Reactions of Some 2(1H)-pyridones Synthesized from 3,4-Methylene-dioxybenzal and 4-Nitrobenzal-p-isopropylacetophenone.

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Summary: Benzalacetophenone derivatives (1) react with ethyl cyanoacetate in the presence of ammonium acetate at 120° to give a mixture of 2(1H) pyridone derivatives (2) and ethyl nicotinate derivatives (3). The behaviour of pyridone derivatives (2) twoards electrophilic reagents e.g., dimethyl sulphate and ethyl chloroacetate, and nucleophilic reagents e.g., phosphorus oxychloride has been investigated. On the other hand, the behaviour of ethyl nicotinate derivative (3a) towards nitrogen and oxygen nucleophiles has also been discussed.

In our programme for investigation of the reactivity of α, β-unsaturated carbonyl compounds [1-5], the author sought to investigate the behaviour of the olefinic double bond activated by electron attracting and repelling groups towards base catalyzed addition of ethyl cyanoacetate as preparative method for substituted 2 (1H)-pyridones. The polar factor of these groups in the benzal moiety does not increase the additive capacity of the double linking under such conditions.

The main aim of our original work in this paper is to synthesize new pyridone and nicotinate derivatives for the sake of their biological evaluation [6]. A mixture of 3-cyano-4,6-disubstituted-2(1H)-pyridones (2) (as a major product) and ethyl 2-amino-4,6-disubstituted nicotinates (3) was obtained from the base catalyzed addition of ethyl cyanoacetate on 3,4-methylenedioxybenzal- and 4-nitrobenzal-p-isopropylacetophenone (1a and 1b) respectively. The reaction was carried out in ammonium acetate at 120°. This is a simpler method for preparing both the pyridone and nicotinate derivatives altogether.

Two routes are possible expalin the formation of compounds (2 and 3) as represented in the following chart (1):

The infrared spectra of the cyanopyridones (2) revealed ν NH at 3400 cm^{-1}, ν CH at 2940 cm^{-1}, ν C≡N at 2200 cm^{-1} and a band in the region (1500-1400 cm^{-1}) characteristic for pyridones [7]. The I.R. spectra of the ethyl nicotinate derivative (3) showed ν NH at 3440 cm^{-1}, ν CO of ester at 1737 cm^{-1} and ν C=N at 1610 cm^{-1}.

The above spectral data revealed the existence of lactam-lactim tautomerism for compounds (2), and amino-imino tautomerism for compounds (3). The predominance of pyridones (2) can be explained as follows: in conformation (A) the ester group on one asymmetric carbon lies between a group of small size (viz.H) and a group of large size (-CH=CAr NH_2) on the other asymmetric carbon which makes this

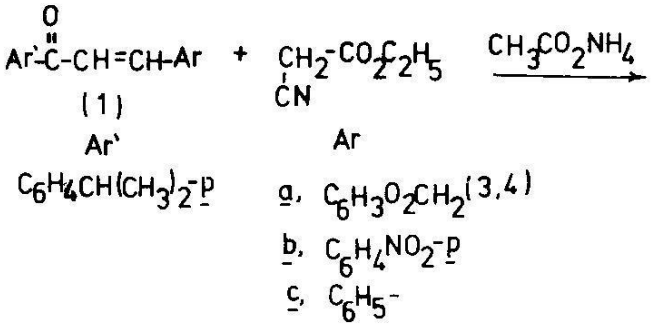
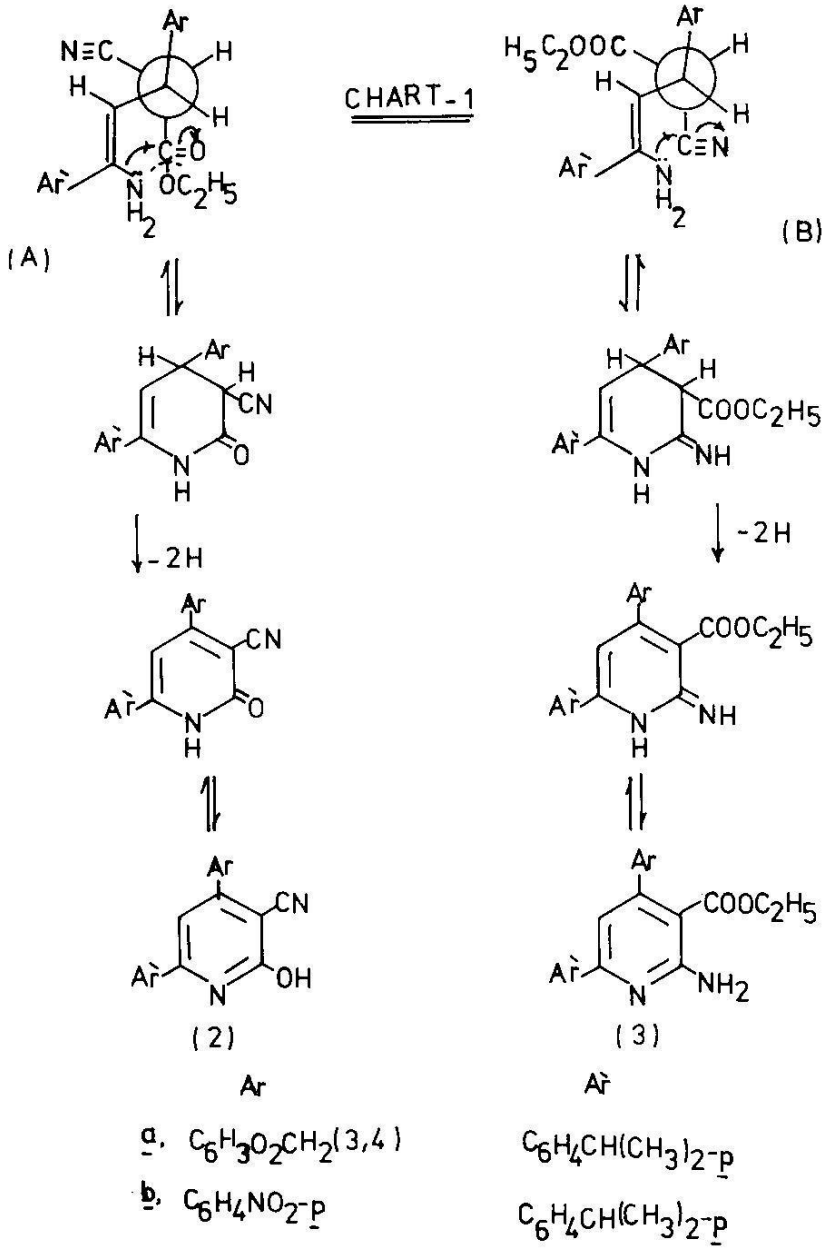

Ar-C(=O)-CH=CH-Ar
(1)
Ar'
C6H4CH(CH3)2-p
+ CH2(CN)-CO2C2H5
CH3CO2NH4
Ar
a. C6H3O2CH2(3,4)
b. C6H4NO2-p
c. C6H5-

CHART-1


(A)
(B)
-2H
-2H
(2)
(3)
Ar
a. C6H3O2CH2(3,4)
b. C6H4NO2-p
C6H4CH(CH3)2-p
C6H4CH(CH3)2-p

conformation the more stable and at the same time the preferred (lowest energy) conformation, it needs a lower activation and can undergo nucleophilic attack on the ester group by the nitrogen nucleophile more readily than conformation (B).

The existence of the lactim form in the cyanopyridnes (2a) and (2b) was proved as follows:

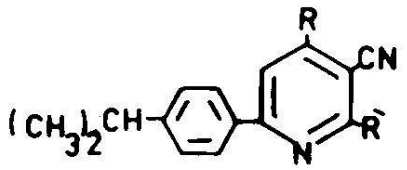
(i) Methylation of (2a) by $(CH_3)_2SO_4$ in the presence of K_2CO_3/acetone mixture gave 2-methoxy-3-cyano-4,6-disubstituted pyridine (4a). No N-alkyl derivative was obtained by this method; this may be due to the rapid interconversion of lactam form to lactim form in the presence of dry acetone and K_2CO_3 which lead to the desired product.

(ii) Similarly, (2b) reacted with $POCl_3$ affording 2-chloro-3-cyano-4, 6-disubstituted pyridine (4b).

Structure (4) was supported by the following:

(a) The I.R. spectra of (4)show ν C≡N at 2200 cm^{-1} and ν CH at 2900 cm^{-1}

(b) Compound (4b) has been reacted with aniline and gave (4c).



(4)

	R	R
a.	$C_6H_3O_2CH_2$(3,4)	$-OCH_3$
b.	$C_6H_4NO_2$-p	-Cl
c.	$C_6H_4NO_2$-p	$-NHC_6H_5$

(iii) Compounds (2a) and (2b) also react with ethyl chloroacetate in the presence of K_2CO_3/acetone mixture and gave the corresponding esters (5a) and (5b) respectively.

The I.R. spectra of the esters (5) revealed the existence of ν CO at 1735 cm^{-1}, ν C≡N at 2200 cm^{-1} and ν CH at 2940-2910 cm^{-1}.

The esters (5a) and (5b) reacted with benzaldehyde in the presence of sodium ethoxide under the Claisen reaction conditions affording ethyl α-substituted cinnamic esters (6a) and (6b) respectively.

On the other hand, the ester (5a) reacted with benzaldehyde in the presence of potassium tert-butoxide under the Stobbe condensation conditions affording the cinnamic acid derivative (7) and a small amount of the Claisen product (6a).

The mechanism presumably involves the attack of the anion derived from the ester (5a) at the carbonyl carbon of benzaldehyde, which cyclizes via a nucleophilic attack of the negatively charged oxygen at the ester carbonyl carbon, followed by the elimination of the ethoxy anion to give the intermediate β-lactone, which undergoes ring opening to give the cinnamic acid derivative (7). This reaction is analogous with our previous work [8].

The mechanism of the reaction is represented by the following Chart (2).

To explain the production of both Stobbe and Claisen products in the presence of potassium tert-butoxide (strong base), earlier [9] it has been reported that the most important factor which leads to the facile occurance of the Stobbe condensation with succinic esters in the presence of a

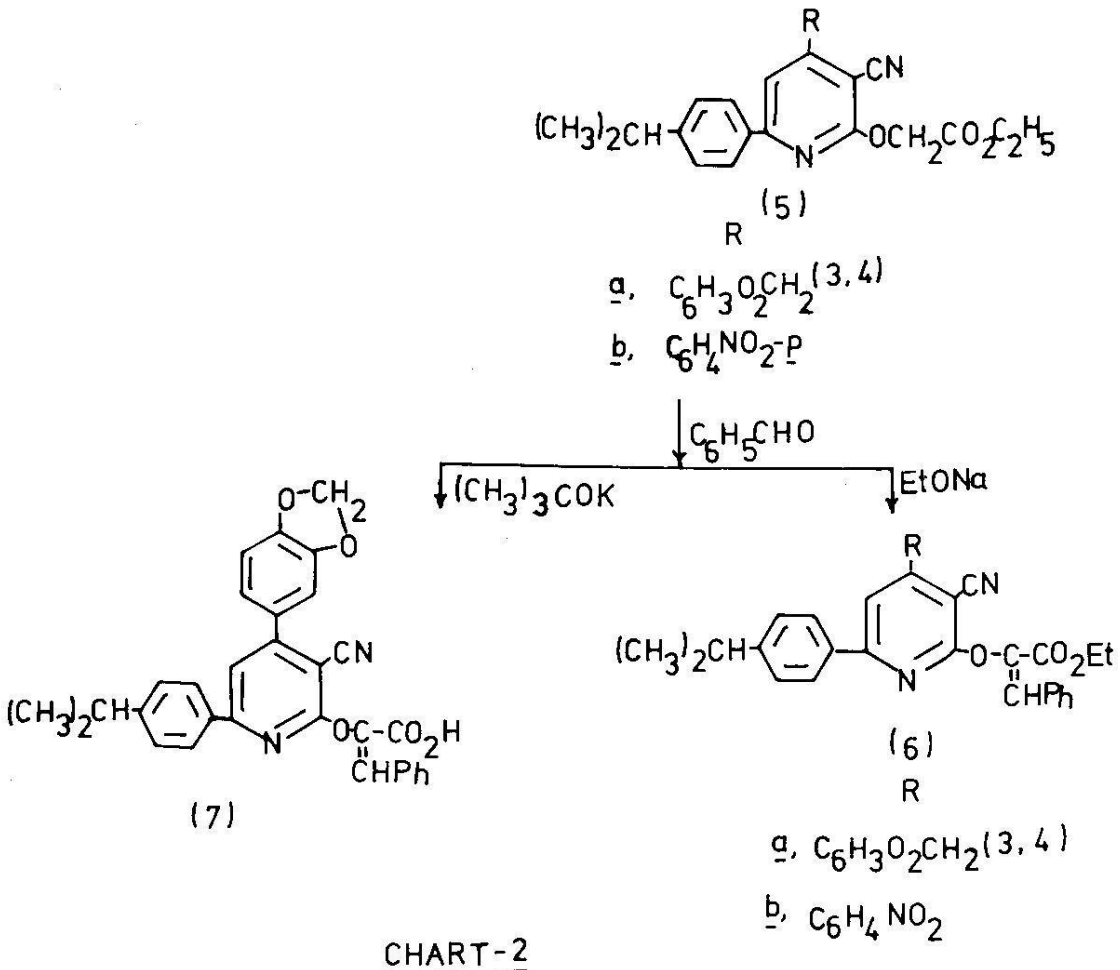
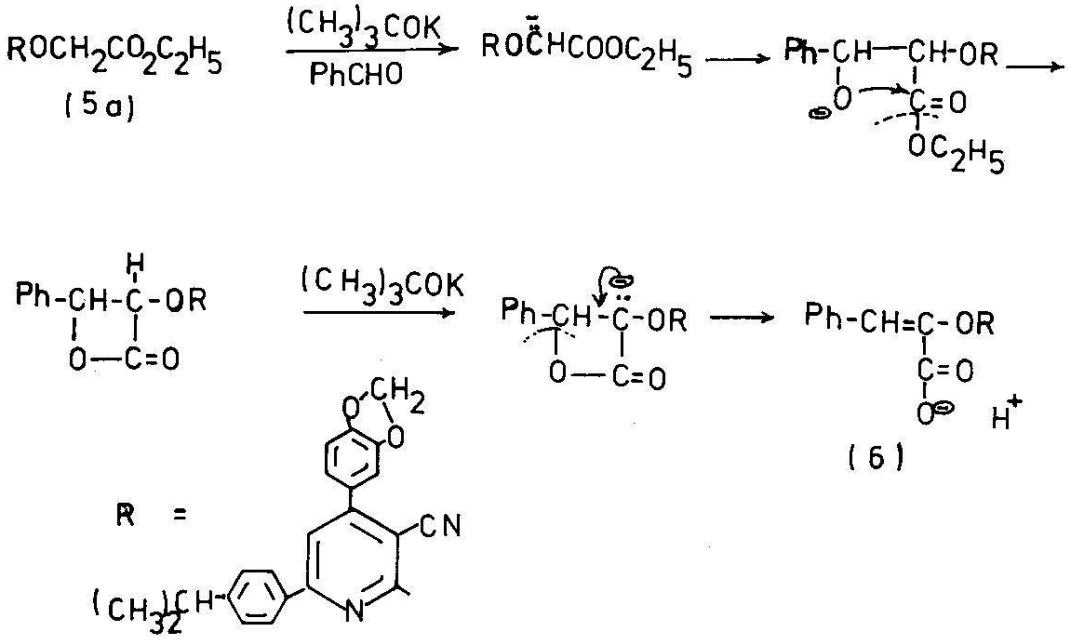

R
CN
(CH3)2CH
N
OCH2CO2C2H5
(5)
R
a, C6H3O2CH2(3,4)
b, C6H4NO2-P
C6H5CHO
(CH3)3COK
EtONa
O-CH2
O
CN
(CH3)2CH
N
O-C-CO2H
CHPh
(7)
R
CN
(CH3)2CH
N
O-C-CO2Et
CHPh
(6)
R
a, C6H3O2CH2(3,4)
b, C6H4NO2

CHART-2


ROCH2CO2C2H5
(5a)
(CH3)3COK
PhCHO
ROCHCOOC2H5
Ph-CH—CH-OR
O
C=O
OC2H5
Ph-CH-C-OR
O—C=O
(CH3)3COK
Ph-CH-C-OR
O—C=O
Ph-CH=C-OR
C=O
O
H+
(6)
R =
O
CH2
O
CN
(CH3)2CH
N

suitably situated carbalkoxy group that enables cyclisation to an intermediate paraconic ester (γ-lactonic ring). In ester (5) under investigation, β-lactonic ring is formed as intermediate which is more easily formed than the γ-lactonic ring produced in the Stobbe condensation, but it is less stable. Consequently, side reactions such as Claisen condensation compete with the Stobbe condensation.

The cinnamic ester derivative (6a) was also converted to the cinnamic acid derivative (7) upon hydrolysis with aq. NaOH (10%). The I.R. spectra for the esters (6) show ν CO of ester at 1730 cm^{-1} and νC=C at 1610 cm^{-1}. Similarly the IR spectrum of the cinnamic acid derivative (7) showed ν CO of acid at 1700 cm^{-1} and $^{\nu}C=C$ at 1610 cm^{-1}.

Further support for the structure of the esters (5) was furnished by the reaction with hydrazine hydrate and p-toluidine to give the corresponding hydrazides (8a), (8b) and N-p-tolylamide derivative (8c) respectively.

Alkaline hydrolysis of ester (5a) by using 10% aqueous NaOH gave the acid (8d) with elimination of cyano group.

The IR spectra of the hydrazides (8a), (8b) and amide (8c) show the existence of ν CONH at (1645-1640 cm^{-1}), ν C≡N at 2220 cm^{-1}, ν CH at (2900-2820 cm^{-1}) and ν NH at (3300-3290 cm^{-1}). On the other hand, the IR spectrum of the acid (8d) shows the absence of the ν CN but shows the existence of νCO of acid at 1700 cm^{-1}

Similarly, the ethyl nicotinate derivative (3a) was also reacted with hydrazine hydrate and p-toluidine affording the hydrazide (9a) and the N-substituted aniline derivative (9b) respectively.

On the other hand, the ester (3b) was hydrolysed with aqueous NaOH to give the corresponding acid (9c).

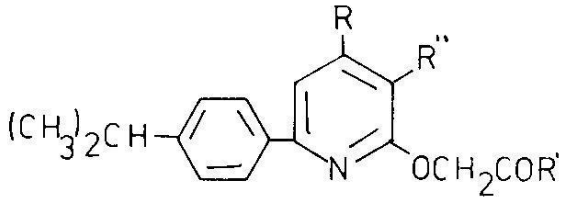
The IR spectra of compounds (9a) and (9b) showed νCONH at 1650-1640 cm^{-1}, ν CH at 2900-2890 cm^{-1} and νNH at 3290 cm^{-1}. On the other hand, the acid (9c) shows νCOO^{-} at 1565, νCO of acid at 1685 cm^{-1}, νCH at 2920 cm^{-1}, νNH_3^{+} at 3220 cm^{-1} and ν NH at 3370 cm^{-1}. All these bands support the existence of the acid (9c) in the following tautomeric equilibrium.

4-Nitrobenzal-p-isopropylacetophenone (1b) undergoes the addition of bromine in CCl_4 to give the dibromide (10a). Compound (10a) was converted to the dimorpholyl derivative (10b) upon boiling with morpholine/ethanol mixture. Compound (10) showed ν CO in their IR spectra at 1680 cm^{-1} and νNH at 2890 cm^{-1}.

Hydrazine hydrate, on the other hand, reacts with the chalcone (1b) in ethanol affording compound (11), and this shows ν C=N at 1610 cm^{-1}, νCH at 2980 cm^{-1} and ν NH at 3300 cm^{-1}. Also, compound (11) gives blue-violet colour upon treatment with $FeCl_3$ in conc. H_2CO_4 which is characteristic of pyrazolines [10].

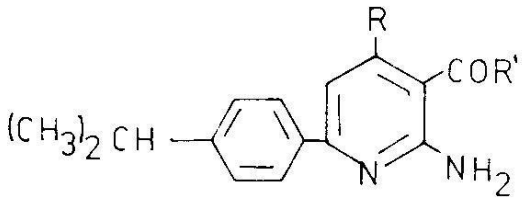
Benzal-p-isopropylacetophenone (1c) was reacted with cyclohexanone under the Michael reaction conditions affording the Michael adduct (12).

On the other hand, ethyl methyl ketone has been added to (1c) under



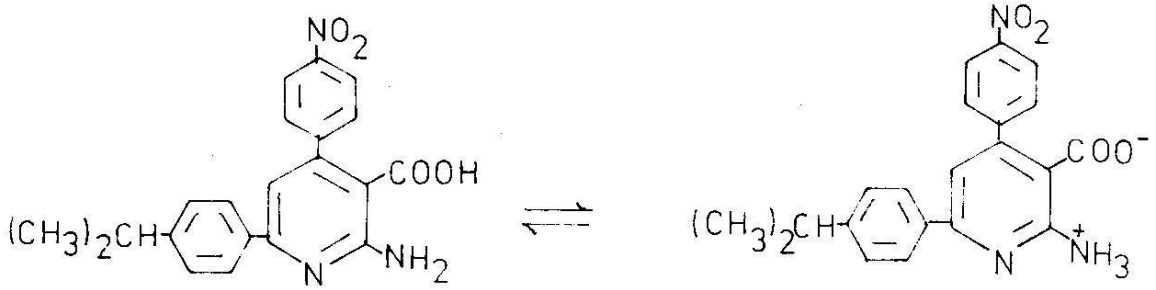
(8)

	R	R'	R''
a,	$C_6H_3O_2CH_2(3,4)$	$-NHNH_2$	-CN
b,	$C_6H_4NO_2$-p	$-NHNH_2$	-CN
c,	$C_6H_3O_2CH_2(3,4)$	$-NHC_6H_4CH_3$-p	-CN
d,	$C_6H_3O_2CH_2(3,4)$	-OH	H



(9)

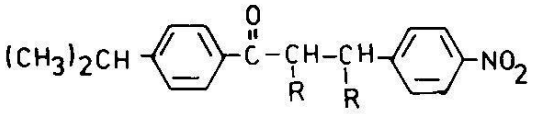
	R	R'
a,	$C_6H_3O_2CH_2(3,4)$	$-NHNH_2$
b,	$C_6H_3O_2CH_2(3,4)$	$-NHC_6H_4CH_3$
c,	$C_6H_4NO_2$-p	-OH



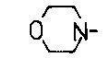
(9c)

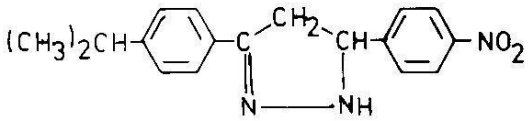
the same reaction conditions and gave the cyclohexenone derivative (13).

The IR spectra of compounds (12) and (13) show CO at 1720,1680 cm^{-1} for (12) and 1705 for (13) νCH at 2960-2920 cm^{-1}, which agree well with the proposed structure.

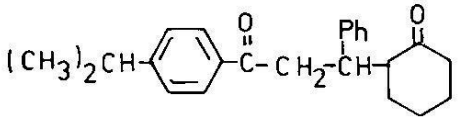


(10)

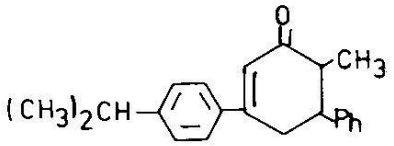
a. Br b. 



(11)



(12)



(13)

Experimental

The infrared absorption spectra were determined with a Unicam SP-1200 spectrophotometer using KBr Wafer technique. All melting points are uncorrected.

Reaction of ethyl cyanoacetate with the , -unsaturated ketones (1). Formation of the cyanopyridones (2) and ethyl nicotinate (3).

A mixture of the chalkones (1) (0.01 mole), ethyl cyanoacetate (4.5 g, 0.04 mole), and ammonium acetate (2.3 g, 0.03 mole) was heated at 140-150° for 8 hours, washed with water and then dried. The oil that formed was fractionally crystallized from the proper solvent to give the cyanopyridones (2) and ethyl nicotinates (3). The results are listed on Table 1.

Methylation of the cyanopyridone (2a); formation of the methoxy derivative (4a)

A mixture of (2a) (0.005 mole), dimethyl sulphate (0.02 mole), anhydrous potassium carbonate (0.02 mole) and dry acetone (50) ml was refluxed for 20 hours, the excess solvent was evaporated, and 100 ml of water was added then. The organic material was extracted with ether, the ethereal layer washed with 50 ml (5% aqueous sodium hydroxide) followed by 50 ml water. Evaporation of dry ether solution left the methoxy derivative (4a). The results are given on Table 1.

Action of phosphorus oxychloride on (2b); formation of 2-chloro-3-cyano-4,6-disubstituted pyridine (4b).

A suspention of (2b) (0.005 mole) and $POCl_3$ (3 ml) was heated on a water-bath for 2 hours. The reaction mixture was poured gradually into crushed ice (100 g) and the solid that separated was filtered off and crystallized from n-butnaol to give (4b) as reddish-yellow crystals. See Table 1.

Reaction of cyanopyridones (2) with ethyl chloroacetate; formation of the esters (5)

A mixture of (2) (0.01 mole), ethyl chloroacetate (0.04 mole), anhydrous

Table-1: Characterisations of the organic compounds (2-13)

Compound	Yield(g.,%) colour	m.p.(°C) solvent	Mol.formula (M.Wt.)		Analysis % Calcd.	Found
2a	1.86(52)	230	$C_{22}H_{18}N_2O_3$	C	73.74	73.50
	yellow	Toluene	(358.23)	H	5.02	5.19
				N	7.82	7.75
2b	1.83(51)	241	$C_{21}H_{17}N_3O_3$	C	70.19	70.00
	yellowish	Ethanol	(359.23)	H	4.73	4.50
				N	11.69	12.05
3a	1.17(29)	195	$C_{24}H_{24}N_2O_4$	C	71.28	70.73
	yellow	Benzene	(404.25)	H	5.94	5.61
				N	6.93	7.28
3b	0.81(20)	177	$C_{23}H_{23}N_3O_4$	C	68.14	68.26
	yellow	P.E.100-120	(405-25)	H	5.67	5.50
				N	10.37	9.75
4a	1.35(73)	134	$C_{23}H_{20}N_2O_3$	C	74.19	74.17
	brown	P.E.100-120	134	H	5.37	4.98
				N	7.52	7.25
4b	1.2(66)	284	$C_{21}H_{16}N_3O_2Cl$	C	66.75	66.37
	reddish	n-Butanol	(377.58)	H	4.23	4.13
				N	11.12	11.82
4c	0.9(21)	235	$C_{27}H_{22}N_4O_2$	C	74.65	74.26
	brown	Benzene	(434.29)	H	5.06	4.62
				N	12.90	13.00
5a	3.19(72)	179	$C_{26}H_{24}N_2O_5$	C	70.27	70.66
	brown	Benzene	(444.27)	H	5.40	5.62
				N	6.30	5.91
5b	2.13(48)	162	$C_{25}H_{23}N_3O_5$	C	67.41	67.79
	brown	Benzene	(445.27)	H	5.16	5.18
				N	9.43	9.28
6a	2.71(51)	159	$C_{33}H_{28}N_2O_5$	C	74.43	74.61
	bale brown	P.E.100-120	(532.35)	H	5.26	5.67
				N	5.26	5.87

6b	3.19(60)	212	$C_{32}H_{27}N_3O_5$	C	72.04	72.60
	yellow	Ethanol	(533.34)	H	5.06	5.56
				N	7.87	8.48
7	0.6(12)	150	$C_{31}H_{24}N_2O_5$	C	73.80	74.23
	yellowish-white	Ethanol	(504.32)	H	4.76	5.12
				N	5.55	6.01
8a	2.83(66)	194	$C_{24}H_{22}N_4O_4$	C	66.97	67.34
	white	Toluene	(430.26)	H	5.11	5.14
				N	13.02	12.43
8b	3.06 (71)	139	$C_{23}H_{21}N_5O_4$	C	64.03	64.51
	yellow	Ethanol	(431.26)	H	4.87	5.08
				N	16.24	16.64
8c	4.14(82)	167	$C_{31}H_{27}N_3O_4$	C	73.66	74.11
	yellowish	Methanol	(505.33)	H	5.34	5.86
				N	8.31	7.93
8d	1.75(45)	230	$C_{23}H_{21}NO_5$	C	70.58	69.96
	grey	Toluene	(391.24)	H	5.37	4.87
				N	3.58	3.60
9a	2.69(69)	227	$C_{22}H_{22}N_4O_3$	C	67.69	68.12
	yellowish	Toluene	(390.25)	H	5.64	5.35
				N	14.35	14.28
9b	1.99(43)	222	$C_{29}H_{27}N_3O_3$	C	74.83	75.06
	pale brown	Ethanol	(465.31)	H	5.80	6.18
				N	9.03	8.88
9c	0.46 (24)	195	$C_{21}H_{19}N_3O_4$	C	66.84	66.37
	yellow	Toluene	(337.23)	H	5.03	5.15
				N	11.14	10.87
10a	3.50(77)	152	$C_{18}H_{17}NO_3Br_2$	C	47.47	47.25
	yellow	Ethanol	(454.99)	H	3.73	4.13
				N	3.07	3.06
10b	0.28(59)	147	$C_{26}H_{33}N_3O_5$	C	66.80	65.99
	brown	Benzene	(467.28)	H	7.06	6.64
				N	8.99	9.00
11	2.53(82)	281	$C_{18}H_{19}N_3O_2$	C	69.90	70.49
	pale yellow	Ethanol	(309.20)	H	6.14	5.85
				N	13.59	14.28

12	0.83(82)	138	$C_{24}H_{28}O_2$	C	82.75	83.13
	colourless	P.E.100-120	(348.24)	H	8.04	7.91
13	1.18(39)	221	$C_{22}H_{24}O$	C	86.84	86.35
	yellowish	Benzene	(304.22)	H	7.89	8.14

potassium carbonate (0.04 mole) and acetone (20 ml per g of 2) was refluxed for 20 hours on a water-bath. The excess of solvent was evaporated and 100 ml of water was added. The organic substance was extracted with ether and the removal of ether gave the desired product (5). The results are given on Table 1.

Condensation of benzaldehyde with the esters (5); formation of cinnamic esters (6) or acid (7)

A solution of benzaldehyde (0.1 mole) in the ester (5a) (0.15 mole) and (20 ml) tert-butanol was added dropwise to a boiling stirred solution of potassium tert-butoxide (0.11 mole) in dry tert-butanol [potassium metal (0.11 g atom); 25 ml of tert-butanol per g of potassium]. The addition lasted half an hour; heating on a water bath and stirring was then continued for another an hour. Most of the alcohol was then removed under reduced pressure and the cooled, residue was rendered slightly acidic with dilute hydrochloric acid. The organic material was taken up in ether, the ethereal solution was washed several times with water, then repeatedly with cold sodium carbonate solution (150 ml; 10%). The alkaline extract was cooled, acidified with hydrochloric acid/ice (20 ml/200 g) and the precipitated material was extracted with ether. Evaporation of the excess ether left the acidic product as an oily product which can be solidified by trituration with light petroleum (b.p. 60-80°). Evaporation of dry ethereal layer, left the cinnamic ester derivative (6a) (1.1 g ca. 21%). The solids obtained were crystallized from the proper solvent to give the cinnamic acid derivative (6a) and (7). When the reaction is carried out in presence of C_2H_5ONa (1.1 mole) in ethanol (50 ml) on steam bath the sole product is the cinnamic ester derivatives (6). The results are given in Table 1.

Conversion of (6a) to (7)

A mixture of the ester (6a) (0.00 mole) and aqueous sodium hydroxide solution (30 ml, 10%) was refluxed for 3 hours. The alkaline mixture was cooled, acidified with hydrochloric acid and ice (15 ml/100 g) and the precipitated material was extracted with ether. Evaporation of ether gave the cinnamic acid derivative (7) which was identified by m.p. and m.m.p. determinations.

Action of hydrazine hydrate on (3a), (5a) and (5b), (1b); formation of the hydrazides (8a) and (8b), (9a) and pyrazoline (11).

A mixture of (3a), (5a) and (5b) or (1b) (0.01 mole), hydrazine hydrate (0.01 mole), and ethyl alcohol (50 ml) was refluxed for 5 hours. The separated solid after cooling was crystallized from the proper solvent to give the corresponding hydrazides (8a) and (8b), (9a) and the pyrazoline (11). cf. Table 1.

Reaction of the esters (3a) and (5a) with p-toluidine and chloro-derivative (4b) with aniline;formation of (9b), (7c) and (4c).

A suspension of (3a), (5a) or (4b) (0.01 mole) and p-toluidine or aniline (0.01 mole) was refluxed for 2 hours and then allowed to cool. The reaction mixture was triturated with methanol, and the separated solid was crystallized from the suitable solvent to give the N-substituted amide or amine derivatives (9b), (8c) or (4c). See Table-1.

Hydrolysis of the ester (3b) with aqueous NaOH; formation of the acid (9c)

A mixture of (3b) (0.005 mole) and sodium hydroxide solution (20 ml; 10%) was refluxed for 2 hours. The alkaline mixture was cooled, acidified with (8 ml HCl/100 g ice) and the precipitated solid was extracted with ether. Evaporation of ether gave the acid (9c).cf. Table 1.

Addition of Bromine to 4-nitrobenzal-p-isopropylacetophenone (1b) formation of the dibromide (10a).

A vigorously stirred solution of (1b) (0.01 mole) in carbon tetrachloride (50 ml) was heated on a water-bath to about 60-70°C and then treated portionwise with bromine (0.01 mole) during a period of 15 minutes. The mixture was stirred for a further period of 3 hours and then poured on iced water (100 g ice; 100 g H_2O). The solid that separated was filtered off and crystallized from ethanol to give the dibromide (10a). The results are listed on Table 1.

Reaction of the dibromide (10a) with morpholine; formation of the dimorpholyl (10b)

A suspension of the dibromide (10a) (0.001 mole) and morpholine (0.002 mole) was refluxed in ethanol for 2 hours, and then allowed to cool. The solid, so obtained, was crystallized from benzene to give the dimorpholyl derivative (10b).

Base-catalyzed Michael addition of cyclohexanone and butanone to benzal-p-isopropylacetophenone (1c); formation of (12) and (13).

A mixture of (1c) (0.01 mole) and cyclohexanone or butanone (0.02 mole) in ethanol (30 ml) was treated with (3 ml; 50%) aqueous sodium hydroxide, then set aside at room temperature for 24 hours. The reaction mixture was poured into crushed ice (50 g) and the solid separated was filtered off, dried and then crystallized from light petrol (b.p. 100-120°) or benzene to give (12) or (13) respectively. cf. Table 1.

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