SYNTHESIS OF SOME NEW BIOLOGICALLY ACTIVE 2,3-DISUBSTITUTED QUINAZOLIN-4-ONES

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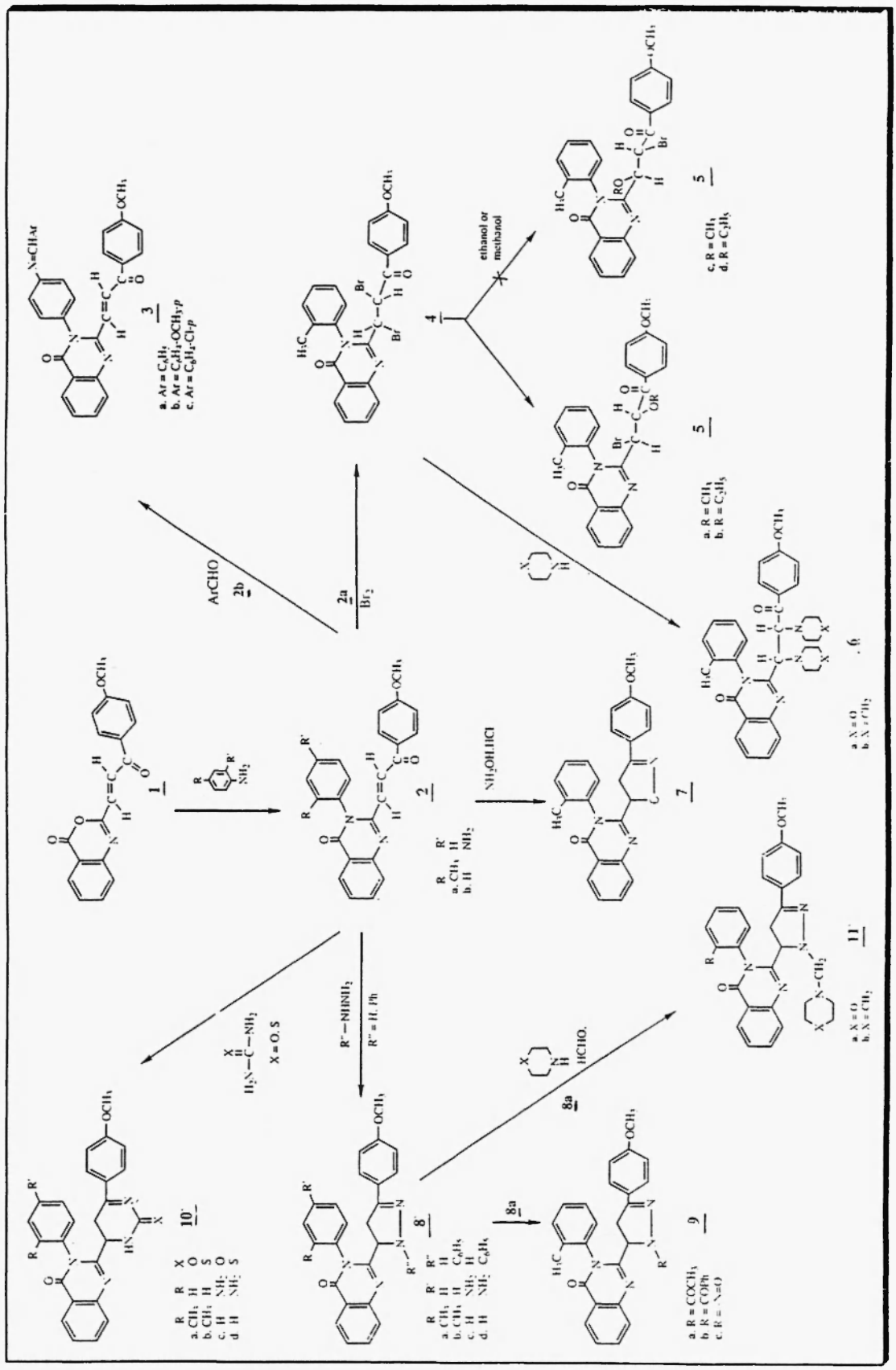
Abstract. The facile synthesis of 2-(2`-4-anisoylvinyl)-3-arylquinazolin--4-ones **(2a,b)** involves the condensation of 2-toluidine or 4-phenylenediamine with the corresponding 2-[2`-(4-anisoylvinyl)]-4*H*-3,1-benzoxazin-4-one (1). Reaction of compound 2 with aldehydes, bromine, alcohols, hydrazine hydrate, urea and thiourea are discussed. The former structure of the products have been characterized by elemental analysis and spectral data. Preliminary screening of some selected compounds for antimicrobial activity is reported.

Introduction. Among a wide variety of nitrogen heterocycles that have been explored for developing pharamaceutical important molecules, the quinazolinones have played an important role in the medicinal chemistry [1-6]. The present work is based on this central and involves the synthesis of 2,3-disubstituted quinazolin-4-ones and investigate the reactivity of the α,β-unsaturated carbonyl group towards some nucleophilic reagents. Also, the biological activity of some newly products has been evaluated and the sequence of the titled reactions is depicted in the scheme.

RESULTS AND DISCUSSION

Condensation of equimolar amount of 2-[2`-(4-anisoylvinyl)]-4*H*-3,1-benzoxazin-4-one **(1)** and 2-toluidine or 4-phenylenediamine in the presence of anhydrous $ZnCl_2$ [7,8] afforded 2-[2`-(4-anisoylvinyl)]-3-(2-tolyl)-4(3*H*) quinazoline **(2a)** 2-[2`-(4-anisoylvinyl)]-3-(4`-aminophenyl)-4(3*H*) quinazolinone **(2b)** respectively.

The methyl group in **2a** increased the yield to 25% higher than of the amino group in **2b**. ^{1}H NMR study of **2b** revealed the presence of signals attributable to the presence of amino, vinyl protons. Schiff bases **3a-c** of compound **2b** were formed from the reaction with different aldehydes.



In the course of this investigation, it was planned to study reactivity of α,β-unsaturated carbonyl group at position **2** in compound **2** toward bromine. Thus, addition of Br_2 to **2a** in chloroform (molar ratio **1:1**) furnished the dibromide derivative **4**. via cycle bromonium ion .

As a point of interest, refluxing of the dibromide 4 with alcohols afforded the corresponding α-bromo-β-alkoxy **5a** and **5b** or the β-bromo-α-alkoxy derivatives **5c** and **5d**. Formation of **5a** and **5b** rather than **5c** and **5d** was substantiated from the following facts: **I**) The electronic view showed that, the α-carbon (adjacent to the carbonyl group) is highly electron deficient than the β-carbon (adjacent to the heteroaryl moiety), therefore, it must be more available to be attacked by nucleophilic species. **ii**) The ^1H NMR spectra of **5a** or **5b** showed the higher value of chemical shifted to methyl groups in etheryl center adjacent to carbonyl group which may be attributable to the interaction between them leading to resonate sufficiently downfield of methyl group at β-alkoxy and provide enough support for structure **5a** and **5b**.

On the other hand, morpholine and piperidine reacts with the dibromide **4** [9] to give the corresponding α,β-dimorpholino **6a** and α,β-dipiperidino derivative **(6a,b)** respectively.

The original objective of the present work is the formation of 2,3-di-substituted quinazolin-4-ones. Thus, the interaction between compound **2a** with hydroxylamine hydrochloride in the presence of sodium acetate/ethanol solution gives 2-[4-(4`-anisoyl)isoxazlin-2-yl]-3-(2-tolyl)-4(3*H*)-quinazolinone **(7)**.

Compound **2a,b** are allowed to condense with hydrazine hydrate and phenylhydrazine in boiling ethanol to give 3-aryl-2(1`,3`-disubstituted pyrazolin-5-yl)-4*H*-quinazolinones (**8a-d**) respectively.

Some displacement reactions of the NH group of pyrazoline moeity were also investigated. Thus, N-acetyl or N-benzoyl derivatives **(9a,b)** were obtained from refluxing compound **8a** with acetyl or N-benzoyl chlorides while the interaction between **8a** and sodium nitrite/concentrated in hydrochloric acid mixture afforded 1-nitroso-2-(1`,3`-disubstituted pyrazolin-5`-yl)-3-(2`-tolyl)-4(3*H*)quinazolinone **(9c)**.

Substituted pyrimidinone and thioxopyrimidinone derivatives were found to exhibit antimicrobial activities [11,12], thus, **2a,b** were easily cyclocondensed with urea or thiourea in boiling ethanol with a few drops of acetic acid to give 3,4,5,6-tetrahydro-4,6-disubstituted pyrimidin-2(1*H*) ones **(10a,c)** or 3,4,5,6-tetrahydro-4,6-disubstituted pyrimidin-2-(1*H*)-thiones **(10b,d)** respectively.

Mannich bases of some heterobicyclic systems were found to be exhibit a remarkable anti-HIV and anticancer agents [13,14]. Thus, compound **8a** on reaction with morpholine or piperidine in the presence of formaldehyde in boiling methanol gave the Mannich bases **11a,b**.

Biological Activities

a. Antimicrobial Activity

The synthesized compounds were evaluated by using Carlson, Douglas Bissell and Abott's [15 . 16] against *B. substilis*, *B. cereus* and *B. mycoides* and the minimum inhibitors concentrations calculated as μg/ml (*Table 1*). Only compound **4** showed a moderate activity towards *B. cereus* and *B. mycoides* while all the newly compounds showed a bacteriostatic effect on *B. substilis*. In addition, the compounds **3a, 3c, 4, 8c, 8d, 10c** and **10d** revealed higher antibacterial activity in comparison with other tested compounds.

In order to understand the relationship between the structure and activity, it found that presence of halogen atom in **3** and **4** or amino groups in **8** and **10** resulted in a much higher order the *B. substilis*. Also, replacement of halogen atom by secondary amine in **6** caused a moderate activity towards *B. mycoides*.

b. Evaluation of the insecticidal activity against Cotton Leaf Worm (Spodoptera Littoralis)

The active compounds towards bacteria were screened for insecticidal activity and tested on the 3rd instar of the larvae of the cotton leaf worm (*Spodoptera littoralis*). The topical application technique has been adopted. Results were recorded after **24** hours from application and percentage mortality was calculated according to Eldefrawi [17] (Table 2).

In view of results, we concluded that presence of bromide radieal and/or amino, mercapto groups in the compounds **4** and **10d** leads to higher activity, while the presence of only amino group in **8c** caused a lowering of activity.

EXPERIMENTAL

All melting points are uncorrected. IR: Unicam SP 1200; NMR: Varian Gemini (90MHz), solvent DMSO, internal standard: TMS: Microanalyses: microanalytical laboratory at Microanalytical Center, Cairo University.

2-(2`,4-Anisoylvinyl)-3-(2`-methylphenyl)quinazolin-4-one (2a)

The mixture of 2-[2`-(4-anisoylvinyl)]-4*H*-3,1-bezoxazin-4-one (**1**) (0.01 mol), 2-toluidine (0.01 mol) and anhydrous $ZnCl_2$ (0.5 g) were heated at 150-160°C for 4 hours. The solid was washed with dilute Hcl (5%) and filtered off then crystallized from the proper solvent.

Yield: 75%; mp.: 188°C (ethanol); IR(KBr): υ = 1720 (s), 1675 (s), 1580(m) cm^{-1}; ^1H NMR: δ = 2.2 (s, 3**H**, CH_3), 3.8 (s, 3**H**, -OCH_3), 6.65 (d, 1**H**, α-C**H**=), 6.45 (d, 1**H**, β-C**H**=), 7.3-8.3 (m, 12**H**, aromatic **H**) ppm; $C_{25}H_{20}N_2O_3$ (396); calcd.: C 75.76, H 5.05, N 7.07; found: C 75.32, H 4.91, N 6.88.

2-(2`,4-Anisoylvinyl)-3-(4`-aminophenyl)quinazolin-4-one (2b)

Table 1. Minimal inhibitory concentration (MIC in μg/ml) of the biological active compounds*.

Compound	B. substilis	B. cereus	B. mycoides
2a	500	-	500
2b	125	-	500
3a	60	-	-
3b	125	-	-
3c	30	-	-
4	30	30	-
5a	125	-	-
5b	125	-	-
6a	-	-	60
6b	-	-	60
7	500	-	-
8a	500	-	-
8b	125	-	-
8c	60	-	-
8d	60	-	-
9a	-	-	-
9b	125	-	-
9c	-	-	-
10a	-	-	-
10b	500	-	-
10c	60	-	-
10d	60	-	-
11a	-	-	-
11b	500	-	500

* Active up to a concentration of 600 μg/ml.

Table 2. Activity of effective compounds against cotton leaf worm.

Compound	Mortality percentage at conc. 1 (%)
3a	60
3c	70
4	100
8c	40
8d	50
10c	70
10d	100

The mixture of 2-[2`-(4-anisoylvinyl)]-4*H*-3,1-bezoxazin-4-one (**1**) (0.01 mol), 4-phenylenediamine (0.01 mol) with anhydrous $ZnCl_2$ (0.5 g) was heated at 150-160°C for 10 minutes. After cooling, triturated with ethanol, the residue was filtered off and crystallized from the proper solvent.

Yield: 60%; mp.: 156°C (ethanol); IR (Kbr): υ = 3380 (s), 1715 (s), 1680 (s) cm^{-1}, 1590 (m) cm^{-1}; ^1H NMR: δ = 2.2 (s, 3**H**, CH_3), 2.4 (s, 3**H**, -OCH_3), 3.8 (s, 3**H**, =OCH_3), 6.7 (d, 1**H**, α-C**H**=), 6.5 (d, 1**H**, β-C**H**=), 6.95-7.4 (m, 11**H**, aromatic **H**), 8.16 (s, 2**H**, NH_2) ppm; $C_{24}H_{19}N_3O_3$ (397); calcd.: C 72.54, H 4.79, N 10.58; found: C 72.15, H 4.28, N 10.40.

Schiff bases (3a-c)

General procedure: The mixture of **2b** (0.01 mol), benzaldehyde, anisaldehyde or 4-chlorobenzaldehyde (0.01 mol) and acetic acid (0.5 ml) in ethanol (30 ml) was refluxed for 4 hours. The solid thus obtained was filtered off and crystallized from the proper solvent.

3a: Yield: 65%; mp.: 156°C (ethanol): $C_{31}H_{23}N_3O_3$ (485); calcd.: C 76.70, H 4.74, N 8.65; found: C 75.84, H 4.56, N 8.42.

3b: Yield: 50%; mp.: 178°C benzene): $C_{32}H_{25}N_3O_4$ (515); calcd.: C 74.56, H 4.85, N 8.16; found: C 73.81, H 4.22, N 7.62.

3c: Yield: 55%; mp.: 204°C (ethanol); $C_{31}H_{22}N_3O_3Cl$ (519.5); calcd.: C 71.61, H 4.24, N. 8.09, Cl 6.38; found: C 71.21, H. 3.93, N. 7.86, Cl 6.51.

α,β-dibromo-β-[3-(2`-tolyl)-4-oxoquinazolin-2-yl]ethylanisyl ketone (4)

To a cold solution of **2a** (0.01 mol) in chloroform (100 ml) was added gradually to a solution of bromine (0.01 mol) in chloroform (100 ml) and the reaction mixture was stirred for one hour. The solvent was evaporated on a steam bath and the separated solid was collected and crystallized from the proper solvent.

Yield: 60%; mp.: 248°C (benzene/ethanol; 5:1); $C_{25}H_{20}N_2O_3Br_2$ (556); calcd.: C 53.96, H 3.60, N. 5.04, Br 28.78; found: C 53.46, H 3.28, N 4.97, Br 27.84.

α-Alkoxy-β-bromo-β-[3-2`-tolyl)4-oxoquinazolin-2-yl]ethylanisyl ketones (**5a,b**)

A mixture of **4** (1 g) and methyl or ethyl alcohol (50 ml) was refluxed for one hour and concentrated. The solid thus obtained was filtered and crystallized.

5a: Yield: 50%; mp.: 211°C (ethanol); $C_{26}H_{23}N_2O_4Br$ (507); calcd.: C 61.54, H 4.54, N 5.52. Br 15.78; found: C 60.77, H 4.40, N 5.21, Br 15.15.

5b: Yield: 70%; mp.: 228°C (ethanol); IR (Kbr): υ = 1700 (s), 1680 (s), 1080 (s), 1050 (s), 650 cm^{-1}; ^1H

NMR: δ = 2.2 (s, 3H, CH_3), 3.3 (q, 2H, CH_2), 3.5-4 (m, 2H, -CH-CH-), 3.8 (s, 3H, $-OCH_3$), 4.0 (s, 2H, OCH_2CH_3), 7.3-8.2 (m, 12H, aromatic H) ppm.

α,β-Dimorpholino/dipiperidinoethylanisyl ketones (**6a,b**)

A mixture of 4 (1 g), morpholine and or piperidine (2 ml) in dry benzene (25 ml) was refluxed for 2 hours, filtered while hot and concentrated. The solid thus obtained was filtered and crystallized.

6a: Yield: 65%; mp.: 181°C (benzene); $C_{33}H_{36}N_4O_5$ (568); calcd.: C 69.71, H 6.34, N 9.86; found: C 69.54, H 5.57, N 9.27.

6b: Yield: 70%; mp.: 201°C (ethanol); $C_{35}H_{40}N_4O_3$ (564); calcd.: C 74.46, H 7.09, N 9.93; found: C 73.78, H 6.66, N 9.27.

2-(4-p-Anisyl-isoxazolin-2-yl)-3-(2-tolyl)quinazlin-4-one (**7**)

A mixture of **2a** (0.01 mol), hydroxylamine hydrochloride (0.01 mol) and sodium acetate (0.02 mol) in absolute ethanol (50 ml) was refluxed for 4 hours, concentrated then filter. The solid thus obtained after dilution of filtrate was crystallized.

Yield: 70%; mp.: 225°C (ethanol); $C_{25}H_{20}N_3O_3$ (410); calcd.: C 75.00, H 4.88, N 10.24; found: C 74.71 H 4.59, N 10.00.

3-Aryl-2-(1,3-disubstituted pyrazolin-5-yl)quinazolin-4-ones (**8a-d**)

Amixture of **2a** and/or **2b** (0.01 mol), hydrazine hydrate and/or phenylhydrazine (0.01 mol) in ethanol (20 ml) was refluxed for 4 hours. The solid products obtained after concentration were crystallized from the proper solvent.

8a: Yield: 60%; mp.: 185°C (acetic acid); $C_{25}H_{19}N_4O_2$ (407); calcd.: C 73.71, H 4.67, N 13.75; found: C 73.18, H 4.06, N 13.47.

8b: Yield: 50%; mp.: 197°C (benzene/ethanol); IR (KBr): υ = 2900 (m), 1680 (s), 1600 (m), 1480 (s), 1050 (s) cm^{-1}; ^1H NMR: δ = 2.3 (s, 3H, CH_3), 2.5 (d, 2H, CH_2), 4.2 (s, 3H, $-OCH_3$), 6.65 (t, 1H, CH pyrazoline), 6.9-7.95 (m, 17H, aromatic H) ppm.

8c: Yield: 55%; mp.: 133°C (benzene); $C_{24}H_{21}N_5O_2$ (411); calcd.: C 70.07, H 5.11, N 17.03; found: C 69.18, H 4.74, N 16.6.

8d: Yield: 70%; mp.: 168°C (ethanol); $C_{30}H_{25}N_5O_2$ (487); calcd.: C 73.92, H 5.13, N 14.37: found: C 73.22, H 4.76, N 13.87.

N-Acetyl/benzoyl pyrazoline derivative (**9a,b**)

A mixture of **8a** (0.01 mol), acetyl chloride and/or benzoyl chloride (0.01 mol) was refluxed for 6 hours, cooled then poured on to ice. The solid thus obtained recrystallized.

9a: Yield: 60%; mp.: 252°C (ethanol); $C_{27}H_{24}N_3O_4$ (452); calcd.: C 71.60, H 5.30, N 12.30; found: C70.90, H 4.90, N 12.00.

9b: Yield: 76%; mp.: 213°C (ethanol); IR (KBr): υ = 2980 (s), 1720 (s), 1700 (s), 1670 (s), 1600-1570 (b), 1480 (b), 1050 (s) cm^{-1}; $C_{32}H_{26}N_4O_3$ (514); calcd.: C 74.70, H 5.06, N 1080; found: C 74.55, H 4.95, N 10.30.

N-Nitrosopyrazoline derivative **(9c)**

A solution of **8a** (0.01 mol) in hydrochloric acid (10 ml) was warmed with a solution of sodium nitrite (0.03 mol, in 3 ml H_2O). The reaction mixture was warmed on water bath for one hour, then poured on to ice. The solid separated was filtered and crystallized.

9c: Yield: 40%; mp.: 232°C (benzene); IR (KBr); υ = 2850 (s), 1700 (s), 1680-1610 (b), 1600-1500 (b), 1300 (s), 750 (s) cm^{-1}; $C_{25}H_{21}N_5O_3$ (439); calcd.: C 68.30, H 4.70, N 15.90; found: C 68.00, H 4.50, N 15.50.

3,4,5,6-Tetrahydro-4,6-disubstituted pyrimidin-2(1H)ones (**10a,c**) and *3,4,5,6-Tetrahydro-4,6-disubstituted pyrimidin-2(1H)thiones* (**10b,d**)

General procedure: A mixture of **2a** and/or **2b** (0.01 mol), urea (0.012 mol) and acetic acid (1 ml) in absolute ethanol (20 ml) was refluxed for 6 hours. The solid product formed after removal of the excess solvent was crystallized.

10a: Yield: 60%; mp.: 160°C (ethanol); $C_{26}H_{19}N_4O_3$ (435); calcd.: C 71.72, H 4.37, N 12.87; found: C 71.02, H 3.97, N 12.24.

10c: Yield: 40%; mp.: 145°C (benzene); $C_{25}H_{21}N_3O_3$ (439); calcd.: C 68.34, H 4.78, N 15.95; found: C 68.60, H 4.42, N 15.62.

10b: Yield: 40%; mp.: 228°C (ethanol); IR (KBr): υ = 3100 (b), 1700 (s), 1600 (b), 1350 (s), 1200 (s), 750 (s) cm^{-1}; ^1H NMR: δ = 2.45 (s, 3**H**, CH_3), 2.6 (d, 2**H**, CH_2), 3.65 (s, 1**H**, N**H**), 4.4 (s, 3**H**, -OCH_3), 6.9 (s, 1**H**, C**H**-pyrimidine), 6.85-7.55 (m, 12**H**, aromatic **H**) ppm; $C_{26}H_{19}N_4O_2S$ (451); calcd.: C 69.18, H 4.21, N 12.42, S 7.10; found: C 68.77, H 3.84, N 12.14, S 6.82.

10d: Yield: 40%; mp.: 262°C (ethanol); $C_{25}H_{21}N_5O_2S$ (455); calcd.: C 65,93, H 4.62, N 15.39, S 7.03; found: C 65,44, H 4.18, N 15.15, S 6.85.

Mannich bases **(11a,b)**

A mixture of **8a** (0.01 mol), morpholine and/or piperidine (0.01 mol) and formaldehyde (0.01 mol) in methanol (50 ml) was refluxed for 4 hours, cooled and poured on to ice. The solid product was filtered and crystallized.

11a: Yield: (70%); mp.: 260°C (ethanol/benzene 1:1); $C_{29}H_{29}N_5O_3$ (495); calcd.: C 77.85, H 6.49, N 15.66; found: C 76.95, H 6.4, N 15.50.

11b: Yield: (75%); mp.: 238°C (ethanol/benzene); IR (KBr); υ = 2900 (s), 2850 (s), 1700 (s), 1600 (s), 1480 (b), 1050 (s), 780 (s) cm^{-1}; $C_{30}H_{11}N_5O_2$ (493) calcd.: C 78.09, H 6.72, N 15.18; found: C 78.00, H 6.50, N 15.00.

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Received on September 17, 1997