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STUDIES ON THIOQUINAZOLINONES AND SYNTHESIS OF 9-IODO-3,4-DIPHENYL [1,2,4,5]TETRAZEPINO[3,2-*b*]QUINAZOLIN-7(1H)-ONE

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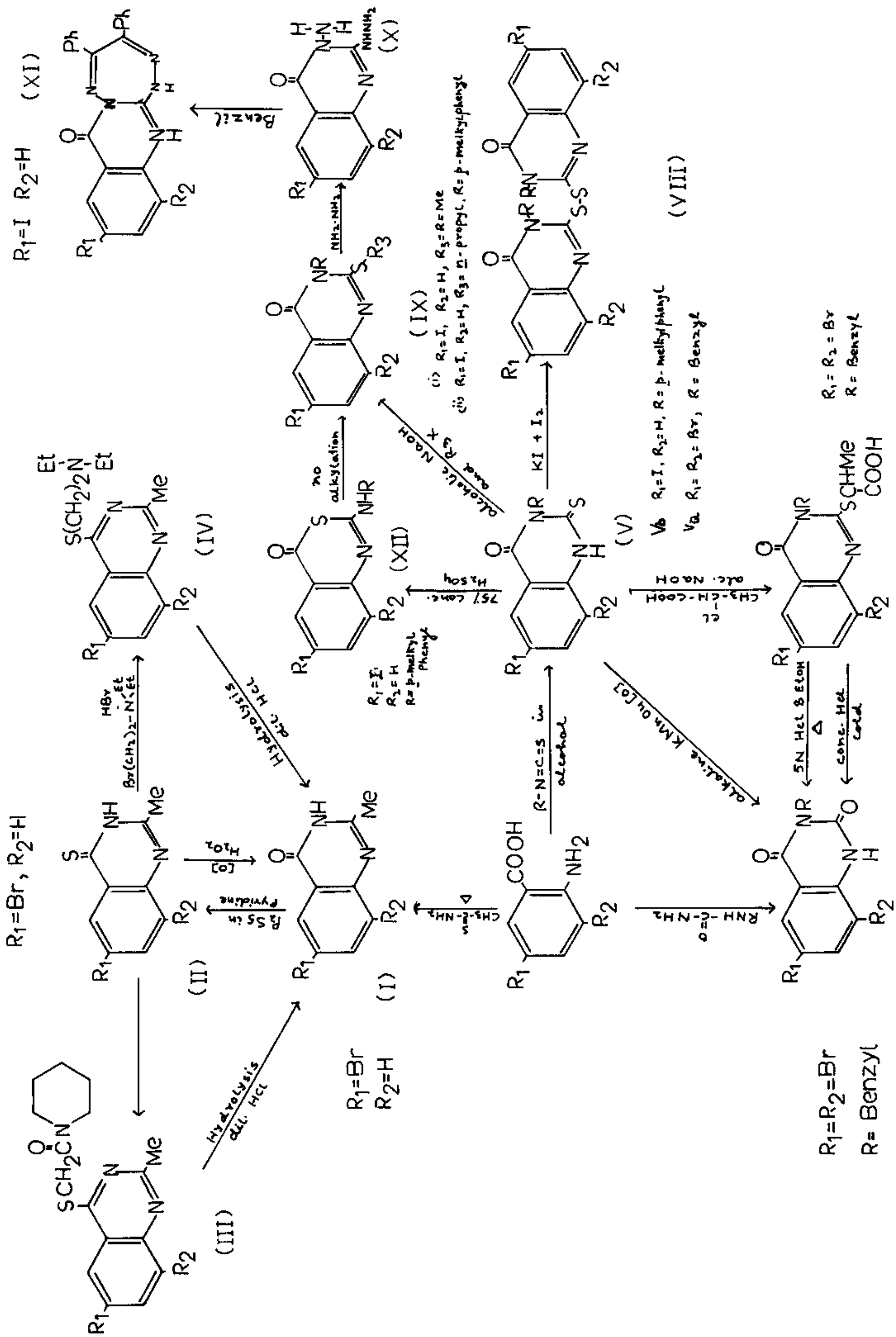
Abstract - Various 6,8-disubstituted 3(aryl) or (alkyl)-2*s*-(substituted)-4(3H)-quinazolinones, 6-bromo-2-methyl-4-*s*-(substituted)-4(3H)-quinazolin ones, bis(6,8-dibromo-3-benzyl-4-oxo-quinazolin-2-yl)disulphide, 9-iodo-3,4-diphenyl-[1,2,4,5]tetrazepino(3,2-*b*)quinazolin-7(1H)-one and 6-iodo-2-(*p*-methylphenylamino)-4H-3,1-benzothiazin-4-one have been prepared. Their structures have been established on the basis of various studies.

The recent findings of scientists establishing 4(3H)quinazolin-one derivatives as potential antileukemic agents[1] have added to the long list of diverse biological activities associated with compounds containing this ring system.

Considering these factors the authors have synthesised various 2-thioquinazolin-2,4(1H,3H)diones, substituted 3,4-diphenyl [1,2,4,5]tetrazepino[3,2-*b*] quinazolin-7(1H)-one and substituted 2-thio-3-(*p*-methylphenyl)quinazolin-2,4 (1H,3H)dione which on treatment with 75% concentrated sulphuric acid rearranges to substituted 2-(*p*-methylphenylamino)-4H-3,1-benzothiazin-4-one.

Various compounds reported here have been synthesised according to the scheme outlined.

6-Bromo-2-methyl-4(3H)-quinazolinone (I) was prepared by heating 5-bromoanthranilic acid[2] with thioacetamide in oil bath for 2 hours[3]. (I) on refluxing with phosphorous pentasulphide in dry pyridine for 2 hours gave 6-bromo-2-methylquinazoline-4(3H)-thione (II). The sodium salt of (II) was treated with N-chloroacetylpiperidine to obtain (III) and with β-diethylaminoethylbromide hydrobromide when (IV) was obtained.


(I)
(II)
(III)
(IV)
(V)
(VI)
(VII)
(VIII)
(IX)
(X)
(XI)
(XII)
R1=Br, R2=H
R1=Br
R2=H
R1=I R2=H
R1=R2=Br
R= Benzyl
R1 = R2 = Br
R = Benzyl
Vb R1 = I, R2 = H, R = p-methylphenyl
Va R1 = R2 = Br, R = Benzyl
(i) R1 = I, R2 = H, R3 = R = Me
(ii) R1 = I, R2 = H, R3 = n-propyl, R = p-methylphenyl
R1 = I
R2 = H
R = p-methyl phenyl
P2S5 in pyridine
H2O2 [O]
HBr Br(CH2)2-N(Et)Et
Hydrolysis dil. HCl
CH3-C(=O)-NH2 Δ
R-N=C=S in alcohol
RNH-C(=O)-NH2
alkaline KMnO4 [O]
75% conc. H2SO4
no alkylation
alcoholic NaOH and R3X
KI + I2
NH2-NH2
Benzil
CH3-CH(Cl)-COOH alc. NaOH
5N HCl & EtOH Δ
conc. HCl cold

The alkylation occurred at the sulphur atom rather than the nitrogen atom is proved by hydrolysis[4] of (III) and (IV) with 6N hydrochloric acid in ethanol when (I) was obtained. Oxidation of (II) with hydrogen peroxide also yielded the parent compound (I).

6,8-Dibromo-2-thio-3-benzylquinazolin-2,4(1H,3H)dione was prepared by condensing 3,5-dibromoanthranilic acid[2] with benzyl isothiocyanate in alcohol by the method of Bhargava et al.[5] 6,8-Dibromo-3-benzyl-2(methylcarboxymethylthio)-4(3H)-quinazolinone (VI) was prepared by treating (V) with chloropropionic acid. Sulphur free (VII) was obtained by the acid hydrolysis of (VI)[6]. (VII) was also obtained by treating substituted anthranilic acid with benzyl urea. These reactions prove that alkylation occurs at the sulphur atom. Oxidation of (V) with alkaline potassium permanganate by the method of Dave et al.[7] also yielded the same product (VII). An interesting observation was made when compound (VII) was also obtained by stirring 6,8-dibromo-3-benzyl-2-(α-methylcarboxymethylthio)-4(3H)quinazolinone (VI) with concentrated hydrochloric acid at room temperature. Bis (6,8-dibromo-3-benzyl-4-oxo-quinazolin-2-yl) disulphide (VIII) was prepared by treating an alkaline solution of (V) with saturated iodine solution in potassium iodide.

5-Iodo anthranilic acid[8] was condensed with methyl isothiocyanate according to a known method[5] to obtain (V). Similarly the benzyl derivative was prepared by using benzyl isothiocyanate. Treatment of 6-iodo-3-methyl-2-thioquinazoline-2,4(1H,3H)dione (V) with methyl iodide in alcoholic sodium hydroxide gave (IX) which was converted to (X) by refluxing with hydrazine hydrate (80%). 9-Iodo-3,4-diphenyl-[1,2,4,5]tetrazepino[3,2-*b*]quinazolin-7(1H)-one (XI) was subsequently obtained by treating (X) with benzil.

The rearrangement of 6-iodo-2-thio-3-(*p*-methylphenyl)quinazolin-2,4(1H,3H)-dione (V) to 6-iodo-2-(*p*-methylphenylamino)-4H-3.1-benzothiazin-4-one (XII) was brought by the action of 75% conc. sulphuric acid on (V).

EXPERIMENTAL

All the melting points were recorded on Gallenkemp apparatus and are uncorrected. IR spectra were recorded on Perkin Elmer 257 and 757 spectrophotometers and a

Coleman analyser used for element analysis.

5-Bromo, 3,5-dibromo, 5-iodo anthranilic acids were prepared by known methods[2,8].

6-Bromo-2-methylquinazoline-4(3H)-thione (II)

It was prepared by refluxing (0.01 M) 6-bromo-2-methyl-4(3H)quinazolinone (I) with phosphorous pentasulphide in dry pyridine for 2 hours. The product was washed with a little dry ether and recrystallised from ethanol to obtain (II) in 81% yield, m.p. 274-75°. Anal. Calcd. for $C_9H_7BrN_2S$: C, 42.35; H, 2.75. Found : C, 42.05, H, 2.95%.

6-Bromo-2-methyl-4(N-piperidinocarboxamidomethylthio)-quinazoline (III)

(II) was dissolved in alcoholic sodium hydroxide solution in a conical flask. N-chloroacetylpiperidine (0.01 M) was added drop by drop into it at 5° and the flask shaken vigorously after each addition. After complete addition the flask was shaken for another 15 minutesand its contents were poured in ice cold water. The product was filtered, washed with water, dried and recrystallised from ethanol in 85% yield, m.p. 239-40°. Anal. Calcd. for $C_{16}H_{18}BrN_3OS$: C, 50.52; H, 4.73. Found : C, 50.31; H, 4.50%.

Similarly, 6-bromo-2-methyl-4[N,N-diethylaminoethylthio]-quinazoline (IV) was prepared in 76% yield, m.p. 291°. Anal. Calcd. for $C_{15}H_{20}BrN_3S$: C, 50.85; H, 5.65. Found : C, 51.02; H, 5.55%.

Hydrolysis of 6-bromo-2-methyl-4-(piperidinocarboxyamidomethylthio)-quinazoline (III)

6N Hydrochloric acid (15 ml) was added to a solution of (III) in absolute alcohol and the resulting solution heated under reflux for 6-7 hours. Ethanol was distilled off and the reaction mixture poured in ice cold water. (I) was isolated and recrystallised from ethanol in 76% yield, m.p. 301° (lit. m.p. 302°)[3].

Similarly (I) was also obtained by the hydrolysis of 6-bromo-2-methyl-4-(N,N-diethylaminoethylthio)quinazoline (IV), m.p. 301°.

Oxidation of 6-bromo-2-methylquinazolin-4(3H)-thione (II)

When (II) was heated with hydrogen peroxide at 50-60° for 2 hours, 6-bromo-2-methyl-4(3H)quinazolinone (I) was obtained, m.p. 300° (lit. m.p. 302°)[3].

6,8-Dibromo-2-thio-3-benzylquinazolin-2,4(1H,3H)-dione (V)

It was prepared by a known method[9] in 88% yield, m.p. 228°. Anal. Calcd. for $C_{15}H_{10}Br_2N_2OS$: C, 42.25; H, 2.35. Found : C, 42.01; H, 2.05%.

Similarly 6-iodo-3-methyl-2-thioquinazoline-2,4(1H,3H)-dione was also prepared.
Yield 60% m.p. 270°. Anal. Calcd. for $C_9H_7IN_2OS$: N, 8.81; S, 10.06.
Found : N, 8.69; S, 9.98%.
IR (KBr) : 3230 (b) (ν NH), 1655 (ν C=0), (δ NH), 1510 (s) ($\nu\ \overset{|}{N}-\overset{|}{C}=S$)[1], 1374 (s) ($\nu\ \overset{|}{N}-\overset{|}{C}=S$)[2], 1110 (w) ($\nu\ \overset{|}{N}-\overset{|}{C}=S$)[3], 850 (s) ($\nu$ C=S).

6,8-Dibromo-3-benzyl-2-(α-methylcarboxymethylthio)-4(3H)quinazolinone (VI)

An equimolar quantity of sodium-α-mono chloropropionate was added to 10% sodium hydroxide solution in ethanol of 6,8-dibromo-3-benzyl-2-thioquinazoline-2,4(1H,3H)-dione. The reaction mixture was stirred for 8 hours at 15°. The product obtained on acidification with dilute hydrochloric acid was dissolved in 5% sodium bicarbonate solution, filtered and reprecipitated with dilute hydrochloric acid. The product (VI) was recrystallised from ethanol in 50% yield, m.p. 240°.
Anal. Calcd. for $C_{18}H_{14}Br_2N_2O_3S$: C, 43.37; H, 2.81. Found : C, 43.50; H, 2.99%.

Hydrolysis of 6,8-dibromo-3-benzyl-2-(α-methylcarboxymethylthio)-4(3H)-quinazolinone (VI)

(VI) was hydrolysed to (VII) as described above, m.p. 254°d (lit. m.p. 255°d)[6]. (VII) was also obtained when an alcoholic solution of 6,8-dibromo-3-benzyl-2-(α-methylcarboxymethylthio)-4(3H)-quinazolinone (VI) was stirred in concentrated hydrochloric acid at room temperature.

Oxidation of (V) by alkaline potassium permanganate

This was carried out by the method of Dave et al.[7], yield 50%, m.p. 255°d.
Found : C, 43.91; H, 2.46. $C_{15}H_{10}N_2O_2Br_2$ requires C, 43.90; H, 2.44%.

Bis-[6,8-dibromo-3-benzyl-4-oxo-quinazolin-2-yl]-disulphide (VIII)

Saturated iodine solution in potassium iodide was added drop by drop to an alkaline solution of 6,8-dibromo-2-thio-3-benzyl quinazolin-2,4(1H,3H)-dione (V). The resulting product was washed with potassium iodide solution and then with water to remove excess iodine. The crude was crystallised from ethanol acetone mixture (1:2) in 55% yield, m.p. 216°d. Calcd. for $C_{30}H_{18}N_4O_2S_2Pr_4$: N, 6.59; S, 7.53. Found : N, 6.44; S, 7.55%.

6-Iodo-2-methylthio-3-methyl-4(3H)-quinazolinone (IX)

It was prepared by treatment of (V) in alcoholic sodium hydroxide with methyl iodide according to the method of Bhargava et al.[10] in 61% yield, m.p. 159°. Calcd. for $C_{10}H_9N_2IOS$: N, 8.43; S, 9.64. Found : N, 8.63; S, 9.81%.

Similarly 6-iodo-(3-p-methylphenyl)-2-propylquinazolinone-4(3H)-thione was prepared, m.p. 164° (lit. m.p. 165°)[11].

6-Iodo-2-hydrazino-3-amino-4(3H)-quinazolinone (X)

(IX), (0.01 M) was refluxed in 80% hydrazine hydrate (0.02 M) for 14 hours. Excess hydrazine hydrate was distilled off and the product washed with water and recrystallised with ethanol to obtain pure (X), yield 78%, m.p. 241°. Calcd. for $C_8H_8IN_5O$: C, 30.28; H, 2.52. Found : C, 30.12; H, 2.59%.
IR (KBr) : 3450 (m) (ν_{as} NH), 3310 (w) (ν_s NH), 1670 (s) (ν C=O), 1620 (b) (δ NH), 1580 (s) (ν C =N), 900 (w) (ν N-N)[12,13].

9-Iodo-3,4-diphenyl[1,2,4,5]tetrazepino[3,2-b]quinazolin-7 (1H)-one (XI)

2.0 g, 6-Iodo-2-hydrazino-3-amino-4(3H)-quinazolinone (X) was dissolved in 50 ml xylene and stirred with (1.5 g) benzil for an hour at room temperature and refluxed for 20 hours. The product obtained after cooling was filtered, washed with benzene and warm distilled water. It was recrystallised from dilute ethanol to obtain (XI), yield 81%, m.p. 155°. Calcd. for $C_{22}H_{14}IN_5O$: C, 53.77; H, 2.85. Found : C, 53.86; H, 3.01%.
IR (KBr) : 3375 (b) (ν NH), 1650 (s) (ν C=O), 1575 (s) (ν C=N), 1455 (m) (ν $\overset{|}{N}-\overset{|}{C}=N$),

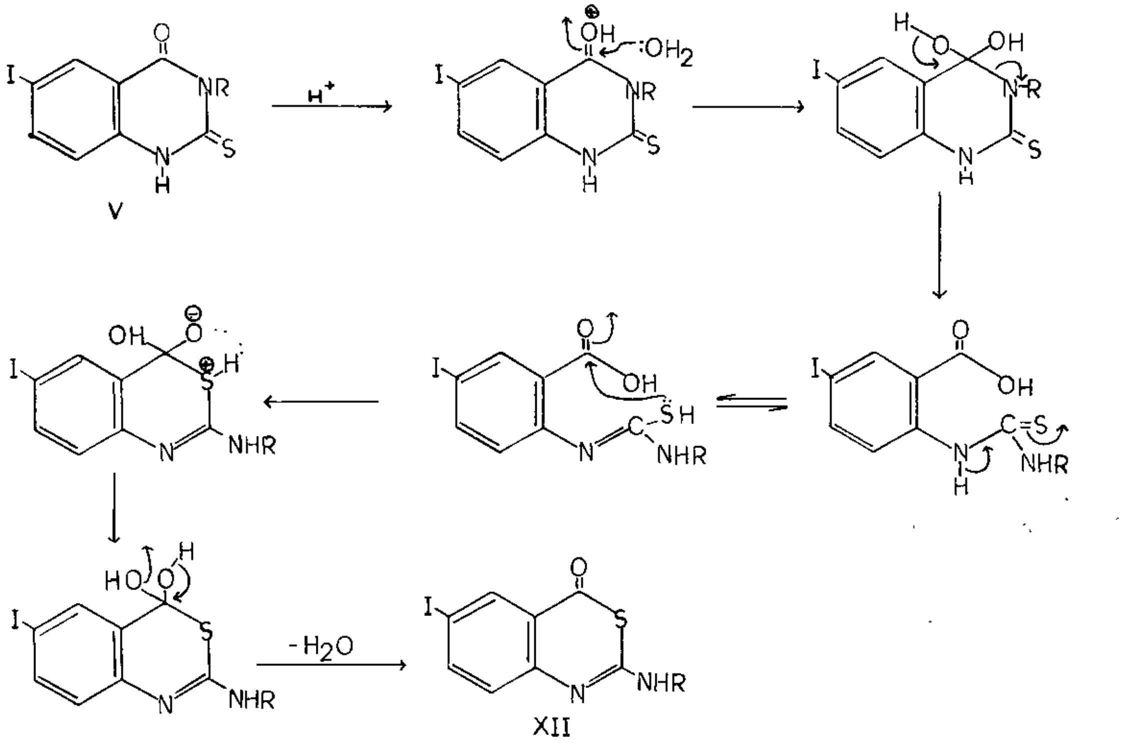
900 (w) (δ N-N) cm^{-1}.

Action of 75% concentrated sulphuric acid on 6-iodo-2-thio-3-(p-methylphenyl)quinazolin-2,4(1H,3H)-dione (V)

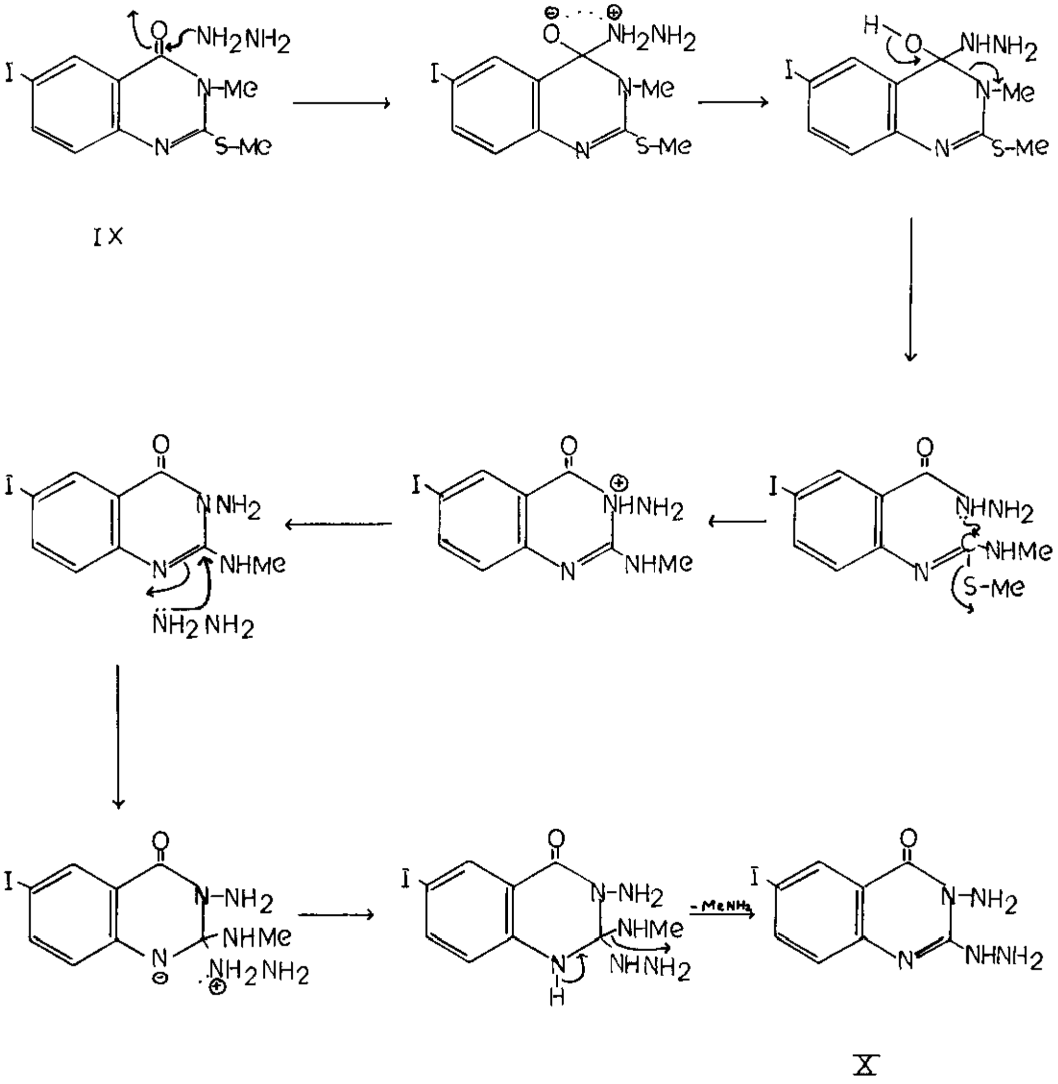
6-Iodo-2-thio-3(p-methylphenyl)quinazolin-2,4(1H,3H)-dione 5.0 g, was refluxed in concentrated sulphuric acid (75%) at 120-130° in oil bath for 7 hours. The reaction mixture was cooled and diluted with water. The product was filtered, washed with 5% sodium bicarbonate solution and finally with water. It was recrystallised from dilute ethanol to obtain shining crystals of 6-iodo-2-(p-methylphenylamino)-4H-3.1-benzothiazin-4-one (XII) in 94% yield, m.p. 110°. Calcd. for $C_{15}H_{11}ION_2S$: N, 7.11; S, 8.12. Found : N, 6.96; S, 8.21%. IR (KBr) : 3500 (b) (ν NH), 1710 (s) (ν C=O), 1660 (s) (δ NH), 1605 (w) (ν C=C), 1575 (w) (ν C=N) cm^{-1}.

DISCUSSION

In the light of various observations[14] the mechanism of the rearrangement is suggested as follows :



The reaction of quinazolinones with amines occurs with the opening of the ring between position 3 and 4 and the nitrogen atom in position 3 of quinazolinone is eliminated as ammonia[15-19]. In the light of the above quoted observations the following mechanism is proposed for the conversion of 6-iodo-2-methylthio-3-methyl-4(3H)quinazolinones (IX) to 3-amino-2-hydrazino-6-iodo-4(3H)-quinazolinone (X) :



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