J.Chem.Soc.Pak. Vol. 9, No. 2, 1987.

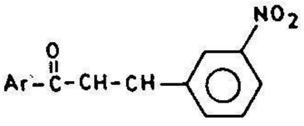
Behaviour of 3-Nitrobenzal-p-Isopropyl or p-Chloroacetophenones Toward Oxygen and Carbon Nucleophiles and Some Studies with the Products

M.A.EL-HASHASH[+], M.EL-MOBAYED[++], A.F.EL-FARARGY[++]
M.A.SAYED[+] AND N.MOSTAFA[++]
[+]*Chemistry Department, Faculty of Science,*
Ain Shams University, Abbasia, Cairo, Egypt
[++]*Chemistry Department, Faculty of Science,*
Zagazig Univeristy, Zagazig, Egypt.

(Received 11th November, 1985, revised 13th May, 1986)

Summary: 3-Nitrobenzylidene-p-isopropylacetophenone (1a) reacts with hydrogen peroxide to give the oxirane derivative (2). The cleavage of the strained oxirane ring with oxygen nucleophiles e.g. OH or nitrogen nucleohpiles e.g. hydrazine hydrate or hydroxylamine has been described. The reaction of (1) with ethylcyanoacetate in the presence of ammonium acetate leads to the formation of nicotinonitrile derivative (7). The behaviour of compound (7) toward some electrophiles e.g. ethylchloroacetate or dimethyl sulphate or some nucleophiles e.g. phosphorous oxychloride has been investigated.

Although many benzalacetophenone derivatives have been synthesised, not much is known about the stereochemistry of the products. We report here the synthesis and spectroscopic studies on some benzalacetophenone derivatives namely m-nitrobenzal-p-isopropyl or p-chloroacetophenones (1), in the hope of obtaining more precise information about the stereochemistry of the products, and their possible use as key starting materials for the syntheses of the derivatives of some heterocyclic compounds. Thus m-nitrobenzaldehyde reacts with p-isopropylacetophenone and/or p-chloroacetophenone in the presence of alcoholic potassiumhydroxide to yield the benzal derivatives (1a and 1b).

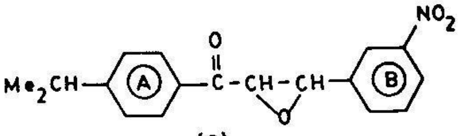


(1)

Ar= a, p-Me_2CH-C_6H_4 Ar= b, p-Cl-C_6H_4

All attempts which we have been made including suitable column chromatography for separation of the two expected isomers have failed possibly due to isomerisation taking place during separation. The structure of m-nitrobenzal-p-isopropylacetophenone (1a) was assigned from its nmr spectrum which showed two isopropyl groups at δ 1.23/1.31 and δ 1.27/1.20 the methin protons of the isopropyl groups between δ 2.8 and δ 3.1, the AB system of the olefinic protons due to C=C was shifted to the aromatic region between δ 7.10 and δ 7.27, the aromatic ring protons of the ring A showed A_2B_2-system at δ 7.27, δ7.57, 7.74, δ7.92 and the aromatic ring protons of ring B between δ 7.99 and δ 8.50. The mentioned data show that the compound (1a) consists of a mixture of two stereoisomers trans and cis in a ratio 2:1. The ratio of the two isomers was obtained from the isopropyl signals and the A_2B_2-system of the aromatic ring protons of ring A. An speculation which explains the appearance of cis/trans signals in nmr spectra is due to the fact that magnetic nuclei can absorb the exciting radiation faster than the rate of isomerisation.

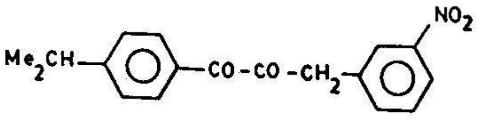
In general, hydrogen peroxide reacts with α,β-unsaturated ketones producing the corresponding epoxy ketones [1-3]. In this study, this reaction was applied to the 3-nitrobenzylidene-*p*-isopropylacetophenone (1a) with the aim of synthesising some new oxirane derivatives. Thus, treatment of the alcoholic solution of (1a) with hydrogen peroxide in alkaline medium yielded the oxirane derivative (2).



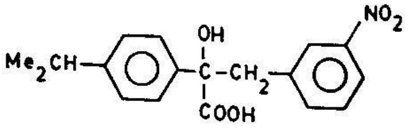
(2)

The structure of (2) was inferred from its analytical data, the infra-red absorption spectrum which showed strong bands at 1675 cm^{-1} (C=O) and at 1290 cm^{-1} (epoxy linkage) and the nmr spectrum which reveals the presence of the isopropyl group at δ 1.27/1.20, the methine proton of the isopropyl group between δ 2.8-3.1 (m), the AB system of the oxirane ring at δ 4.16, 4.18, 4.26, 4.28, the A_2B_2-system of the aromatic ring A at δ 7.37, 7.50, 7.8, 7.9 and the four protons of ring B between δ 7.6 and δ 8.4 (m).

Structure of (2) was further supported by its behaviour towards aqueous sodium hydroxide and gave mixturte of two products, the diketone derivative (3) and the glycolic acid derivative (4). This is parallel to that reported earlier for similar type of compounds [2].

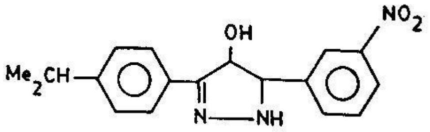


(3)



(4)

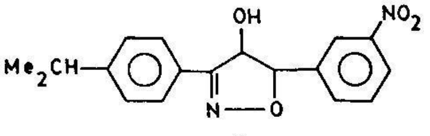
The compound (2) was converted into the pyrazoline derivative (5) by the reaction with hydrazine hydrate in ethanol.



(5)

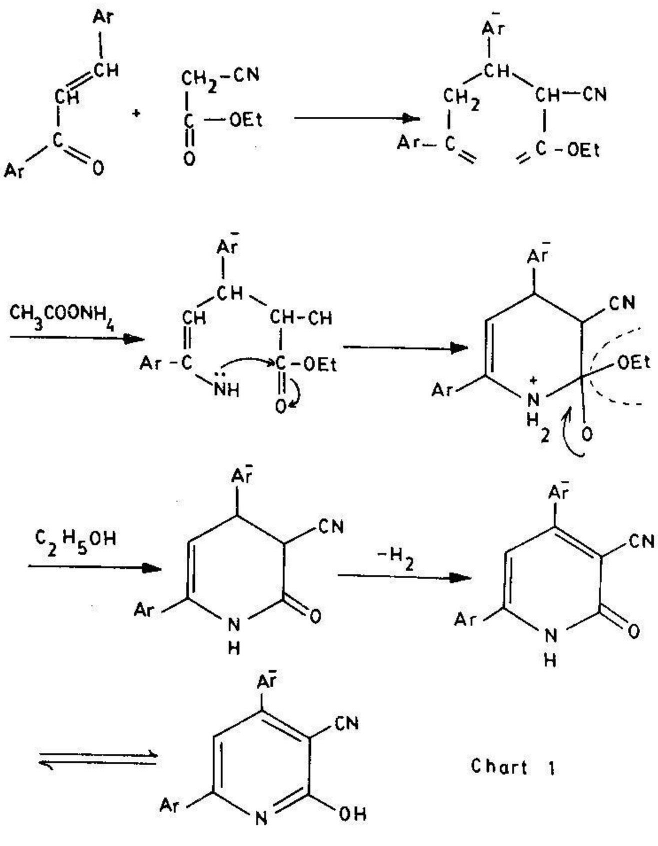
The structure of the pyrazoline (5) was proved from the colour test characteristic for pyrazolines [4], its analytical data and the infrared spectrum which exhibits bands attributed to C=N and OH group at 1640 cm^{-1} and 3400 cm^{-1} respectively.

Treatment of compound (2) with hydroxylamine hydrochloride in ethanol gave the isoxazoline derivative (6) whose structure was proved by its analytical data and its infrared spectrum which reveals the presence of C=N group.



(6)

Recently [5] it has been reported that chalcones reacted with ethylcyanoacetate, giving rise to pyridine derivatives. In the present work, the



(7)

Chart 1

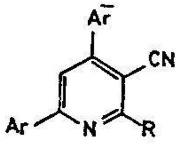
a; Ar= $p-Me_2CHC_6H_4$; $\bar{Ar}$ = $m.NO_2-C_6H_4$

b; Ar= $p-Cl-C_6H_4$; $\bar{Ar}$ = $m.NO_2-C_6H_4$

condensation of 3-nitrobenzylidene-p-chloroacetophenone (1b) with ethylcyanoacetate in the presence of ammonium acetate in a 1:1 molar ratio gave 2-hydroxy-4-(3-nitrophenyl)-6-(p-isopropyl-phenyl)nicotinonitrile (7a)and 2-hydroxy-4-(3-nitrophenyl)-6-(p-chlorophenyl) nicotinonitrile (7b) respectively through Michael reaction (with elimination of one mole of water and hydrogen).

The structure of (7) was established by its analytical and spectral data. Its infrared spectrum shows bands at 2200 cm^{-1} (conjugated C=N), 3420 cm^{-1} (NH) and 1640 cm^{-1} (C=O).

The compounds (7a) and (7b) were reacted with ethyl chloroacetate in the presence of dry acetone and anhydrous potassium carbonate as a catalyst and gave the corresponding ester derivatives (8a) and (8b) respectively. This reaction proves that the nicotinonitrile derivatives realy exists in a lactam-lactim dynamic equilibrium and in the presence of acetone the lactim form is more predominace. The structure of (8) was confirmed by correct analytical data, and the IR spectrum which showed bands at 1740 cm^{-1} (C=O of ester), 2210 cm^{-1} (C≡N) and 1210 cm^{-1} (O-C) which agreed well with the proposed structure.



(8)

(8a)	Ar = P-$Me_2CH.C_6H_4$	Ar' = m.$NO_2C_6H_4$	R = $OCH_2COOC_2H_5$
(8b)	Ar = p-ClC_6H_4	Ar' = m.$NO_2C_6H_4$	R = $OCH_2COOC_2H_5$
(8c)	Ar = p-$Me_2CH.C_6H_4$	Ar' = m.$NO_2C_6H_4$	R = $OCH_2CONHCH_2C_6H_5$
(8d)	Ar = p-ClC_6H_4	Ar' = m.$NO_2C_6H_4$	R = $OCH_2CONHCH_2C_6H_5$
(8e)	Ar = p-ClC_6H_4	Ar' = m.$NO_2C_6H_4$	R = OCH_3
(8f)	Ar = p-ClC_6H_4	Ar' = m.$NO_2C_6H_4$	R = Cl
(8g)	Ar = p-ClC_6H_4	Ar' = m.$NO_2C_6H_4$	R = $NHCH_2ph$
(8h)	Ar = p-ClC_6H_4	Ar' = m.$NO_2C_6H_4$	R = $NHNH_2$

Treatment of (8a) and (8b) with benzylamine gave the corresponding amide (8c) and (8d).

Similarly when compound (7b) was reacted with dimethyl sulphate in presence of anhydrous potassium carbonate in refluxing acetone gave 2-methoxy-4-(3'-nitrophenyl)-6-(p-chlorophenyl)-nicotinonitrile (8e). The structure of (8e) was supported by correct analaytical data and the infrared spectrum which exhibits strong absorption bands at 1100 cm^{-1} (C=O), 2200 cm^{-1} (C≡N).

Additional proof for the lactim form has been obtained from the reaction of (7b) with phosphorus oxychloride which leads to the production of 2-chloro-4-(3'-nitrophenyl)-6-(p-chlorophenyl)-nicotinonitrile (8f) whose structure was confirmed by correct analytical data and the infrared spectrum which reveals strong absorption at 1620 cm^{-1}(C=N) and 2210 cm^{-1} (C≡N). Another proof for the structure of (8f) was obtained chemically by treating (8f) with sodium methoxide in boiling methanol to give the methoxy derivative (8e) which was identified via m.p. and mixed m.p. determination. Also treatment of compound (8f) with benzylamine or hydrazine hydrate gave 2-benzylamino-4-(3-nitro-phenyl)-6-(p-chlorophenyl)-nicotinonitrile) (8g) or 2-hydrazino-4-nitro-phenyl)-6-(p-chlorophenyl)-nicotinonitrile (8h). The infrared spectra of (8g) and (8h) showed bands at 2220 cm^{-1} and 1640 cm^{-1} attributed to C≡N and C=N respectively.

On the other hand, compound (7b) reacts with methyl iodide in presence of least amount of pyridine to afford the N-methyl product (9a) (cf.Chart 2). This explain that pyridine favours the equilibrium towards lactam form. The infrared spectrum of (9a) exhibits strong absorptions at 2210 cm^{-1} and 1650 cm^{-1} due to C≡N and C=O of cyclic amide respectively.

Another proof for the predominance of lactam form in basic medium has been gained from treatment of (7b) with benzene diazonium chloride yielded the corresponding N-Azo-derivative (9b) (cf.Chart 2).

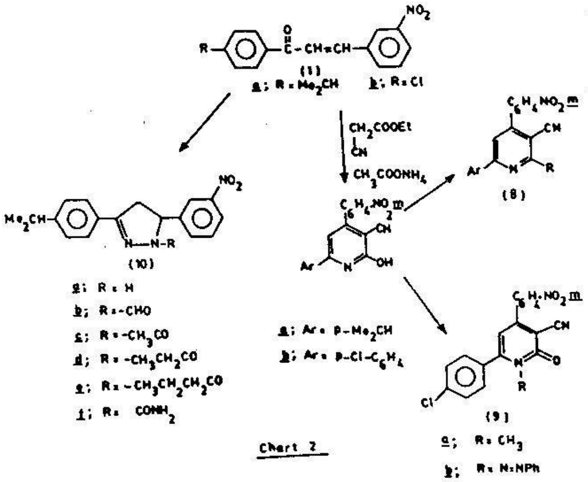


Chart 2

It is well known that treatment of α,β-unsaturated ketones with hydrazines gave pyrazolines [1], thus, the reaction of (1a) with hydrazine hydrate in either ethanol, formic acid, propionic acid and n-butyric acid, yielded the hydrazone as a fleeting intermediate which rearranged immediately to the isomeric pyrazoline derivative (10a-e) (cf.Chart 2). The compounds (10a-e) gave the colour test for pyrazolines (a drop of ferric chloride solution added to a concentrated sulphuric acid solution of the compound gave a blue violet colour). Also the structure was proved from their analytical data and their infrared spectra which showed absorption bands at 1660 cm^{-1} (C=N) and at 3340 cm^{-1} (NH).

Also treatment of (1a) with semicarbazide in boiling pyridine gave the corresponding pyrazoline derivative (10f). The structure of (10f) was confirmed by correct analytical data and infrared spectral data.

Experimental

Melting points are not corrected; infrared spectra (KBr) were measured on a Perkin Elmer infracord 137 spectrophotomer. The nmr spectra on a Varian A 60 equipment using TMS as an internal standard and $CDCl_3$ as solvent. The mass spectra were run at 70 eV on a Varian MAT 711 mass-spectrometer. The analaytical and physical data of all products is described in Table-1.

Preparation of the chalcones (1a) and (1b):

A mixture of (0.01 mole) of p-isopropyl or p-chloro acetophenone and (0.01 mole) of p-nitro benzaldehyde was dissolved in 100 ml ethanol. To the cold stirred mixture, 6.2 g KOH in 65 ml water was added drop by drop over a period of 30 minutes. Stirring continued for 3 hours and left overnight at room temperature. The mixture was poured into ice-cold water and the product obtained was crystallised from suitable solvent to yield the chalcone (1a) and (1b).

Formation of oxirane (2):

A solution of (1a) (0.01 mole) in acetone (40 ml) and methanol (15 ml) was treated with 8% aqueous sodium hydroxide (12 ml) followed by hydrogen peroxide (30%; 5 ml). The solution was shaken and brought overnight at room temperature. A white crystalline product was separated which recrystallised from light petrol (80-100°).

Table-1: Characterisation of compounds 1-10.

Compound	m.p. °C	Solvent yield %	Formula M.Wt.	Analysis % (Found/Calc.)		
				C	H	N
(1a)	125-26	Toluene	$C_{18}H_{17}NO_3^{(a)}$	73.22	5.76	
		82%	295	73.20	5.61	
(1b)	140-41	Toluene	$C_{15}H_{10}ClNO_3$	62.60	3.48	
		86%	287.5	62.47	3.51	
(2)	100-1	L.P	$C_{18}H_{17}NO_4^{(b)}$	69.45	5.47	
		79%	311	69.60	5.50	
(5)	150-51	E	$C_{18}H_{19}N_3O_3$	66.66	5.55	12.96
		74%	325	66.46	5.85	12.92
(6)	180-81	E	$C_{18}H_{18}N_2O_4$	67.08	5.59	8.70
		76%	326	66.86	5.68	8.52
(7a)	245-46	E	$C_{21}H_{17}N_3O_3$	70.19	4.74	11.70
		80%	359	70.10	4.96	11.58
(7b)	230-31	A	$C_{18}H_{10}ClN_3O_3$	61.45	2.86	11.95
		78%	351.5	61.20	2.62	11.78
(8a)	144-45	E	$C_{25}H_{23}N_3O_5$	67.26	5.38	9.42
		69%	445	67.42	5.17	9.43
(8b)	175-76	E	$C_{22}H_{16}ClN_3O_5$	60.20	3.88	9.58
		71%	437.5	60.34	3.65	9.60
(8c)	115-16	E	$C_{30}H_{26}N_4O_4$	71.15	5.14	11.07
		73%	506	71.32	5.20	10.86
(8d)	120-121	A	$C_{27}H_{19}ClN_4O_4$	65.99	3.81	11.23
		79%	498.5	65.12	3.85	11.01

(a) m/e 295(M^+), 280 (M^+-CH_3), 252 ($M^+-C_3H_7$), 176,148,147(100%),119 and 102.

(b) m/e 311(M^+),295 (M^+-O),268 ($M^+-C_3H_7$),252,176,148,147(100%), 104 and 91.

Table-1: (cont'd..)

Compound	m.p°C	Solvent Yield %	Formula M.Wt.	Analysis % (Found/Calc)		
				C	H	N
(8e)	150-51	E	$C_{19}H_{12}ClN_3O_3$	62.38	3.28	11.49
		77%	365.5	62.52	3.44	11.24
(8f)	200-1	E	$C_{18}H_9ClN_3O_2$	64.57	2.69	12.55
		72%	334.5	64.32	2.81	12.38
(8g)	240-41	A	$C_{25}H_{17}ClN_4O_2$	68.10	3.86	12.71
		69%	440.5	68.41	4.12	12.49
(8h)	190-91	E	$C_{18}H_{12}ClN_5O_2$	59.32	3.41	19.02
		72%	365.5	59.45	3.28	19.15
(9a)	185-86	E	$C_{19}H_{12}ClN_3O_3$	62.38	3.28	11.49
		74%	365.5	62.21	3.16	11.19
(9b)	100-1	E	$C_{24}H_{14}ClN_5O_3$	63.23	3.07	15.37
		72%	455.5	62.97	3.15	15.13
(10a)	150-51	E	$C_{18}H_{19}N_3O_2$	69.90	6.15	13.59
		78%	309	69.74	6.32	13.36
(10b)	165-66	E	$C_{19}H_{19}N_3O_3$	67.65	5.60	12.46
		77%	337	67.48	5.40	12.12
(10c)	130-31	E	$C_{20}H_{21}N_3O_3$	68.37	5.58	11.96
		77%	351	68.11	5.70	11.90
(10d)	133-34	E	$C_{21}H_{23}N_3O_3$	69.04	6.30	11.51
		75%	365	69.23	6.42	11.32
(10e)	175-76	E	$C_{22}H_{25}N_3O_3$ (c)	69.66	6.60	11.08
		72%	379	69.33	6.37	10.92
(10f)	230-31	E	$C_{19}H_{20}N_4O_3$	64.77	5.68	15.91
		69%	352	64.63	5.81	15.78

L.p. = Light petrol (80-100); E = Ethanol and A = Acetic acid

(c) m/e 379 (M), 351 (M -CH = CH), 336 (M -CH), 308 (100%), 280, 264, 159 and 102.

Reaction of (2) with hydrazine hydrate; formation of pyrazoline derivative (5):

A solution of (2) (0.01 mole) in ethanol was treated with hydrazine hydrate. The mixture was refluxed for 6 hours. The product obtained after cooling were crystallised from the suitable solvent to give (5).

Reaction of (2a) with hydroxyl amine hydrochloride; formation of isoxazoline derivative (6):

A mixture of (2) (0.01 mole) and hydroxyl amine hydrochloride (0.02 mole) in ethanol (30 ml) was refluxed for 6 hours. The cooled mixture was poured into ice-cold water and the product obtained was recrystallised from ethanol to give the isoxazoline derivative (6).

Reaction of (1a) and (1b) with ethyl cyano acetate; formation of nicotinonitrile derivative (7a) and (7b):

A mixture of ethyl cyano acetate (0.01 mole), chalcone (1a) or (1b) (0.01 mole) and ammonium acetate in ethanol was refluxed for 8 hours. The cooled mixture was poured into ice-cold water and the product obtained was crystallised from suitable solvent to give the nicotinonitrile (7a) and (7b).

Reaction of (7a) and (7b) with ethyl chloro acetate, formation of the ester derivative (8a) and (8b):

(0.01 mole) of the nicotinonitrile (7a) or (7b) was dissolved in (50 ml) dry acetone and (0.01 mole) of ethyl chloro acetate and 2 g of anhydrous potassium carbonate was added. The mixture heated under reflux for 7 hours. The oil produced after evaporation of acetone was crystallised from suitable solvent to give the ester derivative (8a) and (8b).

Reaction of (8a) and (8b) with benzylamine; formation of the amide derivative (8c) and (8d):

A solution of (8a) or (8b) (0.01 mole) in ethanol and benzylamine (0.02 mole) was refluxed for 6 hours. The cooled solution was poured into ice-cooled dilute hydrochloric acid. The solid separated was crystallised from suitable solvent to give (8c) or (8d).

Reaction of (7b) with dimethyl sulphate; formation of (8e):

To a mixture of (0.01 mole) of (7b) and (0.04 mole) of anhydrous potassium carbonate in dry acetone dimethyl sulphate (0.04 mole) was added. The reaction mixture was refluxed for 20 hours. After cooling and slow evaporation of acetone, the reaction mixture was poured into ice-cold water. The solution extracted with ether. The ether layer was dried over anhydrous sodium solphate and the solid separated after evaporation of ether was crystallised from ethanol to give (8e).

Reaction of (7b) with phosphorous pentachloride and phosphorous oxychloride; formation of (8f):

(0.01 mole) of (7b) was refluxed in water bath with (0.5 g) PCl_5 and 5 ml $POCl_3$ for 9 hours. The product poured into ice-cold dilute HCl. The solid separated was filtered and crystallised from suitable solvent to form (8f).

Reaction of (8f) with sodium methoxide; formation of (8e):

(1 g) of sodium metal was dissolved in 40 ml absolute methanol. (0.01 mole) of (8f) was added and the mixture refluxed over oil bath for 3 hours. The cooled mixture was pour-

ed into ice-cold water. The solid separated was crystallised from suitable solvent to give (8e) which identified by melting point determination.

Reaction of (8f) with benzylamine or hydrazine hydrate; formation of nicotinonitrile derivative (8g) and (8h):

(0.01 mole) of (8f) was fused with (1 ml) hydrazine hydrate (or 1.2 ml benzylamine) over an oil bath for 3 hours. The mixture poured into ice-cold dilute hydrochloric acid and the solid separated was crystallised from suitable solvent to give (8g) and (8h).

Reaction of 7b) with methyl iodide; formation of N-methyl nicotinonitrile derivative (9a):

A mixture of (0.01 mole) of (7b) and 0.6 ml of methyl iodide in 5 ml pyridine was refluxed in water bath for 3 hours. The cooled mixture was poured into ice-cold dilute hydrochloric acid. The solid separated was crystallised from suitable solvent to give (9a).

Reaction of (7b) with benzene diazonium chloride; formation of N-azo derivative (9b):

(0.01 mole) of (7b) was dissolved in 50 ml aqueous sodium hydroxide and added to benzene diazonium chloride [7]. A red product was obtained which crystallised from ethanol to give (9b).

Reaction of (1a) with hydrazine hydrate in different solvents; formation of pyrazoline derivative (10a-e):

(0.01 mole) of (1a) and (0.5 ml) hydrazine hydrate in 30 ml either 6 hours. The cooled mixture poured into ice-cold water. The solid separated was crystallised from suitable solvent to give (10a-e).

Reaction of (1a) with semicarbazide in boiling pyridine; formation of (10f):

(0.01 mole) of (1a) and (0.8 ml) semicarbazide in 20 ml pyridine was refluxed for 6 hours. The cooled mixture poured into ice-cold dilute hydrochloric acid. The solid separated was crystallised from suitable solvent to give (10f).

Acknowledgement

The authors wish to thank Professor Dr.A.Rieker, Professor of organic chemistry, the University of Tubingen, West Germany for his help during this work.

References

1. M.A.El-Hashash, M.E.Shaban and M.M.Habshy, *Rev.Roumaine de Chimia*, **26**, *101 (1981)*.
2. M.A.El-Hashash and M.El-Kady, *Rev.Roumaine de Chimie*, **23**, *1581 (1978)*.
3. M.A.El-Hashash, M.El-Kady, M.A.Sayed and A.A.El-Sawy, *Egypt J. Chem., (1983)*.
4. V.Knorr, *Liebigs Ann.Chem.*, **238**, *200 (1878)*.
5. M.M.Mohamed, M.A.El-Hashash, M.A.Sayed and A.A.Sheta, *J. Chem. Soc. Pak., (1984)*.
6. M.A.El-Hashash, S.El-Nagdy and R.Saleh, *J.Chem. and Eng.Data (U.S.A.) Amer.Chem.Soc.*, **29**, *361 (1984)*.
7. Vogel, Text book of practical