

CYANO FURAN ALDİMİNES

2-Salicylidene-amino-4,5-diphenyl-3-Cyano Furan (III)

The orange coloured needle shaped crystals formed from 2-amino 4,5 diphenyl 3-cyano-furan (I) has a melting point of 197°C. The product was 6.3 g (0.017 mol) and the yield was 69 %. The crystals are insoluble in water and alcohol, but soluble in chloroform.

ELEMENTAL ANALYSİS:

Calculated for $C_{24}H_{16}N_2O_2$(%)	C 79.12 H 4.38 N 7.68
Found	C 79.00 H 5.00 N 7.46
UV ($CH_3COOC_2H_5$)λ_{max}nm(loge)	404 (4.55) 281 (3.31), 3,52.10^{-4}M
IR (KBr) $\upsilon\upsilon_{max}cm^{-1}$	3500–3300 (OH), 2225 (C ≡ N) 1600–1550 (C = N)
HNMR ($CDCl_3$); δ(ppm)	11.13 s (OH), 8.76 s (H—C=N) 7.38-6.68 (phenyl multiplies)

The pKa' value found by titrating it with TBAH in pyridine is 14,2 (Table 2).

2-(β-hydroxy-α-naphthylidene)-amino-4,5 diphenyl 3-cyano furan (IV).

The melting point, the yield and the % yield of the red coloured crystasl formed from the reaction of amine I with β-hydroxy-naphthaldehyde is 219°C, 8.24 g (0.020 mol) and 80 % respectivel. The crystals are insoluble in water and alcohol but soluble in the chloroform and ethylacetate.

ELEMENTAL ANALYSİS:

Calculated (for $C_{28}H_{18}N_2O_2$) (%)	C 81.16 H 4.34 N 6.76
Found (%)	C 81.26 H 3.99 N 6.51
UV ($CH_3COOC_2H_5$)λ_{max}nm(loge)	455 (4.29), 252 (4.28), 2.5×10^{-5}m
IR (KBr) $\upsilon_{max}(cm^{-1})$	3500–3300 (OH), 2225 (C ≡ N) 1610–1540 (C = N)
HNMR ($CDCl_3$) (ppm)	11.73 (s) (OH), 9.80 (s) (H-C=N) 8.25-7.30 (m) (phenyl-nafthyl)

pKa′= 12.5 (Table 3)

2-Salicylidene-amino-4,5-difuryl-3-cyano-Furan (V)

The red-brown needle shaped crystals formed by the reaction of 2-amino-4,5-difuryl-3-cyano furan (II) with salicylaldehyde, have a melting point of 177°C, product yield of 3 g (0.008 mol) and yield of 87 %. The crystals are not soluble in water, alcohol and ether but soluble in chloroform and ethyacetate.

ELEMENTAL ANALYSİS:

Calculated for ($C_{20}H_{12}N_2O_4$) (%)	C 69.76 H 3.48 N 8.14
Found (%)	C 69.55 H 3.20 N 8.18
UV ($CH_3COOC_2H_5$)λ_{max}nm(loge)	430 (4.27), 2.99 (4.46), 2.44×10^{-5} M
IR (KBr) $\upsilon_{max}(cm^{-1})$	3500–3300 (OH), 2200 (C ≡ N) 1560–1540 (C = N)
HNMR ($CDCl_2$) (ppm)	11.60 (s) OH, 8.70 (s) (H-C = N)

pKa′= 14.3 (Table 2)

2-(β-hydroxy-α-naphthylidene)-amino-4,5-difuryl-3-cyano-furan (VI)

The melting point, the product yield, and the yield of the dark red needle shaped crystals are 210°C, 2.8 g (0.007) mol and 72 % respectively. The crystals are insoluble in water, alcohol and ether and slightly soluble in chloroform and ethyl acetate.

ELEMENTAL ANALYSİS:

Calculated (for $C_{24}H_{14}N_2O_4$) (%)	C 73.37 H.3.55 N 7.10
Found (%)	C 72.95 H 3.46 N 7.12
UV ($CH_3COOC_2H_5$)λ_{max}nm logε	468 (4.26), 458 (4.27) 327 (4.21), 265 (4.25) 2.5 x 10^{-5}M
IR (KBr) $\upsilon_{max}(cm^{-1})$	3500-3300 (OH), 2220 (C ≡ N) 1600-1450 (C = N)
HNMR ($CDCl_3$) (ppm)	12.5 (s) (OH), 8.53 (s) (-H-C=N) 8.20-7.50-6-58 (m) (furyl, nafthyl

pKa' = 12.3 (Table 3).

THE APPARATUS USED DURİNG THİS STUDY

Hitachi model 200-2Q Double Beam UV-VIS spectrophometer, Perkin-Elmer-337 IR spectrophometer, Varian-T-60A, 60 mHz and Perkin-Elmer R 32 90 HNMR spectrophometer, Orion 801 A pH meter and elecrocapilary melting point determination instrument.

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