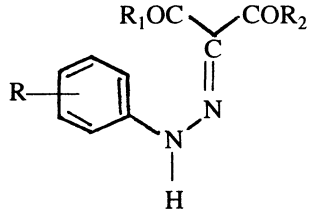
# Studies on Arylhydrazones, Part IX: Action of Perchloric Acid-Formic Acid on Diethyl Mesoxalate Phenylhydrazones, 2,3-Dioxo-2-(Phenyl-hydrazono)Butyrate and Cyano Phenylhydrazones.

N. PRASAD*, R.M. PRASAD, A. SAHAY†, A.K. SRIVASTAVA and J. PRASAD‡
*Department of Chemistry*
*Bihar University, Muzaffarpur-842 001, India*

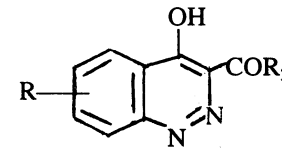
The action of strong acids such as perchloric acid, hydrochloric acid and sulphuric acid on several arylhydrazones (prepared by coupling aryldiazonium salts with diethyl malonate, ethyl aceto-acetate and cyanoacetic ethyl ester) has been studied. It has been found that even under a variety of reaction conditions hydrolysis of diethyl mesoxalate phenylhydrazones proceeds only up to the half ester stage whereas that of ethyl-2,3-diaxo-2-(phenyl-hydrazono) butyrate yields the corresponding keto acid. Ethyl cyano-(arylhydrazono) acetates resist such hydrolysis.

## INTRODUCTION

Several unfructuous attempts were made to cyclise the hydrazones (I) to 4-hydroxy cinnolines (II) either by heating[1] or by using various acidic reagents such as conc. $H_2SO_4$, a mixture of conc. $H_2SO_4$ and acetic anhydride[2], polyphosphoric acid, phosphorus oxychloride, anhydrous hydrofluoric acid, fluorosulphonic acid and boron trifluoride-ether complex.[3] In all these attempted




(I)



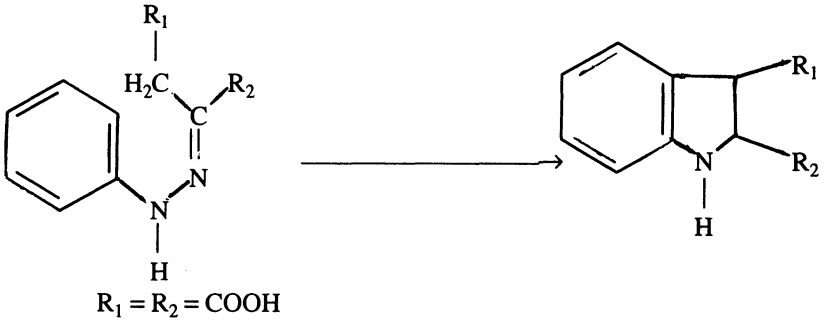

(II)

R = H, $CH_3$, Cl, Br, $NO_2$, –OMe etc.
$R_1 = R_2 = OEt$.
$R_1 = OEt$, $R_2 = CH_3$.
$R_1 = OEt$, $COR_2$,—C≡N.

†Department of Chemistry, S.R. Sandhay College, Raja Bazar, Patna-800 014, India.
‡Department of Chemistry, M.S. College, Motihari, India.

cyclisations either the starting material was recovered unchanged or intractable tarry material was obtained. Cyclisation of (I, $R_1 = Cl$, $R_2 = OEt$) to 3-carbethoxy-4-hydroxy cinnoline (II, $R_2 = OEt$) under Friedel Craft reaction condition was also unsuccessful except in the case of (I, $R = p\text{-}CH_3$, $R_1 = Cl$, $R_2 = OEt$) where low yield of corresponding 4-hydroxy cinnoline was obtained.[4] But N-alkylated acid chloride (I, $R_1 = R_2 = Cl$) cyclised to desired 4-hydroxy cinnolines[5] and this led them to believe that the hydrazones (I) resist cyclisation under above conditions presumably on account of the steric restriction imposed by the N=C double bond as well as of the presence of proton on the nitrogen atom of anilino group.

Indolization of phenylhydrazones (III) using various acid catalysts as cyclising agent has been known for a long time.[6,7] Formic acid[8] or a formic acid-ethanol mixture[9] has been used as a potential acid catalyst in Fischer-Indole synthesis.




(III)

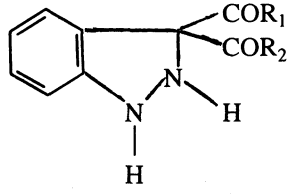
Anhydrous formic acid is a very good solvent for the hydrazones (I) dissolving them at room temp. The combination of formic acid and perchloric acid as a potent acid catalyst has not been tried on the hydrazones (I) for their cyclisation to either cinnolines or indazoles so far. We, therefore, employed this reagent under a variety of conditions with a view to cyclising the hydrazones (I) to 4-hydroxy cinnolines and/or indazoles. Contrary to our expectations, the reaction took an entirely different course and our findings are described in this communication.

## EXPERIMENTAL

The arylhydrazones were prepared by the method available in literature. The arylhydrazone (0.003 mol) was dissolved in anhydrous formic acid (50 ml) and perchloric acid (3 drops) was added to it. The yellow colour of the hydrazone solution was changed to deep orange red on addition of the catalytic amount of perchloric acid. After seven days at room temperature a yellowish solid was separated out from the reaction mixture, which was removed by filtration and recrystallised from aqueous ethanol. Purity of the product was ascertained by TLC examination.

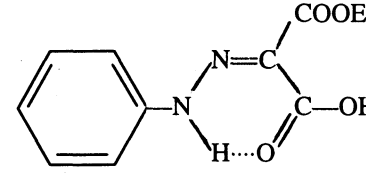
## RESULTS AND DISCUSSION

The hydrazone (I, $R_1 = R_2 = OEt$), which is conveniently prepared by coupling benzenediazonium chloride with diethyl malonate, when dissolved in anhydrous formic acid and treated with catalytic amount of perchloric acid either at room temperature or at 60–70°C gave nearly quantitative yield of pale yellow crystals (in case when R = H) having m.p. 115–6°C. This product gives wine-red colour with $FeCl_3$ and dissolves in $NH_4OH$ and $NaHCO_3$ solutions (without effervescence) from which it precipitates out on acidification with dil. HCl. The pale yellow compound could be II ($R_2$=OH) or the indazole derivative (IV) resulting from cyclization of the hydrazone (I, $R_1 = R_2 = OEt$).

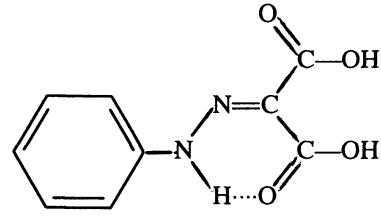


$R_1 = R_2 = OH$
$R_1 = OH, R_2 = OEt$

(IV)



(V)



(VI)

Alternatively, partial or complete hydrolysis of the hydrazone (I, $R_1$=$R_2$=OEt) could result in V and VI respectively. The product is partially hydrolysed product (V) which is confirmed by comparing with known compounds and spectra such as IR and $^1H$ NMR. The physical constants and analytical data of other derivatives (R = $CH_3$, Cl, Br, $OCH_3$, $NO_2$ etc.) of partially hydrolysed product (half ester V) of hydrazones (I, $R_1 = R_2 = OEt$) are listed in Table 1.

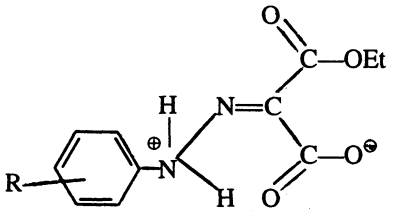
Analysis of the product corresponds to mol. formula $C_{11}H_{12}N_2O_4$ (if R = H). Its characteristic IR absorptions at around 1640 $cm^{-1}$ (C=N stretching), 1710 $cm^{-1}$ (ester >C=O stretching), 1410 $cm^{-1}$ (—C(=O)—O stretching) and a series of relatively weak bands at 3020 $cm^{-1}$, 3045 $cm^{-1}$ and 3120 $cm^{-1}$ ($>\overset{+}{N}H_2$) showed that the pale yellow compound was the partially hydrolysed product—

half ester (V) in the form of a zwitter ion (VII)[10,11] The structure was also corroborated by $^1$H NMR evidences. It showed resonances at around δ 4.45 (q) (solvent dependent) for two methylene protons and at δ 1.8 (t) in $CDCl_3$ (δ 1.3 in DMSO $d_6$) for three methyl protons. Resonance at δ7.4 (m) (δ 7.2 (m) in DMSO $d_6$) could be assigned to five aromatic protons. The phenyl

TABLE 1
PHYSICAL CONSTANT AND ANALYTICAL DATA OF ETHYL HYDROGEN MESOXALATE PHENYLHYDRAZONES (I, $R_1 = R_2 = OEt$, $R_2 = OH$)

| Compound/ Colour | m.pt. (°C) | % yield | % Found (Calcd.) | | |
|---|---|---|---|---|---|
| | | | N | C | H |
| R = H (Pale yellow) | 115–6 | 75 | 11.41 (11.86) | 55.01 (55.93) | 5.23 (5.08) |
| R = *p*-$CH_3$ (Golden yellow) | 141 | 80 | 10.89 (11.2) | 56.93 (57.6) | 5.21 (5.6) |
| R = *p*-Cl (Pale yellow) | 167 | 88 | 10.71 (10.35) | 48.03 (48.798) | 3.94 (4.06) |
| R = *p*-Br (yellow) | 177–9 | 90 | 8.12 (8.88) | 41.04 (41.9) | 3.86 (3.49) |
| R = *p*-$NO_2$ (yellow) | 203–4 | 90 | 15.54 (14.94) | 48.2 (46.975) | 4.54 (3.91) |
| R = *o*-MeO (Deep yellow) | 167–8 | 85 | 9.95 (10.52) | 53.9 (54.13) | 5.06 (5.26) |
| R = *o*-$NO_2$ (Yellow) | 145 | 88 | 14.67 (14.94) | 47.01 (46.975) | 3.14 (3.91) |
| R = *o*-Cl (Yellow) | 111–2 | 90 | 10.13 (10.35) | 47.2 (48.79) | 4.54 (4.06) |

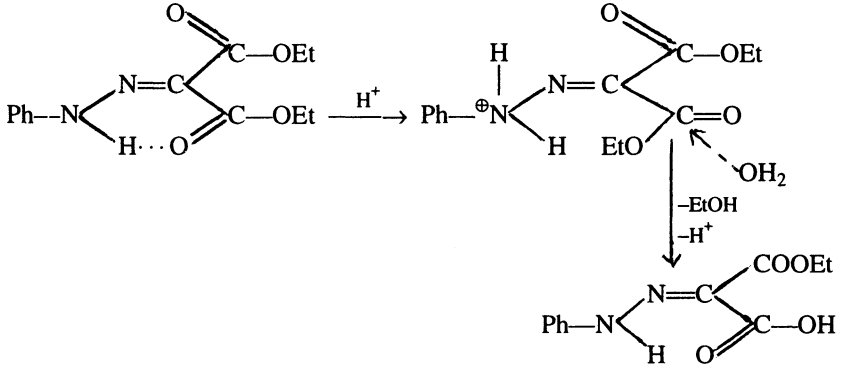
amino proton in these type of unchelated compound resonates between δ5–7 (solvent dependent). However, when intramolecular H-bonding occurs the NH proton suffers a characteristic deshielding[12] and observed at around δ 12. In present case, the characteristic NH signal is observed at δ 13.3 in DMSO $d_6$. It has been observed that δNH at 13.3 in DMSO $d_6$ shifts to δ 13.1 in $CDCl_3$. The resonance at δ 9.37(s) is assignable for single carboxylic proton.




(VII)

Finally the identity of the compound was established by comparing it with an authentic sample of ethyl hydrogen mesoxalate phenylhydrazone (V) prepared by controlled alkaline hydrolysis of the hydrazone (I, $R_1 = R_2 = OEt$).[13]

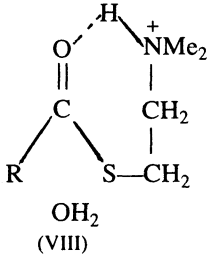
Ethyl hydrogen mesoxalate phenylhydrazone (V) is the sole product from the acid catalysed hydrolysis of the hydrazone (I, $R_1 = R_2 = OEt$) under different reaction conditions, *e.g.* HCl in formic acid or 10% aq. $H_2SO_4$ in acetic acid. Complete hydrolysis of the hydrazones (I, $R_1 = R_2 = OEt$) to mesoxalic acid phenylhydrazone (VI) was not observed either by increasing the amount of acid or the reaction time or temperature. The partial hydrolysis of ester group commands explanations. The proposed mechanism of this selective hydrolysis demonstrates the profound role of acid catalysts like perchloric, hydrochloric or sulphuric acids in the protonation of nitrogen atom of anilino group (Scheme-1). Development of deep colour ranging from violet to intense blood red of the solution on addition of acid catalyst to formic acid solution of the hydrazone (I, $R_1 = R_2 = OEt$) indicates that the protonation at nitrogen of anilino group nitrogen attached to the aromatic nucleus has a great tendency to undergo protonation and protonation at nitrogen in phenylhydrazone derivative in acetic



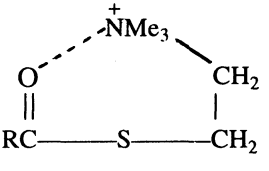

Scheme 1

acid-perchloric acid combination has previously been observed.[14] Nucleophilic attack of water on the *cis* ester carbonyl, followed by elimination of alcohol, affords the half ester.

The protonated amino group is a particularly effective intramolecular acid catalyst *e.g.* the rate of hydrolysis of 2-N,N-dimethylaminoethyl thioacetate (VIII) in acid solution is about 240 times faster than that for the ester (IX) which lacks the acidic proton[15, 16]. A similarly caused, but smaller (about 20 fold) rate is found



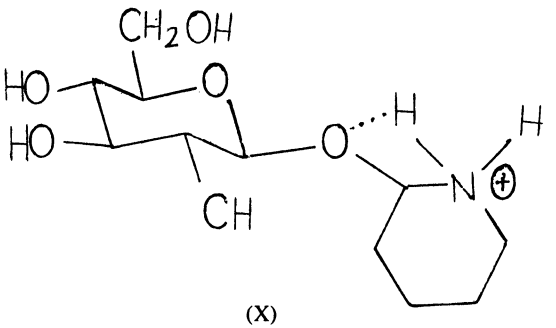

(VIII)




(IX)

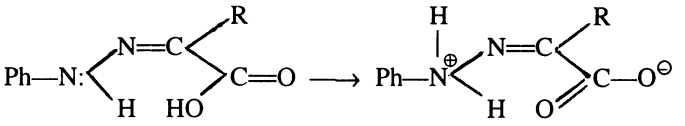
in the hydrolysis of 2-N,N-dimethylamino ethyl benzoate[17]. The rate of acid catalysed hydrolysis of 2-pyridyl glucoside (X) is much higher and 2-pyridazinyl glucosides are hydrolysed even faster than 2-pyridyl glucosides.[17]

There could be at least three possible explanations for the inability of the hydrazone (I, $R_1 = R_2 = OEt$) to be hydrolysed to mesoxalic acid phenyl-hydrazone (VI). Firstly, the carbethoxy group resisting hydrolysis in *trans*



(X)

disposed to the anilino group and hence lacks the anchimeric assistance of the protonated amino group towards such hydrolysis. Secondly, the half ester (V), being only partially soluble in formic acid or acetic acid precipitates out making the medium heterogeneous rendering further hydrolysis difficult. Thirdly, the half ester may exist in the dipolar ion form (VII) which restrains hydrolysis of the remaining carbethoxy group in acid solution due to electrostatic forces acting between the positive nitrogen and the carboxylate anion.



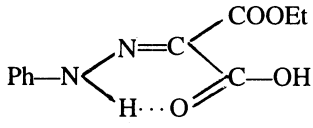
(XI) (XII)

It has been reported that the hydrazones of α-keto acids (XI) which are prepared either by the condensation of arylhydrazines with α-keto acids or by Japp-Klingemann reaction exist in the dipolar ion (XII). On the basis of easy cleavage of N—N bond leading to α-amino acids by hydrogenation under neutral conditions[18], it is to be noted that alkaline hydrolysis of the hydrazone (I, $R_1 = R_2 = OEt$) is facile, much faster and affords di acid(VI).

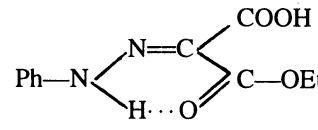
The m.p. of ethyl hydrogen mesoxalate-*o*-chloro-phenylhydrazone (I, R = *o*–Cl, $R_1$ = OEt, $R_2$ = OH) is reported to be 63°C[19], obtained by heating ethyl mesoxalate-*o*-chlorophenylhydrazone (I, R = *o*–Cl, $R_1 = R_2$ = OEt) in acetic acid and 10% $H_2SO_4$. The product obtained in formic-perchloric acid by us has m.pt. 111–2°C. Repetition of Pelkis work[19] showed that the compound, m.pt. 63°C, was a mixture of the half-ester and the hydrazone (I, $R_1 = R_2 = OEt$, R = *o*–Cl) (TLC). However, when the reaction mixture was left for several hours

more than the reported time, the half ester having m.p. 111–2°C was obtained which did not depress the m.p.t. of our sample.

Ethylhydrogen mesoxalate phenylhydrazones could exist in (E—) (XIII) and (Z—) (XIV) forms. Further, there would be H-bonding between N—H and >C=O of carboxyl group (E-) (XIII) and >C=O of carbethoxy group (Z-) (XIV). The half ester obtained by the partial hydrolysis of the hydrazones (I, $R_1 = R_2 = OEt$) seems to be pure isomer existing in (E-) (XIII) form. In $^1H$ NMR signal triplet at δ1.8 for ester methyl and single quartet at δ 4.45 for ester methylene protons were obtained. Moreover, δN—H in $CDCl_3$ (13.1) is shielded



(XIII) (E-)



(XIV) (Z-)

by 0.2 ppm in DMSO-$d_6$ solution. It has been observed in the case of di-acid (VI) that δNH at 13.1 in $CDCl_3$ shifts to δ13.2 in DMSO-$d_6$ whereas in the case of the hydrazone (I, $R_1 = R_2 = OEt$) the shift is from δ 12.9 to δ 12.1[20]. Thus, on the basis of slight chemical shift of N—H in two solvents the half ester can be deduced to exist in (E-) form (XIII). Attempts to isomerise it into the (Z-) form (XIV) either by shining UV-light or heating or alkali treatment always failed.

Likewise ethyl-2,3-dioxo-2-phenylhydrazonobutyrate (I, $R_1 = OEt$, $R_2 = CH_3$) on treatment with perchloric acid in anhydrous formic acid afforded the keto acid (XVII) which analysed for $C_{10}H_{10}N_2O_3$ (if R = H) and its IR, $^1H$ NMR and $^{13}C$ NMR were consistent with its structure. The physical constants and analytical data of other derivatives are listed in Table 2.

TABLE 2
PHYSICAL CONSTANTS AND ANALYTICAL DATA OF KETO ACIDS
(I, $R_1 = CH_3$, $R_2 = OH$)

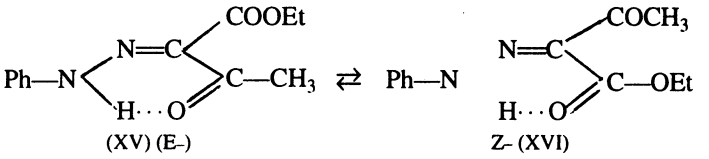
| Compound/ Colour | m.p. (°C) | % Yield | % Analysis, Found (Calcd.) | | |
|---|---|---|---|---|---|
| | | | N | C | H |
| R = H (Yellow) | 160–1 | 90 | 13.19 (13.59) | 57.78 (58.25) | 4.26 (4.85) |
| R = *p*-OMe (Bright yellow) | 170 | 85 | 12.31 (11.86) | 54.87 (55.93) | 4.61 (5.08) |
| R = *p*-Br (Yellow) | 200 | 80 | 9.67 (9.82) | 41.79 (42.10) | 3.54 (3.16) |
| R = *p*-Cl (Yellow) | 195 | 82 | 11.34 (11.64) | 49.21 (49.89) | 3.21 (3.74) |
| R = *p*-Me (Yellow) | 198–9 | 90 | 12.67 (12.727) | 59.14 (60.00) | 4.96 (5.45) |
| R = *p*-$NO_2$ (Yellow) | 194–5 | 80 | 17.12 (16.73) | 46.6 (47.8) | 3.96 (3.58) |

Again, the characteristic IR absorptions at around $1610 \pm 20\ cm^{-1}$ (C = N stretching), $1690\ cm^{-1}$ (>C = O stretching), $1415\ cm^{-1}$ (—C(=O)—O stretching) and a series of relatively weak bands at around $3010\ cm^{-1}$, $3060\ cm^{-1}$ and $3100 \pm 20\ cm^{-1}$ ($>\overset{+}{N}H_2$) showed that the compound was the hydrolysed product (keto acid) in the form of zwitter ion[10,11].

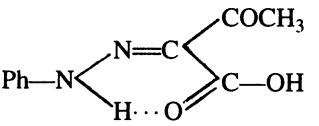
On $^1H$ NMR examination, keto acid (R = H) showed resonances at δ2.5 (d), δ7.5 (m) and δ3.5 (s) in $CDCl_3$. It showed resonances at around δ2.5 for two methylene protons. Resonances at δ7.4 (m) could be assigned to five aromatic protons. The resonance at δ9.3 (s) is assignable for single carboxylic proton.

On $^{13}C$ NMR examination, the keto acid (R = H) showed resonance at δ161, 132, 112.5, 104.5, 102.5, 99, 95 and 40 in $CDCl_3$. The first two peaks *i.e.*, δ161 and δ132 were assigned to two carbonyl C atoms, δ99 to amino C atom and δ40 to keto methyl C atom. Thus appearance of two different carbonyl groups in $^{13}C$ NMR are suggestive of different environments for these groups. The remaining peaks were assigned to six phenyl C atoms.

The concept of anchimeric assistance of the protonated group in the hydrolysis of carbethoxy group which is *cis* with respect to the amino group can also be invoked in this case. Ethyl-2,3-dioxo-2-phenylhydrazono butyrate (I, $R_1$ = OEt, $R_2 = CH_3$) can also exist in *E*- (XV) and *Z*- (XVI) forms. It has been observed




(XV) (E-) Z- (XVI)

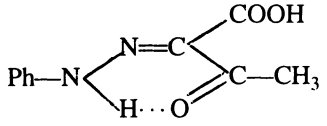



(XVII)

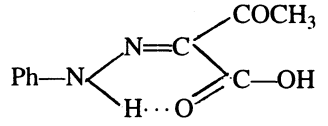
that it could be isolated in the *E*- (XV) form, but exist in equilibrium with the *Z*- (XVI) forms in solution in the ratio 70 : 30 (*E* : *Z*).[21] The *E* form (XV) of ethyl-2,3-dioxo-2-phenylhydrazono butyrate is obtained either by repeated crystallisation of the crude coupling product of benzene diazonium chloride with ethyl acetoacetate in sodium acetate buffer solution with methanol or by standing the product in dilute formic acid.

In formic acid solution equilibration takes place giving 30% of the *Z*-form (XVI) which is now readily hydrolysed in acid solution. The equilibrium is displaced and thus the whole of the ester is hydrolysed as the yield of 2,3-dioxo-2-phenylhydrazono butyric acid (XVII) is also quantitative. The hydrolysis is quite general and several nuclear substituted phenylhydrazones (I, $R_1$ = OEt, $R_2 = CH_3$) similarly afforded the keto acids in quantitative yield (Table 2).

Again the keto acid can exist in *E*- (XVIII) and *Z*- (XIX) forms.

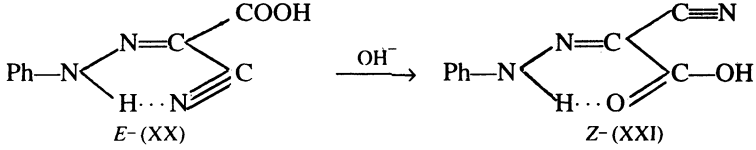


*E*-(XVIII)



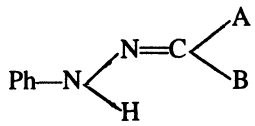
*Z*-(XIX)

The products obtained by this procedure are pure single isomers. Attempts to isomerise this pure isomer into the other form either by shining UV light or heat or alkali treatment were unsuccessful. Hydrolysis of the hydrazone (I, $R_1 = R_2 = OEt$ or $R_1 = OEt$, $R_2 = CH_3$) in boiling methanolic sodium hydroxide gave mixture of products from which pure *E*-isomers could not be separated. Crystallisation of this crude alkaline hydrolysis product always resulted in the isolation of pure single isomer identical with the keto acid obtained by direct acid hydrolysis of the hydrazone. The acids, both half esters and acid ketones seem to exist in *Z*- configuration and failure of transforming this into the *E*- form is presumably due to locking of configuration by way of either strong hydrogen bonding with the acid carbonyl or by electrostatic attraction due to inner salt. Locking of configuration by H-bonding and/or electrostatic attraction in case of cyano acetic acid phenylhydrazone (I, $R_1 = H$, $COR_2 = CN$) has been observed, since the *E*- form (XX) can easily be converted into *Z*- form (XXI) either by heating or by keeping in solvents or by alkali treatment, but the reverse could not be achieved.



*E*-(XX) *Z*-(XXI)

The envisaged anchimeric assistance of protonated amino group in preferential hydrolysis of *cis*-ester group in acid solution can also be deduced by studying the action of acid catalysts like perchloric acid, HCl or aq. $H_2SO_4$ on ethyl cyano hydrazono acetates (I, $R_1 = OEt$, $COR_2 = C{\equiv}N$). On teatment of formic acid solution of cyano hydrazones with perchloric acid, the starting material were always obtained in the pure *Z*-form (XXI). No deepening of colour of formic acid solution was observed after the addition of acid catalyst which indicated that there was no protonation at the nitrogen atom of anilino group as contrary to the evident change of colour in the case of mesoxalate hydrazone (I, $R_1 = R_2 = OEt$). In the case of the hydrazone (I, $R_1 = OEt$, $R_2 = CH_3$) the change was moderate, but in the case of cyano hydrazone (I, $R_1 = OEt$, $COR_2 = CN$) there was no change in colour indicating the lack of protonation at the N-atom of anilino group. The nitrogen of anilino group is $sp^2$ hybridised and the extent of this $\pi$-conjugation of lone pair of electrons on nitrogen depends on the nature of A and B groups. When the electron withdrawing group A or B is changed from—COOEt to >C=O to —C≡N, the nitrogen of anilino group becomes more and more $sp^2$ hybridised ($\pi$-conjugation increases) and the extent of protonation gradually



decreases. This behaviour was observed by judging the change in colour of formic acid solutions in the presence of acid catalyst. The failure of hydrolysis of the ester group in cyano hydrazones thus could be due to lack of protonation at the nitrogen of anilino group which subsequently does not provide anchimeric assistance in the hydrolysis of the ester group.

## REFERENCES


1. N.J. Leonard, S.N. Boyd and H.F. Herbrandson, *J. Org. Chem.*, **12**, 47 (1947).
2. B.P. Bangdiwala and C.M. Desai, *J. Indian Chem. Soc.*, **30**, 655 (1953).
3. H.J. Barber, K. Washbourn, W.R. Wragg and E. Lunt, *J. Chem. Soc.*, 2841 (1961).
4. H.J. Barber, K. Washbourn, W.R. Wragg and E. Lunt, *J. Chem. Soc.*, 2828 (1961).
5. _____, *J. Chem. Soc.*, 1468 (1965).
6. B. Robinson, *Chem. Rev.*, **63**, 383 (1963).
7. _____, *Chem. Rev.*, **69**, 227 (1969).
8. C.U. Rogers and B.B. Corson, *J. Am. Chem. Soc.*, **69**, 2910 (1947).
9. M.M. Kidwai, N.H. Khan and S. Saleha, *Indian J. Chem.*, **16B**, 1122 (1978).
10. R.J. Kogel, J.P. Greenstein, M. Winitz, S.M. Birnbaun and R.A. Mccallum, *J. Am. Chem. Soc.*, **77**, 5708 (1955).
11. D.N. Chaturvedi and R.A. Kulkarni, *J. Indian Chem. Soc.*, **55**, 161 (1978).
12. N. Prasad and A. Sahay, *Asian J. Chem. Rev.*, **4**, 23, 33 (1993).
13. H.J. Barber, *loc. cit.* (1961).
14. H.S. Isbell and A.J. Fatiade, *Carb. Res.*, **11**, 303 (1969).
15. Hansen, *Acta Chem. Scand.*, **12**, 324 (1958).
16. B. Capon, *Quart. Rev.*, **18**, 64 (1964).
17. Agren, Hedsten and Jonsson, *Acta Chem. Scand.*, **15**, 1532 (1961).
18. N.H. Khan and A.R. Kidwai, *J. Org. Chem.*, **38**, 822 (1973).
19. E.P. Nesynov, Besprozvannaya and P.S. Pelkis, *Zh. Organ. Khim.*, **2(77)**, 1213 (1966); *Chem. Abstr.*, **66**, 75771y (1967).
20. F. Kaberia, B. Vickery, G.R. Wiley and M.G.B. Drew, *J. Chem. Soc., Perkin Trans.*, 1623 (1980).
21. A. Mitchell and D.C. Nonhebel, *Tetrahedron*, **35**, 2013 (1979).


(*Received*: 26 August 1993; *Accepted*: 22 January 1994) AJC-770