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SYNTHESIS OF SOME QUINOXALINE-6-MORPHOLYL SULPHONAMIDE DERIVATIVES

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Condensation of (III) with amines furnished (IV_{a-c} and $V_{a,b}$), while interaction of (III) with sulphanilamide in the presence of anhydrous potassium carbonate yielded (VI). Treatment of (III) with thiourea caused cyclization and gave (IXa,b and X). Cyclization reaction of (III) with acetonethiosemicarbazone furnished (XI). The reaction of the free base (XII) with carbon disulphide afforded (XVI), which reacted with hydrazine hydrate to give (XVIII). Cyclization of (XVIII) with benzoyl chloride furnished the triazolo-derivative (XIX).

Key words: Quinoxalines-6-Morpholyl, Sulphonamide, Application to pharmacological agents.

Introduction

Quinoxalines have become of considerable interest due to their wide application particularly as pharmacological agents e.g., polypeptide antibiotics such as levomycin, Antinoleukin, Echinomycin and Quinomycin. Also a number of 2,3- and 2,3,6-di and tri- substituted quinoxalines exhibited some antimicrobial activity [1-6]. As a point of interest, we have studied the behaviour of 2,3-dichloroquinoxaline-6-morpholyl sulphonamide towards different nucleophiles. It was reported that [7-8] electron withdrawing groups at the 6-position activate the chlorine atom at the 2-position, while electron donating groups male the chlorine at the 3-position more active.

Experimental

Melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratories of the Faculty of Science, Cairo University and El-Nasr Pharmaceutical Chemical Co., results were collected in Table 1, IR spectra were measured on Shimdzu I.R. 440 spectrophotometer using KBr technique, Department of Chemistry, Faculty of Science, and ^{1}H-NMR spectra were measured on varian EM-360-60 MHz in same department of Al-Azhar University.

Synthesis of 2,3-dihydroxyquinoxaline-6-morpholyl sulphonamide (II). A mixture of 2,3-dihydroxyquinoxaline-6-sulphonyl-chloride (I[7]; 0.01mol), morpholine (0.012 mol) and pyridine (0.5 ml) in ether (30 ml) was heated under reflux for 2 hrs. The obtained product was recrystallized from dimethyl formamide to give (II): IR spectra showed bands at 3420, 2990 and 1600 cm^{-1} (COH, Ch-alipatic and C=N respectively).

Preparation of 2,3-dichloroquinoxaline-6-morpholyl sulphonamide (III). A mixture of (II; 0.01 mol) and phosphorous pentachloride (0.01 mol) in phosphorous oxychloride (30 ml) was refluxed for 5 hrs. After cooling the reaction mixture was poured into crushed ice and the obtained solid was recrystallized from benzene to afford (III): IR spectra showed the disappearance of γOH bands present in the parent compound. The ^{1}H-NMR spectrum of (III; in CD_3COCD_3) revealed two signals at δ = 3.2, 3.7 corresponding to 8 protons of morpholinyl and mutiplet at δ = 8.3-8.6 ppm corresponding to 3 aromatic protons.

Interaction of (III) with amines to give (IV). A solution of (III; 0.01 mol) in ethanol or dimethyl formamide (50 ml) was treated with the requisite amine (0.012 mol). The reaction mixture was heated under reflux for 2 hrs and the obtained product was recrystallized from ethanol to give (IV_{a-c}): IR spectrum of (IV_a) exhibited a broad absorption band around 3350 cm^{-1} (γNH). The ^{1}H-NMR (IV; in $CDCl_3$) showed signals at δ = 1.03 (6H, 2d, 2 x CH_3), 2.04 (1H, m, CH), 3.04 (4H, t, $N\langle^{CH_2}_{CH_2}$ morpholinyl), 3.45 (2H, to, CH_2-CH), 3.71 (4H, t, $O\langle^{CH_2}_{CH_2}$ morpholinyl), 5.93 (1H, to, NH) and 7.80-8.20 ppm (3H, m, Ar-H). While mass spectrum of (IV_a) gave a molecular ion peak at m/e 384 (43%) with a base peak 328 (100%) and other significant peaks at 343 (31%), 242 (6%), 178 (11%), 143 (1%), 128 (16%) and 101 (10%).

Formation of 2-sulphanilamido and 2-sulphaguanidino-3-chloroquinoxaline-6-morpholyl sulphonamides ($V_{a,b}$). A mixture of (III; 0.01 mol) and sulphanilamide or sulphaganidine (0.012 mol) in dimethyl formamide (30 ml) was refluxed for 12 hrs. The obtained product was recrystallized from dimethylformamide to furnish (Va,b): IR spectrum of (Va) revealed bands at 3400, 3380 and 3300 cm^{-1} corresponding to NH and SO_2NH_2 respectively.

Synthesis of 2,3-Disulphanilamidoquinoxaline-6-morpholyl sulphonamide (VI). A solution, of (III; 0.02 mol)

Table 1. Physical Data of the Prepared Compounds.

Comp. No.	M.P. (°C)	Yield (%)	Mol. formula	Analysis Required/Found			
				C	H	N	S
II	>300	82	$C_{12}H_{13}N_3O_5S$	46.30	4.18	13.50	10.29
				46.10	4.00	13.70	10.40
III	190	78	$C_{12}H_{11}N_3O_3SCl_2$	41.38	3.16	12.06	9.20
				41.40	3.20	12.10	9.30
IVa	146	74	$C_{16}H_{21}N_4O_3SCl$	49.95	5.46	14.56	8.32
				49.60	5.10	14.10	8.60
b	133	76	$C_{16}H_{21}N_4O_3SCl$	49.93	5.46	14.56	8.32
				49.60	5.50	14.50	8.50
c	173	75	$C_{16}H_{19}N_4O_4SCl$	48.18	4.77	14.50	8.03
				48.20	4.50	14.10	8.10
Va	>300	72	$C_{18}H_{18}N_5O_5S_2Cl$	44.67	3.72	14.48	13.24
				44.80	3.10	14.80	13.10
b	>300	72	$C_{19}H_{20}N_7O_5S_2Cl$	43.39	3.80	18.64	12.18
				43.23	4.10	18.84	12.20
VI	238	75	$C_{24}H_{25}N_7O_7S_3$	46.53	4.04	15.83	15.51
				46.23	4.38	15.49	15.83
VIIa	>300	72	$C_{38}H_{33}N_7O_7S_3$	57.36	4.15	12.33	12.07
				57.50	4.54	12.78	12.58
b	>300	74	$C_{40}H_{37}N_7O_9S_3$	56.14	4.33	11.46	11.23
				56.10	4.40	11.50	11.20
VIII	>300	70	$C_{28}H_{29}N_7O_9S_3$	47.79	4.12	13.94	13.65
				47.80	4.30	13.70	13.40
IX	>300	56	$C_{24}H_{22}N_6O_6S_4$	46.60	3.56	13.59	20.71
				46.30	3.80	13.60	20.40
X	222	7	$C_{13}H_{13}N_5O_3S_2$	44.44	3.70	19.94	18.23
				44.50	3.80	19.60	18.10
XI	258	75	$C_{13}H_{15}N_6O_3S_2Cl$	38.76	3.73	20.87	15.90
				38.64	3.14	20.53	15.80
XII	250	72	$C_{13}H_{14}N_6O_3S_2$	42.62	3.82	22.95	17.49
				42.95	3.75	23.10	17.55
XIIIa	248	72	$C_{20}H_{18}N_6O_3S_2$	52.86	3.96	18.50	14.10
				52.60	3.80	18.80	14.20
b	236	70	$C_{21}H_{20}N_6O_4S_2$	52.07	4.13	17.35	13.22
				52.20	4.10	17.40	13.40
XIV	245	80	$C_{19}H_{20}N_6O_6S_2$	46.34	4.06	17.07	13.01
				46.45	4.15	17.10	13.15
XV	>300	75	$C_{20}H_{16}N_6O_3S_2$	53.10	3.54	18.58	14.16
				53.20	3.40	18.25	14.00
XVI	>300	70	$C_{13}H_{13}N_5O_3S_3$	40.73	3.39	18.28	25.06
				40.30	3.52	18.50	25.50
XVII	228	76	$C_{15}H_{17}N_5O_3S_3$	43.79	4.14	17.03	23.36
				43.35	4.35	17.25	23.40
XVIII	>300	75	$C_{13}H_{15}N_7O_3S_2$	40.94	3.94	25.72	16.80
				40.75	3.95	25.80	16.75
XIX	>300	86	$C_{20}H_{17}N_7O_3S_2$	51.39	3.64	20.98	13.70
				51.45	3.50	21.00	13.50

and sulphanilamide (0.04 mol) in DMF (50 ml) was treated with anhydrous K_2CO_3 (3g) and the reaction mixture was refluxed for 6 hrs. After cooling the reaction mixture was poured into crushed ice and the obtained product was recrystallized from dimethylformamide to give (VI): IR spectra showed γNH_2 at 3490, 3390 and γSO_2NH at 3300 cm^{-1}.

Preparation of schiff's bases ($VII_{a,b}$). A solution of (VI; 0.01 mol) in ethanol (50 ml) was refluxed with benzaldehyde or anisaldehyde (0.02 mol) for 2 hrs. The obtained product was recrystallized from ethanol to afford ($VII_{a,b}$): IR spectra showed the disappearance of NH_2 bands present in the parent compound.

Acetylation of compound (VI). A solution of (VI; 0.01 mol) in acetyl chloride (25 ml) or acetic anhydride (25 ml) was refluxed for 4 hrs. The reaction mixture was cooled, poured into crushed ice (100 g) and the obtained product was recrystallized from acetic acid afford to (VIII): IR spectra exhibited the presence of CO band at 1700cm^{-1}.

Interaction of (III) with thiourea. Thiourea (0.01 mol) was added to a suspension of (III; 0.01 mol) in ethanol (50 ml) and the mixture was refluxed for 30 mins. The obtained product was recrystalized from acetic acid furnished the dithiien derivative (IX): IR measurements showed γC=N at 1530 and γC-S-C at 750 cm^{-1}.

Synthesis of 2-Imino-2,3-dihydrothiazolo [5,4-blquinoxaline-6-morpholyl sulphonamide (X). The filtrate from the method of the preparation of the dithiien (IX) was poured into water (100 ml) and the obtained product was recrystallized from ethanol to give (X): IR spectra showed wide absorption band (γNH) around 3400 cm^{-1}.

Interaction of (III) with acetonethiosemicarbazone. A mixture of (III; 0.01 mol) and acetonethiosemicarbazone (0.01 mol) in ethanol (50 ml) was refluxed for 30 mins. The obtained solid was recrystallized from dimethyl formamide to give (XI).

Formation of the free base (XII). The hydrochloride salt (XI; 0.02 mol was treated with sodium hydroxide (10%; 50 ml) or sodium acetate solution (10%; 50ml) at 50°C for 1 hr. The obtained substance was filtrated and recrystallized from ethanol to give the corresponding free bases (XII): IR spectra revealed the presence of bands at 3450, 3380 and 3330 cm-1 corresponding to NH2 and NH groups. The ^{1}NHMR of (XII; in $DMSOd_6$) which showed singals at δ = 3.0, 3.7 (8H, corresponding for morpholinyl + 2H of NH_2, 5.6 (1H, hump, NH), 8.2, 8.5 ppm (3H, m, Ar-H).

Action of nitrous acid on (XII) to give (X). $NaNO_2$ solution (5N; 100 ml) was added dropwise to a solution of (XII; 0.02 mol) in conc. HCl (50 ml) at -50°C during 2 hrs. The reaction mixture was left to stand at room temperature for 2 hrs, with occasional shaking then added to crushed ice (100 g). The obtained solid was filtered and recrystallized from ethanol to give (X) in 20-35% yielded.

Reaction of (XII) with aldehydes. A mixture of (XII; 0.02 mol) and benzaldehyde or anisaldehyde (0.02 mol) in ethanol (50 ml) was refluxed for 4 hrs. The obtained solid was recrystallized from acetic acid to give the corresponding shiff's bases ($XIII_{a,b}$). IR spectra showed the disappearance of γNH_2 and the ^{1}HNMR spectrum of (XIIIb; in $DMSOd_6$) exhibited signals at δ = 3.1-3.7 (8H, 2, morpholinyl), 4.0 (3H, s, OCH)3, 7.3-8.4 (8H, m, Ar-H + NH), 9.8 ppm (1H, s, CH).

Acetylation of (XII). A solution of (XII; 0.02 mol) in acetyl chloride (25 ml) or acetic anhydrode (10 ml) was refluxed for 4 hrs. After cooling the reaction mixture was poured into crushed ice (100 g) and the obtained product was recrystallized from acetic acid to give the corresponding triacetyl derivative (XIV). IR spectra revealed the disappearance of γNH_2 and NH bands present in the parent compound and the presence of γCO bands at 1720, 1700 cm^{-1}.

Preparation of triazolo derivative (XV). A solution of (XII; 0.02 mol) in benzoyl chloride (20 ml) was refluxed for 5 hrs, the solid that obtained was recrystallized from dimethyl formamide to give (XV). IR spectra revealed the complete disappearance of both γHN_2 and γNH bands.

Interaction of (XII) with carbon disulphide. Carbon disulphide (0.04 mol) was added to a solution of (XII; 0.02 mol) in anhydrous pyridine (50 ml). The reaction mixture was heated under reflux for 6 hrs with stirring. The obtained product was recrystallized from acetone furnished (XVI). IR, spectra showed γNH, at 3120 and γCH at 2980 cm^{-1}.

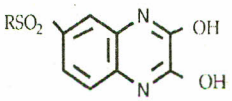
Methylation of (XVI). Dimethylsulphate (0.04 mol) was added dropwise to a solution of (XVI; 0.02 mol) in sodium hydroxide (10%; 50 ml). The reaction mixture was stirred at 60°C for 3 hrs and the obtained product was recrystallized from ethanol to give (XVII). IR spectra showed the disappearance of γNH present in the parent compound. The ^{1}HNMR spectrum of (XVII; in $DMSOd_6$) revealed signals at δ = 2.8 (3H, s, SCH_3), 3.1-3.8 (11H, morpholinyl with NCH_3) and 8.2-9.1 ppm (3H, m, Ar-H).

Interaction of (XVI) with hydrazine hydrate. A mixture of (XVI; 0.02 mol) and hydrazine hydrate (98%; 0.04 mol. excess) was stirred at room temperature for 30 mins. The obtained solid was recrystallized from dimethyl formamide furnished (XVIII). IR spectra exhibited sharp band at 3380 and broad band aroun 3100 corresponding of NH_2 and NH.

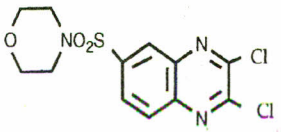
Cyclization reaction of (XVIII) with benzoyl chloride. A solution of (XVIII; 0.02 mol) in benzoyl chloride (20 ml) was heated under reflux for 2 hrs. The obtained solid was recrystallized from dimethyl formamide to give the corresponding triazolo derivative (XIX). IR spectra revealed the disappearance of γNH_2.

Results and Discussion

2,3-Dihydroxyquinoxaline-6-sulphonyl chloride (1)[9] was reacted with morpholine to afford 2,3-dihydroxyquinoxaline-6-morpholyl sulphonamide (II). Chlorination of (II) with a mixture of $PCl_5/POCl_3$ yielded 2,3-dichloroquinoxaline-6-morpholyl sulphonamide (III).



(I), (II)

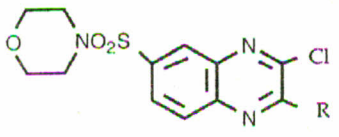


(III)

I, R = Cl
II, R = morpholinyl

Condensation of (III) with amines in ethanol or DMF produced a product with analytical data indicating that one chlorine atom only was reacted according to the reactivity of the sulphonamide group. The product was established as the 2-substituted amino-3-chloroquinoxaline-6-morpholyl sulphonamide (IV).

The reaction between (III) and sulphonamides through N^1 and N^4 was discussed. Thus, direct interaction between (III) and sulpha derivatives such as sulphanilamide or sulphaguanidine in DMF under reflux conditions yielded ($V_{a,b}$) that gave a negarive azo dye tests and their analysis indicated that one mole of sulpha derivatives were consumed in the reaction with the chlorine atom at 2-position.

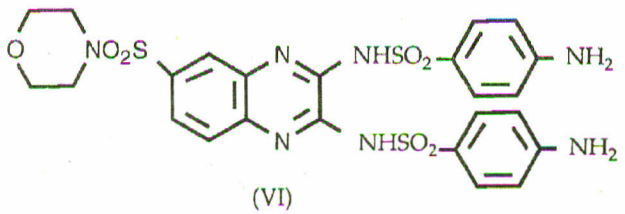


(IV, V)

IVa, R = NH-C_4H_9-iso
b, R = $N(C_2H_5)_2$
c, R = Morpholinyl

Va, R = NH-C_6H_4-SO_2NH_2
b, R = NH-C_6H_4-SO_2NH-C(=NH)-NH_2

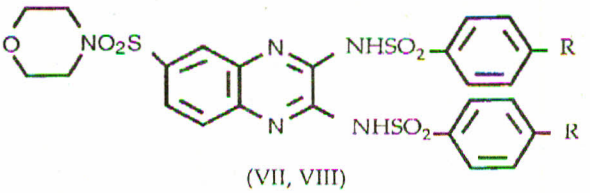
The reaction of (III) with sulphanilamide was repeated in the presence of anhydrous potassium carbonate. The product obtained gave a positive azo dye test and its analytical data showed that two moles of sulphanilamide were consumed to give (VI).



(VI)

It seems that in the absence of anhydrous potassium carbonate, the amino group of sulphanilamide is the only reactive centre which is capable of the reaction with the chlorine atom. While in the presence of anhydrous potassium carbonate, sulphonamide gave the potassium salt (H_2N-C_6H_4-$SO_2NH^-K^+$) which made the sulphonamide group more active than the amino group toward the reaction with the chlorine atoms. The reactivity of the formed sulphonamide anion is responsible for the reaction with the less reactive chlorine in 3-position.

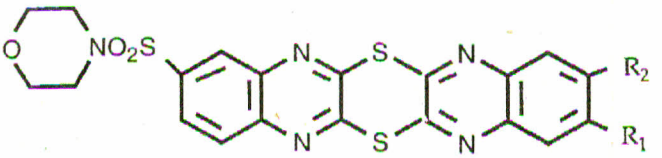
A further evidence for structure (VI) was arrived at from the interaction of (VI) with aldehydes and acetyl chloride to give the corresponding shiff's bases ($VII_{a,b}$) and acetanilide derivative (VIII) respectively.



(VII, VIII)

VIIa, R: N = CH-C_6H_5
b, R: N = CH-C_6H_4. OCH_3-p
VIII, R: NH-$COCH_3$

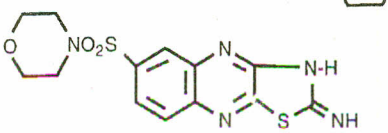
As a part of our program, directed towards the examined synthesis of used heterocyclic nitrogen compounds, we have the reaction of (III) with other nucleophiles.



(IXa,b)

IXa, R_1=SO_2N(morpholinyl), R_2=H

IXb, R_1=H, R_2=SO_2N(morpholinyl)

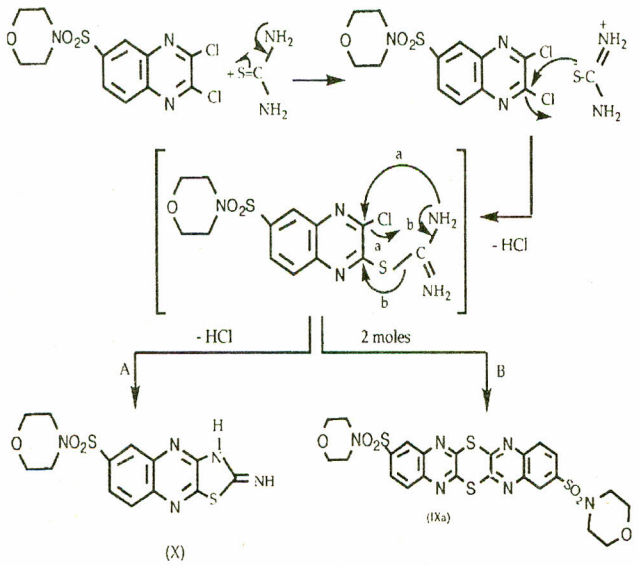


(X)

Thus interaction of (III) with thiourea in ethanol furnished two products, the first, was separated from the reaction mixture and was analysed as the dithien derivatives (IX), which can exist in two isomeric forms (IX_a or IX_a). The second product which was isolated from the filterate and exhibited similar spectroscopic data as the thiazoloquinoxaline (X). The sulphonyl group make the 2-chlorine atom to react first to

give the intermediate which then cyclized to give 2-imino-2,3-dihydrothiazolo-[5,4]-blquinoxaline derivative (X), while in the case of 6-methyl-2,3-dichloro quinoxaline, the product was 6-methyl-2-imino-2,3-dihydrothiazol-[4,5-b] quinoxaline (XI) [7,8].

The mechanism of formation of (IX,X) can be rationalized as follows:

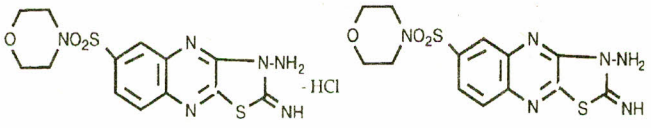


(X)

The above proposed mechanism for the formation of (X) (route B) favours the isomeric structure (IXa).

Condensation of (III) with acetonthiosemicarbazone caused cyclization and gave 6-morpholyl sulphomamide-3-amino-2-imino-2,3-dihydrothiazolo [5,4-b] quinoxaline hydrochloride (XI).

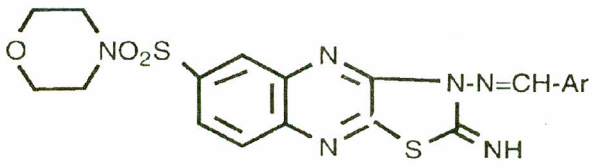
The free base (XII) was released from (XI) by treatment with either aqueous solution of sodium hydroxide (10%) or sodium acetate (10%). Compound (XII) was deaminated by using nitrous acid to give 2-imino-2,3-dihydrothiazolo [5,4-b] quinoxaline derivative (X). This affords an additional proof for structure (XII).



(XI) (XII)

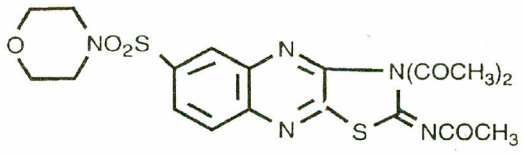
The amino group in compound (XIII) was also demonstrated through its condensation with aromatic aldehydes to give the shiff's bases 3-arylideneimino-2-imino-2,3-dihydrothiazolo[5,4-b]quinoxaline (XIII).

XIIIa, Ar = C_6H_5
b, Ar = C_6H_4-OCH_3-p



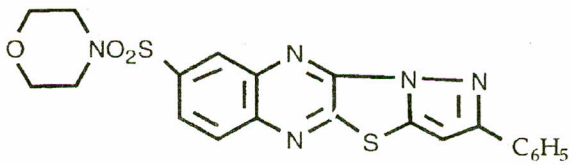
(XIII)

The 3-amino-2-imino derivative (XII) was used as a starting material in the synthesis of polyfused cyclic compounds. Acetylation of the free bases (XII) with acetyl chloride or acetic anhydride furnished the corresponding triacetyl derivative (XIV).



(XIV)

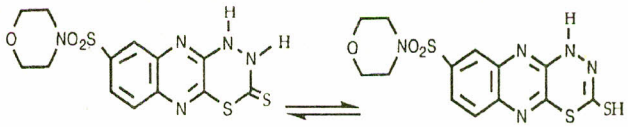
Again the free base (XII) underwent cyclization with benzoyl chloride to give the triazolo (3', 2', 2, 3) thiazolo[5,4-b]-quinoxaline derivative (XV).



(XV)

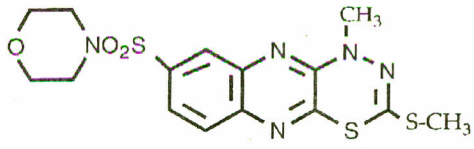
The effective cyclization of aromatic acid chloride rather than acetic anhydride can be attributed to steric factors.

Carbon disulphide caused ring expansion for 3-amino-2,3-dihydrothiazolo[4,5-b]quinoxaline and gave 2-mercapto-4H-1,3,4-thiadiazino-[5,6-b]quinoxaline [7-8].



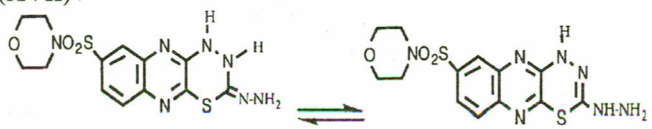
(XVI)

Similar, reaction of the free amino derivative (XII) with carbon disulphide in pyridine or sodium hydroxide gave 2-mercapto-4H-1,3,4-thiadiazino-[6,5-b]-quinoxaline (XVI).



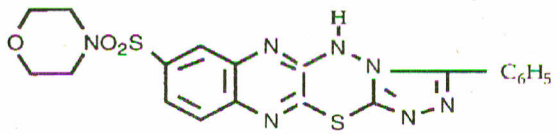
(XVII)

Methylation or (XVI) by using dimethyl sulphate furnished 2-methylmercapto-4-methyl thiazinoquinoxaline (XVII)



(XVIII)

Condensation of (XVI) with hydrazine hydrate gave (XVIII) that can exist in the hydrazono or hydrazino forms.



(XIX)

The 2-hydrazino derivative (XVIII) underwent cyclization with benzoyl chloride to give the corresponding triazolof[2', 3', 2, 3]-1, 3,4-thidiazino-[6,5-b]quinoxaline (XIX).

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