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3-Methyl[1,3,4]thiadiazino[2,3—*b*]quinazolin-6-ones

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4*H*,6*H*-[1,3,4]Thiadiazino[2,3—*b*]quinazolin-6-one with a methyl group in position 3 (**6a**) has been synthesised by the condensation of 3-amino-2-mercapto-3*H*-quinazolin-4-one (**1**) with allyl bromide (**2**) followed by treatment with bromine and subsequent dehydrohalogenation of the brominated product (**4**) with ethanolic sodium hydroxide. Its isomeric 3-methyl-2*H*,6*H*-[1,3,4]thiadiazino[2,3—*b*]quinazolin-6-one (**6b**) has also been obtained by condensation of **1** and bromoacetone (**7**) followed by cyclisation of the intermediates (**8** or **9**) with hydrobromic acid or with concentrated sulphuric acid. The structures have been established on the basis of IR and PMR data.

(Keywords: Heterocycles; Synthesis)

3-Methyl[1,3,4]thiadiazino[2,3—b]chinazolin-6-one

Zur Synthese von 4*H*,6*H*-[1,3,4]thiadiazino[2,3—*b*]chinazolin-6-on (**6a**) wurde die Kondensation von 3-Amino-2-mercapto-3*H*-chinazolin-4-on (**1**) mit Allylbromid mit nachfolgender Behandlung mit Brom und Dehydrohalogenierung des bromierten Produktes **4** mit ethanolischer Natronlauge herangezogen. Das zu **6a** isomere 2*H*,6*H*-Produkt **6b** wurde ebenfalls durch Kondensation von **1** mit Bromaceton und nachfolgender Cyclisierung der Zwischenprodukte **8** bzw. **9** mit HBr oder H_2SO_4 erhalten. Die Strukturen wurden mittels IR und NMR abgesichert.

Introduction

Quinazoline, by virtue of its diverse medicinal properties, has been seized upon by many synthetic chemists to prepare therapeutically important fused heterocycles. Recently, *Lempert* et al.[1] reported the synthesis of some [1,3,4]thiadiazino[3,2—*c*]quinazolines. Later on *Sunder* et al.[2] reported the synthesis of isomeric [1,3,4]thiadiazino[2,3—*b*]quinazolines and this was followed by some work on the latter system from our laboratories[3,4]. Here, we wish to report the synthesis of 4*H*,6*H*-[1,3,4]thiadiazino[2,3—*b*]quinazolin-6-one with methyl group in position 3 (**6a**) by a new route.

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Results and Discussion

Condensation of 3-amino-2-mercaptoquinazolin-4(3*H*)one (**1**) and allyl bromide (**2**) in the presence of sodium hydroxide resulted in the formation of 3-amino-2-allylmercapto-3*H*-quinazolin-4-one (**3**). The structure of **3** has been confirmed on the basis of IR and PMR studies.

It gave IR absorption bands at 3 280 and 3 160 cm^{-1} due to $-NH_2$. Besides, it also showed absorption bands at 1 670 due to —CO—N≤ and at 924 assignable to allylic double bond. Its PMR in $CDCl_3$ showed a doublet (2 H) at 3.90 assignable to two allylic protons (—CH_2—CH=CH_2). It also gave two multiplets one at 5.83-6.34 (1 H) and the other at 5.10-5.60 (2 H), the former may be assigned to one vinylic proton (—CH=CH_2) and the latter to two vinylic protons (—CH=CH_2). It also gave a singlet at 4.93 (2 H) exchangeable with D_2O due to two protons attached to nitrogen ($-NH_2$). The four aromatic protons appeared as multiplet at 7.30-8.37 (values in δ/ppm).

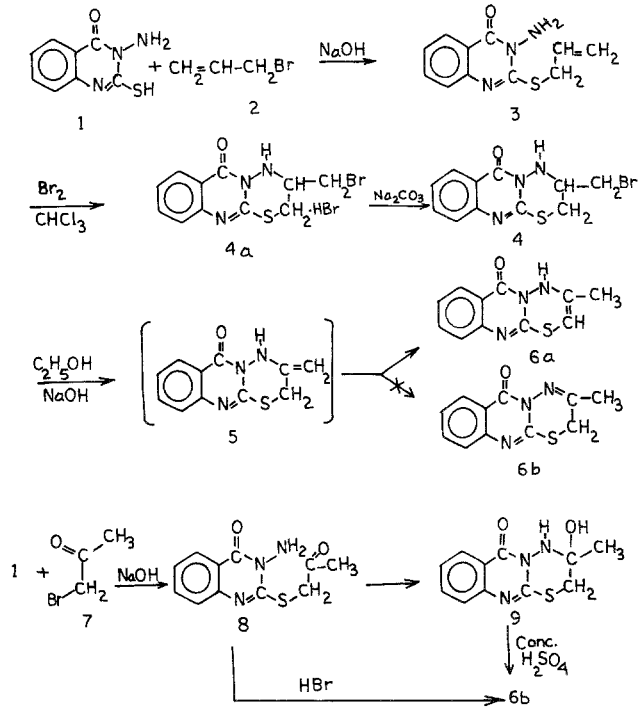
3 on treatment with bromine in chloroform at 5° underwent cyclisation to give the hydrobromide of 2,3-dihydro-3-bromomethyl-4*H*,6*H*-[1,3,4]thiadiazino[2,3—*b*]quinazolin-6-one (**4a**) which on basification with 10% sodium carbonate solution liberated its free base (**4**). The structure of **4** has been confirmed on the basis or IR and PMR studies.

IR absorption bands originally present in **3** at 3 280 and at 924 due to NH_2 and allylic double bond respectively were absent in **4**. Its PMR spectrum in $CDCl_3$-*TFA* showed two distorted triplets of two proton intensity each, because of the coupling among themselves and with the neighbouring proton, at 3.60 and 4.32 assignable to two non-equivalent methylene protons adjacent to sulphur (—S—CH_2—) and two non-equivalent methylene protons near halogen (≥CH—CH_2Br) respectively. Besides, it also gave two multiplets one at 6.48 (1 H) due to methine proton (≥CH—CH_2Br) and the other at 7.50-8.50 due to four aromatic protons. The proton attached to nitrogen did not appear in the range 0-10.

4 on treatment with 2% alcoholic sodium hydroxide underwent dehydrohalogenation and gave rise to **6a** instead of the expected product **5**. This may be due to greater stability of **6a** as compared to **5** i.e., the latter might have re-arranged to the former. In fact **5** could have undergone rearrangement to **6b** also but we have assigned structure **6a** on the basis of IR and PMR studies.

6a showed no IR absorption band around 890 due to exocyclic double bond. Its PMR in $CDCl_3$ exhibited a doublet (3H) because of allylic splitting, at 3.50 which could be assigned to three methyl protons (—CH=C—CH_3). It also

showed a quartet (1 H) again because of allylic splitting at 4.90 assignable to one vinylic proton (—C**H**=C—CH_3). Besides, it also gave a multiplet (4 H) at 6.75-8.30 due to four aromatic protons. The single proton attached to nitrogen appeared as a singlet (1 H) exchangeable with D_2O at 8.97. This eliminates the possibility of structure **6 b** and confirms structure **6 a**.



Sometimes even a minor variation brings a lot of change in antibacterial properties. Hence, it was thought desirable to prepare isomeric 3-methyl-2*H*,6*H*-[1,3,4]thiadiazino[2,3—*b*]quinazolin-6-one (**6 b**) also, by an alternative route.

1 if allowed to react with bromoacetone (**7**) in the presence of sodium hydroxide resulted in the formation of 3-amino-3*H*-quinazolin-4-one-2-thioacetone (**8**) and 2,3-dihydro-3-hydroxy-3-methyl-4*H*,6*H*-[1,3,4]-thiadiazino[2,3—*b*]quinazolin-6-one (**9**). The structures **8** and **9** have been confirmed on the basis of IR and PMR.

8 exhibited its characteristic IR absorption bands at 3 420-3 350 and 3 120 due to NH_2. It also showed absorption bands at 1 670 due to carbonyl group of the cyclic amide (—CO—N≤) and at 1 685 due to the carbonyl group of the

ketone (—S—CH_2—CO—). PMR spectrum of **8** in $CDCl_3$ showed two singlets one at 2.53 (3 H) and the other at 3.57 (2 H) due to three methyl protons (—CO—C**H**$_3$) and two methylene protons (—C**H**$_2$—CO—) respectively. The signals due to four aromatic protons and two protons attached to nitrogen merged to give a multiplet (6 H) at 7.30-8.43.

PMR of **9** in $CDCl_3$ also showed two singlets at 2.57 (3 H) and 3.60 (2 H) due to three methyl protons [$\rightleftharpoons$C(OH)—C**H**$_3$] and two methylene protons [—C**H**$_2$—C(OH)—CH_3] respectively. In addition, it also showed another singlet (1 H) exchangeable with D_2O at 1.68 assignable to hydroxyl proton. The four aromatic protons appeared as multiplet at 7.47-8.50, while the proton attached to nitrogen did not appear within the range 0-10.

8 on refluxing with hydrobromic acid in ethanol or **9** on treatment with concentrated sulphuric acid gave the required 3-methyl-2*H*,6*H*-[1,3,4]thiadiazino[2,3—*b*]quinazolin-6-one (**6 b**). The structure of **6 b** again finds support from IR and PMR.

It gave an absorption band at 1 680 due to —CO—N$\leqslant$ but the bands at 3 420-3 350 and 3 120 due to NH_2 and 1 685 due to carbonyl of ketone (—CH_2—CO—), originally present in **8**, disappeared. Its PMR in $CDCl_3$ exhibited a singlet (3 H) at 2.40 assignable to three methyl protons. Besides, it also gave two close singlets at 4.02 and 4.10 due to non-equivalent methylene protons (—S—C**H**$_2$—). The four aromatic protons appeared as a multiplet at 7.40-8.40. This eliminates the possibility of structure **6 a** and confirms structure **6 b**.

The structures of all these compounds have further been confirmed on the basis of analytical results.

Experimental

Melting points were determined in open glass capillaries using liquid paraffin bath and are uncorrected. IR spectra were recorded in nujol on Perkin-Elmer 337 and PMR on Varian EM-390 90 MHz spectrometer using *TMS* as the internal reference. The analytical values (C,H,N) agree with thre proposed structures (**3, 4, 6 a, b, 8, 9**).

3-Amino-2-allylmercapto-3H-quinazolin-4-one (**3**)

To a solution of 3-amino-2-mercapto-3*H*-quinazolin-4-one[5] (**1**) (1.93 g, 0.01 mol) in 5% sodium hydroxide solution (8 ml, 0.4 g, 0.01 mol) was added allyl bromide (0.85 ml) dissolved in ethanol (20 ml) dropwise with stirring at room temperature. There was immediate separation of a new compound. After keeping over night, it was diluted with water, collected under suction, washed with water and crystallised from ethanol, m.p. 118°; yield 1.74 g (75%). $C_{11}N_{11}N_3OS$.

IR (in nujol): 3 280, 3 160, 1 670, 1 620, 1 260, 1 190, 1 155, 1 050, 1 020, 924, 905, 860, 835 and 765 cm^{-1}.

2,3-Dihydro-3-bromomethyl-4H,6H-[1,3,4]thiadiazino[2,3—b]quinazolin-6-one hydrobromide (**4a**)

A solution of bromine (0.5 ml, 0.01 mol) in chloroform (10 ml) was added dropwise to a solution of 3 (2.33 g, 0.01 mol) in 50 ml of the same solvent with constant stirring at 5°. The contents were kept at room temperature for 4 h, by which time the colour of bromine had completely disappeared. On evaporating the solvent, the solid thus obtained was the desired product **4a** with m.p. 236°; yield 3.53 g (90%).

2,3-Dihydro-3-bromomethyl-4H,6H-[1,3,4]thiadiazino[2,3—b]quinazolin-6-one (**4**)

4a (3.53 g) was treated with 10% sodium carbonate solution, filtered, washed with water and crystallised from ethanol, m.p. 192°; yield 2.54 g (91%). $C_{11}H_{10}BrN_3OS$.

IR (in nujol): 3160, 1670, 1620, 1290, 1250, 1190, 1020, 1060, 940 and 770 cm^{-1}.

3-Methyl-4H,6H-[1,3,4]thiadiazino[2,3—b]quinazolin-6-one (**6a**)

To a solution of **4** (1 g) in 60% Ethanol (50 ml) was added 2% ethanolic sodium hydroxide (60.5 ml) at 45°. The contents were maintained at this temperature for 20 min. After cooling it to room temperature, crushed ice (100 g) was added. The separated product was collected under suction and crystallised from ethanol, m.p. 107°; yield 0.458 g (62%). $C_{11}H_9N_3OS$.

3-Amino-3H-quinazolin-4-one-2-thioacetone (**8**) *and 2,3-dihydro-3-hydroxy-3-methyl-4H,6H-[1,3,4]thiadiazino[2,3—b]quinazolin-6-one* (**9**)

To a solution of **1** (1.93 g, 0.01 mol) in 5% sodium hydroxide (8 ml, 0.4 g, 0.01 mol), bromoacetone[6] (0.84 ml, 0.01 mol) dissolved in ethanol (10 ml) was added dropwise with constant stirring at room temperature. There was immediate separation of **8**, m.p. 158°; yield 2.12 g (85%). $C_{11}H_{11}N_3O_2S$.

IR (in nujol): 3420-3350, 3120, 1685, 1670, 1620, 1260, 1195, 1125, 1010, and 755 cm^{-1}.

However, when the above contents were kept over night, after diluting with water another compound was obtained which was collected under suction and washed with water. Crystallisation from ethanol yielded **9** with m.p. 184°; yield 154 g (62%). $C_{11}H_{11}N_3O_2S$.

IR (in nujol): 3440-3280, 3160, 1670 and 1620 cm^{-1}.

3-Methyl-2H,6H-[1,3,4]thiadiazino[2,3—b]quinazolin-6-one (**6b**)

Via **8**

To a solution of **8** (1.245 g, 0.005 mol) in ethanol (150 ml) was added 48% hydrobromic acid (0.25 ml). The contents were refluxed over a water bath for 1 h. Ethanol was distilled off completely. On basification with 10% sodium carbonate solution **6b** separated and was collected under suction, washed with water and crystallised from ethanol into brown crystals with m.p. 170-172°; yield 0.62 g (54%). $C_{11}H_9N_3OS$.

Via **9**

9 (1 g) was dissolved in cold concentrated sulphuric acid (5 ml). After keeping the contents overnight, the solution was heated gently at 70-80° for 5 min. It was cooled, poured on crushed ice (100 g) and basified with 10% sodium carbonate solution. The solid thus separated was filtered under suction, washed with water and crystallised from chloroform into brown crystals of the desired product **6b** with m.p. 172-173° in 48% yield.

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References

[1] *Lempert S. M., Lempert K., Bruck P., Toth G.*, Acta chim. Acad. Sci. hung. **94**, 391 (1977); C. A. **88**, 170106y (1978).
[2] *Sunder S., Peet N. P.*, J. Heterocyclic chem. **16**, 1339 (1979); C. A. **92**, 128884h (1980).
[3] *Gakhar H. K., Gupta S. C., Kumar N.*, Indian. J. Chem. **20B**, 14 (1981); C. A. **95**, 25003c (1981).
[4] *Gakhar H. K., Jain A., Kumar N.*, J. Indian Chem. Soc. **58**, 166 (1981); C. A. **94**, 208807s (1981).
[5] *Cherbuliez E., Willhalm B., Jaccard S., Rabinowitz J.*, Helv. chim. acta **50**, 2563 (1967).
[6] *Levene P. A.*, Org. Synth. Coll. Vol. II, p. 88. New York: Wiley. 1943.