HETEROCYCLES, Vol. 14, No. 11, 1980

SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS WITH BRIDGEHEAD NITROGEN ATOMS

M. R. Chaurasia and Surendra K. Sharma
Department of Chemistry, D. A. V. (P. G.) College, Dehra Dun,
India

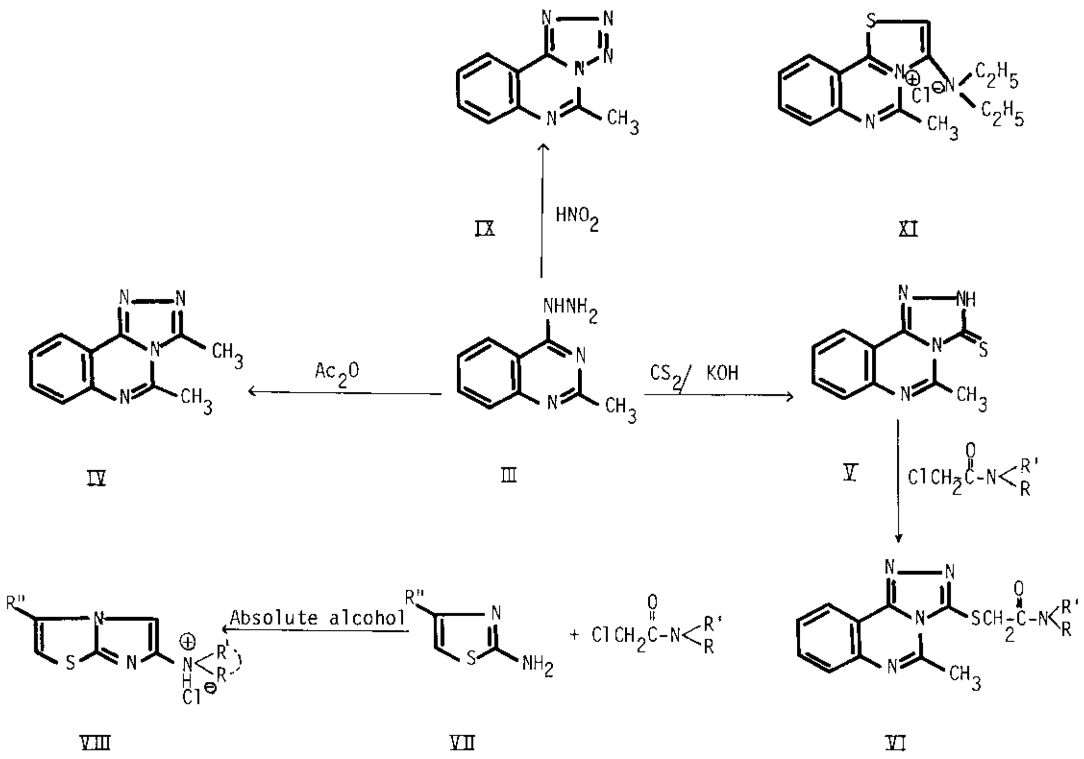
Abstract—— 3,5-Dimethyltriazolo[4,3-c]quinazoline, 5-methyltetrazolo-[1,5-c]quinazoline, 5-methyl-s-triazolo[4,3-c]quinazoline-3(2H)-thione, 2-[(5-methyl-s-triazolo[4,3-c]quinazolin-3yl)-thiol]-N,N-benzyl-phenylacetanilide, hydrochlorides of 3-substituted phenyl-6-diethylaminoimidazolo[2,1-b]thiazoles and 5-methyl-3-(N,N-diethyl-amino)thiazolo[3,2-c]quinazolin-4-ium chloride have been synthesised. The pharmacological screening of some compounds is also reported.

Several biological activities have been attributed to 4(3H)-quinazolinones and their derivatives[1-6]. They have been found to exhibit pesticidal[7], antiinflammatory[8], antifertility[9], herbicidal[10], muscle relaxant[11], analgesic, CNS depressant[12] and various other activities[13-16].

Thiazoles too have attracted the attention of chemists on account of their wide ranging activities. Several derivatives of thiazoles have been successfully tested as local anaesthetics[17-19]. Benzimidazoles have been widely used in medicines and agriculture. Several reviews on this subject are available[20,21]. They have also been reported as potent bactericidal[22], fungicidal [23] and tuberculostatic[24] and antidiabetic[25] agents.

In view of these significant properties several condensed quinazolinone and thiazole derivatives have been synthesised incorporating the triazole, tetrazole and imidazole nucleus in quinazolinone and thiazole ring systems respectively. Some of the compounds have also been tested for various biological activities. Further testing of some compounds is in progress in N.I.H. (U. S. A.). The compounds reported here have been prepared according to the scheme outlined.

The starting compound of quinazolinone derivatives (I) was prepared by heating a mixture of anthranilic acid and thioacetamide in oil bath at 140-150° for 2 hr.[26]



4-Chloro-2-methylquinazoline (II) was obtained by refluxing (I) with phosphorous oxychloride and phosphorous pentachloride for 7 hr on water bath.[27] The corresponding 4-hydrazinoquinazoline (III) was synthesised by refluxing (II) with hydrazine hydrate (80%) in absolute alcohol for 5 hr. The compound (III) was cyclised to 3,5-dimethyltriazolo[4,3-*c*]quinazoline (IV), 5-methyltetrazolo[1,5-*c*]quinazoline (IX) and 5-methyl-*s*-triazolo[4,3-*c*]quinazoline-3(2H)-thione (V) by refluxing (III) with excess acetic anhydride for 2 hr, stirring with nitrous acid at room temperature for 1 hr and by heating with carbon disulphide and potassium hydroxide on water bath for 12 hr respectively. An alcoholic sodium hydroxide solution of (V) was stirred with N-benzylchloroacetanilide[28] for 2 hr at room temperature and left overnight to obtain 2-[(5-methyl-*s*-triazolo[4,3-*c*]quinazolin-3-yl]-N,N-benzylphenylacetanilide (VI). The N,N-disubstituted chloroacetamide with substituted aminothiazoles gave (VIII). On heating (I) with phosphorous pentasulphide in dry pyridine for 2 hr, 2-methylquinazolin-4(3H)-thione (X) was obtained which was refluxed with N,N-diethylchloroacetamide in absolute alcohol for 6 hr to obtain (XI).

EXPERIMENTAL

All melting points were taken in open capillary in liquid bath and are uncorrected. IR spectra were recorded on a Perkin Elmer 257 spectrophotometer and a Coleman analyser used for elemental analysis.

4-Hydrazino-2-methylquinazoline (III).—— 4-Chloro-2-methylquinazoline (1 M) and (80%) hydrazine hydrate (2.2 M) were refluxed in absolute alcohol for 5 hr. Excess alcohol was distilled off. The product was cooled and washed thoroughly with distilled water. It was dried and recrystallised from ethanol to obtain 4-hydrazino-2-methylquinazoline as shining crystals in 95% yield; m.p. 199°. Anal. Calcd. for $C_9H_{10}N_4$: C,62.07 ; H, 5.74. Found : C. 61.92 ; H. 6.01%. IR (KBr) cm^{-1} 3400 m, 3200 m, 3120 w, 1610 m, 1550 s, 1495 s, 1380 s, 850 w.

3,5-Dimethyltriazolo[4,3-c]quinazoline (IV).—— A mixture of 4-hydrazino-2-methylquinazoline (0.01 M) and acetic anhydride (0.02 M) were heated under reflux in a round-bottomed flask for 2 hr. Excess acetic anhydride was distilled off and the reaction product was washed with 5% sodium bicarbonate solution and distilled water. It was dried and recrystallised from ethanol to obtain 3,5-dimethyltriazolo [4,3-c]quinazoline in 78% yield; m.p. 155°. Anal. Calcd. for $C_{11}H_{10}N_4$: C, 66.67; H, 5.05. Found : C, 66.45; H, 4,86%. IR (KBr) cm^{-1}: 2930 w, 1600 m, 1550 s, 1495 s, 1380 s, 860 w.

5-Methyltetrazolo[1,5-c]quinazoline (IX).—— A mixture of 4-hydrazino-2-methylquinazoline (0.01 M), acetic acid (1.5 ml), and sodium nitrite (0.01 M) was stirred at room temperature for 1 hr. The reaction mixture was left overnight. Cold distilled water was added to the flask and the resultant product was filtered. It was washed with 5% sodium bicarbonate solution and cold distilled water. 5-Methyltetrazolo[1,5-c]quinazoline was obtained by recrystallising the crude product from dilute ethanol in 83% yield; m.p. 180°. Anal. Calcd. for $C_9H_7N_5$: C, 58.38; H, 3.78. Found : C, 58.21; H, 3.91%. IR (KBr) cm^{-1}: 2930 w, 1605 m, 1555 s, 1495 s, 1380 s, 860 w.

5-Methyl-s-triazolo[4,3-c]quinazoline-3(2H)-thione (V).—— A mixture of 4-hydrazino-2-methylquinazoline (0.01 M), carbon disulphide (5 ml) and potassium hydroxide (0.01 M) was refluxed in a round-bottomed flask on water bath for 12 hr. Excess carbon disulphide was distilled off and the reaction product was cooled and washed thoroughly with distilled water and dried. Pure 5-methyl-s-triazolo[4,3-c]quinazoline-3(2H)-thione was obtained by recrystallisation of the crude product with dilute ethanol in 86% yield; m.p. 140°. Anal. Calcd. for $C_{10}H_8N_4S$: N, 25.92; S, 14.81. Found: N, 26.16; S, 15.02 %. IR (KBr) cm^{-1}: 3280 w, 3090 s, 1590 m, 1550 m, 1380 s, 1120 m, 770 m.

2-[(5-Methyl-s-triazolo[4,3-c]quinazolin-3-yl)-thiol]-N,N-benzylphenylacetamide (VI).—— 5-Methyl-s-triazolo[4,3-c]quinazoline-3(2H)-thione (0.01 M) was dissolved in minimum quantity of alcoholic sodium hydroxide solution. To the above solution N-benzylchloroacetanilide[28] (0.01 M) was added and the mixture stirred at room temperature for 2 hr and left overnight. The product was filtered and thoroughly washed with distilled water. It was dried and recrystallised from dilute ethanol to obtain the required product in 72% yield; m.p. 89°. Anal. Calcd. for $C_{25}H_{21}N_5OS$: N, 15.95; S, 7.29. Found : N, 16.21; S, 7.37 %.

Hydrochlorides of 6-(N,N-Diethylamino)-3-phenylimidazolo[2,1-b]thiazole (VIII).—— A mixture of 2-amino-4-phenylthiazole (0.01 M), diethylchloroacetamide (0.01 M) and absolute alcohol (60 ml) was refluxed for 6 hr. Excess alcohol was distilled off and the reaction product was cooled and washed with a little dry ether. It was recrystallised from alcohol to obtain a pure sample of the required product (VIII) in 71% yield; m.p. 148-152°. Anal. Calcd. for $C_{15}H_{18}ClN_3S$: N, 13.66; S, 10.41. Found : N, 13.78; S, 10.23 %. IR (nujol) cm^{-1}: 3175 b, 1605 s, 1535 m, 1525 s, 815 w.

Similarly other hydrochlorides of N,N-disubstituted 6-amino-3-arylimidazolo[2,1-b]-thiazoles were prepared by refluxing 2-amino-4-arylthiazoles[29] and N,N-disubstituted chloroacetamides in absolute alcohol. IR (KBr) cm^{-1}: 3360 m, 1650 w, 1570 s, 1450 m, 900 m.

3-(N,N-Diethylamino)-5-methylthiazolo[3,2-c]quinazolin-4-ium Chloride (XI).—— A mixture of 2-methylquinazolin-4(3H)-thione (0.01 M), N,N-diethylchloroacetamide (0.11M) and absolute alcohol (150 ml) were refluxed for 6 hr. Excess alcohol was distilled off and the required product was washed with a little dry ether and recrystallised from absolute alcohol to obtain (XI) in 76% yield; m.p. 232°. Anal. Calcd. for $C_{15}H_{18}N_3$ ClS: N, 13.66; S, 10.41. Found : N, 13.51; S, 10.14 %. IR (nujol) cm^{-1}: 3190 m, 1680 s, 1615 m, 1385 s, 1300 s, 1260 s, 1150 s, and 885 s.

Table 1

Hydrochlorides of N,N-Disubstituted 6-Amino-3-arylimidazolo[2,1-*b*]thiazoles

No.	Substituents X	Substituents R	Melecular Formula	Mp °C	Yield %	Nitrogen % Found	Nitrogen % Calcd.	Sulphur % Found	Sulphur % Calcd.
1.	H	Diethylamino	$C_{15}H_{17}ClN_3S$	148-152	61	13.56	13.70	10.24	10.44
2.	*p*-Br	diethylamino	$C_{15}H_{16}BrClN_3S$	165	65	11.01	10.89	8.46	8.30
3.	H	piperidino	$C_{16}H_{17}ClN_3S$	208	54	13.01	13.18	9.96	10.04
4.	*p*-Me	piperidino	$C_{17}H_{19}ClN_3S$	>230	69	12.81	12.63	9.51	9.62
5.	*p*-Cl	piperidino	$C_{16}H_{16}Cl_2N_3S$	160	56	12.01	11.89	8.90	9.06
6.	H	methylanilino	$C_{18}H_{15}ClN_3S$	137	71	12.13	12.33	9.26	9.41
7.	H	ethylanilino	$C_{19}H_{17}ClN_3S$	198	66	12.01	11.84	9.27	9.03

DISCUSSION

Compounds containing a thioamide moiety(H-N-C=S) have been studied by several workers and it has been suggested that such compounds give rise to four thioamide bands[30-33] in their infrared region. The four thioamide bands of 5-methyl-s-triazolo-[4,3-*c*]quinazoline-3(2H)-thione (V) are observed at 1540 s, 1320 w, 1120 m, and 850 m cm^{-1} and these are contributed by (δNH + νC=S + δC-H), (δNH, δCH + νC=N + νC=S), (νC=N + νC=S and ($\nu C\underline{\cdots}S$), respectively. The broad band at 3375 cm^{-1} corresponds to the NH stretching vibration. The disappearance of νNH and the four thioamide bands in compound (VI) and the new (νC=O) band at 1655 s cm^{-1} confirms the structure of 2-[(5-methyl-*s*-triazolo[4,3-*c*]quinazolin-3-yl)-thiol]-N,N-benzylphenylacetanilide (VI). Compound (III) shows absorption bands at 3400 m, 3200 m, and 3120 w[34] of νNH. These bands are absent in the IR spectra of compounds (IV) and (IX) confirming their structure. The IR spectra of (VIII) shows absorption peaks at 3175 b ($-\overset{+}{N}HEt_2$) 1605 s, 1535 m, 1525 s, 815 w cm^{-1}. The absence of NH_2 peaks (3450-3300 cm^{-1}) in (VIII) confirms its structure. The disappearance of νNH and four thioamide bands[30-33] in compounds (XI) confirms its structure.

PHARMACOLOGICAL SCREENING

3-(N,N-Diethylamino)-5-methylthiazolo[3,2-*c*]quinazolin-4-ium chloride (XI) was tested for CNS depressant, antiinflammatory, cardiovascular and antiallergic activities and found to be inactive. Further testing of compounds IV,V,VI,VIII and IX for antitumour and anticancerous activity is in progress at the N.I.H., Maryland, U.S.A. and shall be reported at a later date.

ACKNOWLEDGMENTS

The authors are thankful to the CSIR for the award of a Senior Research Fellowship to SKS, Dr. Ram Lakhan, Reader in Organic Chemistry, BHU, Varanasi for valuable help and encouragement. Thanks are also due to the Director, Bristol Laboratory, Syracuse, U.S.A. for biological screening and the authorities of D.A.V.(P.G.) College, Dehra Dun for providing necessary facilities.

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Received, 10th June, 1980