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Studies on Synthesis and Heterocyclisation Reactions of Michael Products and Formation of New 1,4-Thiazine Quinoxaline Derivatives

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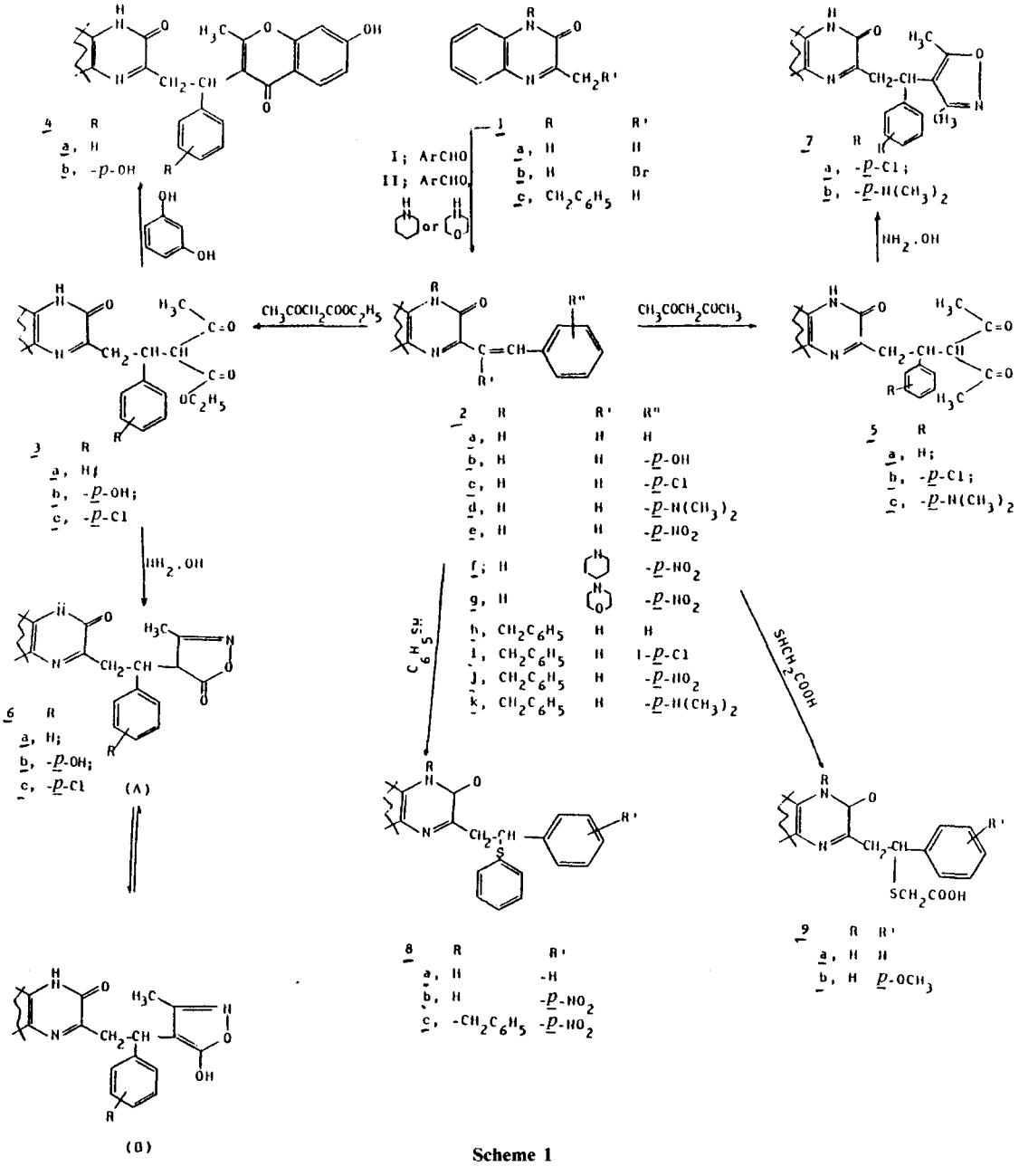
Abstract□Synthesis of α-piperidino and α-morphelino styryl quinoxalinone **2f, 2g** respectively by facile one step method is reported. The Michael adducts **(3a-d)** obtained by the interaction of 2-styryl-2 (1H) quinoxalinone **(2)** and ethylacetoacetate have been treated with resorcinol and hydroxylamine separatly. With resorcinol the chromones **(4)** are obtained whereas with hydroxylamine isoxazolones **(6)** are the products. Michael addition of acetylacetone to **2** leads to 3-[1'-aryl-2'-(2'-hydroxy-3'-quinoxalinyl)ethyl]-2,4-pentanediones **(5)** which undergo cyclisation with hydroxylamine to give isoxazoles **(7)**. Addition of thiophenol and thioglycolic acid to **2** gives 3-α-[β-(phenyl)-β-(plenylthio)]ethyl-2(1H)-quinoxalinone **(8)** and 3-α-[β-phenyl)-β-(hydroxycarbonylmethylthio)]-ethyl-2(1H)-quinoxalinone **(9)** respectively. 2-Bromomethyl-2(1H)-quinoxalinone **(1b)** reacts with thioglycolic acid to gives S-[2 (1H)-oxoquinoxalin-3-yl-methyl]mercaptoacetic acid **(10)** which on cyclisation with acetic anhydride/pyridine affords 1,2,5,6-tetrahydro[1,4]thiazino[4,3-a] quinoxaline-1,6-dione **(11)**.

Keywords□Michael products, 1,4-thiazine quinoxaline.

Quinoxalines and several compounds containing isoxazoles and 1,4-thiazine moiety constitute a class of biologically active compounds[1]. In continuation of our interest in the synthesis of different heterocycles[2] of expected biological potential. Now this study is to synthesis new quinoxalinone, thier isoxazoles, chromones and fused 1,4-thiazino derivatives. Thus the reactivity of the 3-methyl group in N-substituted and unsubstituted quinoxalinone towards condensation reation into the corresponding styryl compounds [2b, 3] **(2)** have been reported from our laboratory. The present investigation deals with the synthesis of a series of new styryl compounds **(2f-k)**. The structures of compounds **(2f-k)** were established based on their analytical data (Table I) and their IR spectral analysis which showed at 1665-1650 cm^{-1} for (C=O) gorup, at 1630-1610 cm^{-1} for (C=C) group and at 1580 cm^{-1} (C=N), and it is also suggested that compounds **(2)** are of trans configuration since a strong absorption band appeared in the region 990-980 cm^{-1} characteristic of trans olefinic configuration. I also succeeded in preparing 3-(α-piperidino-*p*-nitrostyryl-2 (1H)-quinoxalinone **(2f)** by a facile one step route. Thus refluxing a mixture of equimolar amounts of 3-bromomethyl-2(1H)-quinoxalinone[3] **(1b)**, *p*-nitrobenzaldehyde and piperidine in dry dioxane for 1 hr yield a product with molecular formula $C_{21}H_{20}N_4O_3$ (Scheme 1). Its structure was ruled by mixed mp. with an authentic sample[3]. Similarly I prepared α-morphilino compound **2g** (Table I).

The synthesis of the title compounds **(4)** was accomplished in a two-step reaction sequence starting from 3-(*p*-substituted styryl)-2(1H)-quinoxalone[3] **(2)**. Michael addition of ethylacetoacetate and/or acetylacetone to **2** were carried out in boiling triethyl amine to give β-ketoesters namely ethyl 2-[1-phenyl-2'-(2'-hydroxy-3'-quinoxalinyl]-ethyl acetoacetates **(3a-c)** and β-diketones namely 3-[1'-aryl-2'-(2'-hydroxy-3'-quinoxalinyl)-ethyl]-2,4-pentanediones **(5a-c)** respectively. The structures of compounds **(3a-d)** and **(5a-c)** were established based on their analytical and spectral data (Table I and II).

The β-ketoesters **(2a, b)** on condensation with resorcinol furnished 7-hydroxy-2-methyl-3-[2-(2(1H)-quinoxalinonyl)-1-arylethyl]-chromones **(4a, b)**. The heterocyclization was supported by the elemental analysis and ^{1}H-NMR (absence of ethyl group and presence of D_2O washable signal at δ 10.3). This is in keeping with the observation that compound **(2)** and resorcinol under Pechmann conditions resulted in a chromone rather than a coumarin as revealed by the appearance of ν C=O at 1690 cm^{-1} rather than at 1725 cm^{-1} in the case of coumarin[4]. β-Ketoester **(3)** the michael adduct, when boiled in ethanol with an equimolar amount of hydroxylamine hydrochloride



Scheme 1

for 3 hr, underwent cyclization to give the isoxazolones **(6a, b)** which exist in their enol-keto form as revealed by their IR spectra which showed no ester carbonyl at 1720 cm^{-1} but the appearance of a broad peak in the carbonyl region for the isoxazolone and quinoxalone rings at 1680-1655 cm^{-1} and other IR peak for OH group at 3160-3180 cm^{-1}. The heterocyclization was supported by the elemental analysis and ^{1}H-NMR (absence of ethyl group); ^{1}H-NMR (DMSO) of **6b** showed the methyl at δ 2.15, the two methylene protons appeared as a multiplet centered at δ 3.2, the lone tertiary proton showed up as a broad signal with fine structure at δ 4.3, and presence of D_2O washable signal at δ 12 for an enolic OH proton of the isoxazolone ring and at δ 12.2 for OH proton of the phenyl ring. The signal in ^{1}H-NMR at δ 12

Table I. Characterization data of compounds 2-10

Compd.	mp. (°C) Solvent	Yield (%) Colour	Mol. Formula	Found /Calc. (%)		
				C	H	N
2f	230 Dioxan	70 Orange	$C_{21}H_{20}N_4O_3$	67.01 67.00	5.36 5.37	14.89 14.94
2g	240 Dioxan	80 Yellow	$C_{20}H_{18}N_4O_4$	63.48 63.53	4.80 4.79	14.81 14.80
2h	155 Ethanol	70 Orange	$C_{23}H_{18}N_2O$	81.63 81.57	5.36 5.37	8.28 8.25
2i	205 Ethanol	80 Green	$C_{23}H_{17}N_2OCl$	74.10 74.00	4.59 4.59	7.51 7.50
2j	195 Ethanol	60 Brown	$C_{23}H_{17}N_3O_3$	72.05 72.12	4.47 4.48	10.96 10.97
2k	170 Ethanol	80 Red	$C_{25}H_{23}N_3O$	77.90 77.87	6.01 6.00	3.63 3.65
3a	200 Ethanol	75 Colourless	$C_{22}H_{22}N_2O_4$	69.82 69.81	5.86 5.87	7.40 7.35
3b	218 Ethanol	65 Colourless	$C_{22}H_{22}N_2O_5$	66.99 66.95	5.62 5.63	7.10 7.13
3c	198 Ethanol	70 Colourless	$C_{22}H_{21}N_2O_4Cl$	63.99 63.95	5.13 5.13	6.79 6.77
4a	250 Ethanol	90 Yellowish	$C_{26}H_{20}N_2O_4$	73.57 73.58	4.75 4.81	6.60 6.59
4b	265 Ethanol	70 Colourless	$C_{26}H_{20}N_2O_5$	70.90 70.89	4.58 4.59	6.36 6.43
5a	270 Methanol	50 Colourless	$C_{21}H_{20}N_2O_3$	72.39 72.29	5.79 5.78	8.04 8.01
5b	180 Dioxan	45 Colourless	$C_{21}H_{19}N_2O_3Cl$	65.87 65.85	5.00 5.00	7.31 7.34
5c	279 Methanol	60 Yellowish	$C_{23}H_{25}N_3O_3$	70.57 70.63	6.44 6.43	10.74 10.69
6a	202 Aq. ethanol	80 Greenish	$C_{20}H_{17}N_3O_3$	69.15 69.21	4.93 4.91	12.10 12.00
6b	204	80 Violet	$C_{20}H_{17}N_3O_4$	66.11 66.07	4.72 4.72	11.57 11.60
6c	320 Methanol	75 Colourless	$C_{20}H_{16}N_2O_2Cl$	62.90 62.87	4.22 4.23	11.00 10.90
7a	170 Ethanol	50 Colourless	$C_{21}H_{18}N_3O_2Cl$	66.39 66.41	4.78 4.78	11.07 11.07
7b	200 Aq. ethanol	60 Greenish	$C_{23}H_{24}N_4O_2$	71.11 71.11	6.23 6.22	14.42 14.43
8a	160 Pet-ether (60-80)	70 Yellowish	$C_{22}H_{18}N_2OS$	73.73 73.81	5.06 5.11	7.82 7.80
8b	170 Pet-ether (60-80)	80 Yellowish	$C_{22}H_{17}N_3O_3S$	65.50 65.49	4.25 4.25	10.42 10.40
8c	100 Pet-ether (60-80)	30 Yellowish	$C_{29}H_{23}N_3O_3S$	70.58 70.57	4.70 4.81	8.52 8.51
9a	165 Benzene	60 Yellowish	$C_{18}H_{16}N_2O_3S$	63.52 63.53	4.74 4.74	8.23 8.24
9b	195 Benzene	82 Yellowish	$C_{19}H_{18}N_2O_4S$	61.61 61.70	4.90 4.92	7.56 7.62
10	220 Aq. methanol	75 Red	$C_{11}H_{10}N_2O_3S$	50.42 50.37	4.23 4.24	11.76 11.77

Table II. Spectral data of the prepared compounds

Compd.	IR (KBr)	^{1}H-NMR ppm
3a	1720 (ester C=O) 1700 (acetyl C=O) 1660 (ring C=O)	0.9 (t, 3H, OCH_2CH_3), 1.25 (s, 1H, COCHCO), 2.35 (s, 3H, $COCH_3$), 3.25 (q, 2H, OCH_2CH_3) 3.85 (m, 2H, CH_2-CH), 4.1 (s, 1H, CHAr), 7.1-8.0 (m, 10H, NH_2Ar).
3b	3170 (OH) 1730 (ester C=O) 1700 (acetyl C=O) 1665 (ring C=O).	
3c	1720 (ester C=O) 1700 (acetyl C=O) 1660 (ring C=O)	0.99 (t, 3H, OCH_2CH_3), 1.25 (s, 1H, COCHCO), 2.3 (s, 3H, $COCH_3$), 3.2 (q, 2H, OCH_2CH_3), 3.85 (m, 2H, CH_2-CH), 4.05 (s, 1H, CHAr), 7-7.8 (m, 9H, NH, Ar).
5a	1700, 1680 (acetyl C=O), 1655 (ring C=O).	
5b	1690, 1680 (acetyl C=O), 1650 (ring C=O).	1.2 (s, 1H, OH), 3.6 (s, 3H, CH_3 isoxazol), 3.65 (s, 3H, CH_3 isoxazol), 4.1 (m, 2H, CH_2), 4.3 (s, 1H, CH), 6.5-7.8 (m, 8H, Ar).
5c	1710, 1690 (acetyl C=O), 1665 (ring C=O).	1.0 (s, 1H, OH), 1.85 (s, 3H, $COCH_3$), 2.3 (s, 3H, $COCH_3$), 2.3 (s, 3H, $COCH_3$), 2.85 (s, 3H, $N(CH_3)_2$), 3.4 (m, 2H, CH_2), 4.3 (s, 1H, CH), 6.5-7.8 (m, 8H, Ar).
7a	1655 (ring C=O).	1.7 (m, 2H, CH_2), 1.8 (s, 3H, CH_3), 1.9 (s, 3H, CH_3), 3.75 (s, 1H, CH), 6.6-8.7 (m, 8H, Ar).
8a		3.35 (m, 2H, CH_2), 5.05 (t, 1H, CH), 6.7-7.6 (m, 15H, 1NH, 14 Ar).
8b		3.5 (m, 2H, CH_2), 5.2 (t, 1H, CH), 6.5-8.1 (m, 14H, 1NH, 13 Ar).
9a		2.4 (s, OCH_3) 3 (m, 2H, CH_2, COOH), 3.4 (m, 2H, CH_2), 4.75 (t, 1H, CH), 6.9-7.7 (10H, 1NH, 9 Ar).
9b		2.9 (m, 2H, CH_2-COOH), 3.3 (m, 2H, CH_2) 4.7 (t, 1H, CH), 6.7-7.7 (10H, 1NH, 9 Ar).

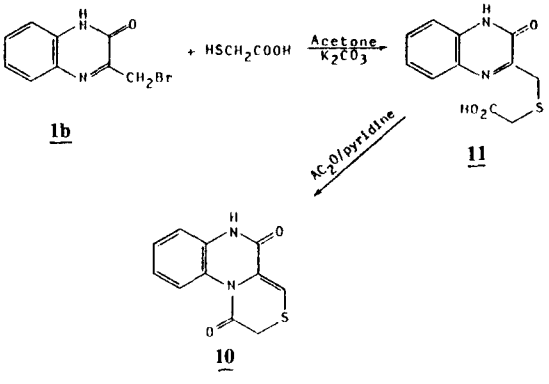
for an enolic OH proton provides an ample evidence to show that the isoxazolone (A) product also exists in the enolic-form (B).

However, when β-diketone compounds (**5**) were boiled in ethanol with an equimolar amount of hydroxylamine hydrochloride for several hours, underwent cyclization to give isoxazoles namely 3-[ω-(3,5-dimethyl-4-isoxazolyl)-ω-arylethyl]2 (1H)-quinoxalone (**7a, b**). The heterocyclization was supported by the elemental analyses (Table I), IR spectra showed absorption between 1665-1655 cm^{-1} for (C=O) of the ring while revealed the disappearance of absorption band between 1710-1690 cm^{-1} for two acetyl group and the ^{1}H-NMR spectrum of **7a** in ($CDCl_3$) revealed absence of OH group (Table II).

Thiophenol was added to 1-substituted-3-substituted styryl-quinoxalin-2-ones (**2**) to produce 1-substituted-3-α-[β-substituted phenyl)-β-(phenylthio)] ethylquinoxalin-2-ones (**8a-c**) whose IR spectra showed band at 1665-1670 cm^{-1} for (C=O) group and revealed the disappearance of (C=C) band at 1620-1610 cm^{-1}. The ^{1}H-NMR spectra of compounds (**8a, b**) in DMSO were in agreement with the suggested structures (Table I). Thioglycolic acid undergone addition to 3-styryl-2(1H)quinoxalinone (**2a, e**) giving the products, 3-α[β-substituted pehnyl)-β-(hydroxycarbonylmethylthio)]ethyl-2(1H)-quinoxalone (**9a, b**) (Table I). The IR spectra of (**9a, b**) showed

bands at 1680 cm^{-1} (C=O) of quinoxalinone nucleus, at 1700-1710 cm^{-1} (C=O) of carboxylic acid and a broad band at 2700-2500 cm^{-1} (assoc. OH). The PMR spectra of compound (**9a, b**) in DMSO were in agreement with the suggested structures (Table II).

Treatment of 3-bromomethyl-2(1H)-quinoxalinone[3] (**1b**) with thioglycollic acid in presence of K_2CO_3 in dry acetone gave S-[2(1H)-oxoquinoxalin-3-ylmethyl]mercaptoacetic acid (**10**) (Table I) whose IR spectrum showed absorption bands at 1720 cm^{-1} for (C=O) of the carboxylic acid and at 1660 cm^{-1} (C=O) of quinoxalinone nucleus cyclization of (**10**) with acetic anhydride and pyridine gave a new enamine type heterocyclic system charactrized as 1,2,5,6-tetrahydro[1,4]thiazino[4,3-a]quinoxaline-1,6-dione (**11**) on the basis of elemental analysis (Table I) and whose IR spectrum showed a broad band between 1645-1675 cm^{-1} for two (C=O) group and revealed the disappearance of (C=O) at 1720 cm^{-1}.



1b **11** **10**

EXPERIMENTAL

Melting points are uncorrected. IR (KBr) spectra were recorded on a Beckman 408-26 spectrophotometer and ^{1}H-NMR spectra in DMSO-d_6 or $CDCl_3$ on a Varian EM-390 spectrometer using TMS as internal standard. Elemental analyses were carried out at the Chemistry Departments of Assiut University. The characterization data of all compounds **2-10** are given in Table I.

Preparation of 1-substituted-3-(substituted styryl) quinoxalin-2-one (2)

1-Substituted-3-methyl-quinoxalin-2-one [2b, 3] (**1**) (0.01 mol) was fused with the corresponding aromatic aldehyde (0.012 mol) for 10 min in presence of few drops of piperidine. The product was isolated from the reaction mixture by adding ethanol, filtered and crystallised from the suitable solvent to give 3-(substituted styryl)-2-(1H)quinoxalinone[3] (**2a-d**) and 1-benzyl-3-(substituted styryl)-2-quinoxalin-2-one (**2h-k**) (Table I).

Preparation of 3-(α-piperidino/or morphilino-p-nitrostyryl)-2(1H)-quinoxalone (2f, g)

A mixture of 3-bromomethyl-2(1H)-quinoxalone (**1b**) (2.39g, 0.01 mol), *p*-nitrobenzaldehyde (1.7g, 0.012 mol) and piperidine or morphiline (0.01 mol) was refluxed in dry dioxane for one hr. The reaction mixture was concentrated and cooled then triturated with ethanol and the solid obtained was crystallizd from the suitable solvent (Table I).

Michael addition (3a-d and 5a-c)

A mixture of compound **2** (0.01 mol), the ethylacetoacetate or acetylacetone (0.05 mol) and triethylamine (50 m*l*) was refluxed for three days. After the removal of triethylamine the residue was triturated with petroleum ether and finally decomposed in ethanol and filtered colourless crystal of Michael adducts (**3a-d, 5a-c**) were obtained from the suitable solvent (Table I).

Condensation of Micahel adduct with resorcinol: Formation of the chromones (4a, b)

A mixture containing compound **2** (0.01 mol) resorcinol (1.10g, 0.01 mol) and 70% H_2SO_4 was stirred for 3 hr at 15°C. After the stirring time the reaction mixture became a clear solution. A crystalline compound obtained by pouring the solution into ice water, was filtered and washed with water. Recrystallization was effected from suitable solvent (Table I).

Condensation of Micahel adduct (3 and 5) with hydroxylamine: Formation of the isoxazolones (6a-c) and isoxazoles (7a, b)

The Michael adduct (**3** and/or **5**) (0.01 mol) and hydroxylamine (0.33g, 0.01 mol) were refluxed in ethanol for three six hours,cooled and poured into ice water. A crystalline compound which separated out was filtered, washed with water and recrystallized from suitable solvent (Table I).

Addition of thiophenol and thioglycolic acid to (2): Formation of (8, 9)

A mixture of 1-substituted-3-(substituted styryl) quinoxalin-2-one (**2**) (0.002 mol) and thiophenol (0.004 mol) and or thioglycolic acid (0.002 mol) was heated at 100°C for 2 hr. The yellow-brown oil formed was triturated with petr. ether (40-60°) and the product

obtained were crystallized from the proper solvent (Table I).

Reaction of 3 bromomethyl-2-(1H)-quinoxalone (1b) with thioglycollic acid: Formation of (10)

To a solution of **1b** (1.5g, 0.0063 mol) in acetone (37 m*l*) were added K_2CO_3 (0.995g, 0.0072 mol) and thioglycollic acid (0.882g, 0.0096 mol) and the mixture was refluxed on a water-bath. The progress of the reaction was monitored by TLC. After nine hours the reaction mixture was filtered acetone distilled off and the product obtained was crystallized (Table I).

Reaction of (10) with acetic anhydride and pyridine: Formation of (11)

A mixture of **10** (400 mg) acetic anhydride (14 m*l*) and pyridine (9 m*l*) was heated on a water-bath temperature for 1 hr, and the reaction mixture poured into water and aq. layer extracted with chloroform. The combined chloroform extracts were evaported at a low temperature and reduced pressure, and the residue was chromatographed over silica gel column using ethylacetate as eluant to give pure (**11**), mp > 320 with decomposition, yield 30%, (Found: C, 54.48; H, 3.65; $C_{11}H_8N_2O_2S$ Calced C, 54.55; H, 3.66%).

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