

## USE OF N-PHENYL-2-AMINO-4H-3, 1-BENZOXAZIN-4-ONE IN THE SYNTHESIS OF HETEROCYCLES AND THEIR DERIVATIVES

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5-(N-phenyl-2-aminoquinazoline-4-yloxomethyl)-1,2,4-triazole-3-thiol (4) was prepared via alkylation of N-phenyl-2-amino-4(3H)-quinazolinone (2) with ethylchloroacetate yielding 4-carbomethoxymethoxy-N-phenyl-2-aminoquinazolinone (3), followed by condensation of 3 with thiosemicarbazide. Compound 4 reacts as a thiol with nitrogen nucleophiles, alkylation and activated olefinic compounds to yield the 5-substituted-1,2,4-triazole-3N-substituted-amino derivative (5a,b), the 5-substituted 1,2,4-triazole-3-ylthioalkyl (8a,b) and the Michael adducts (11, 12). Treatment of 4 and 5 a,b with aromatic aldehydes yielded  $\alpha$ -arylidene-5-substituted-1,2,4-triazole-3-thiol (9a,b), 5-substituted-1H-3-arylidenehydrazino-1,2,4-triazole (6 a,b) and N-( $\beta$ -cyano-3-nitrocinnamoyl)-N'-(5-substituted-1,2,4-triazole-3-yl)-hydrazine (7).

**Key words.** Synthesis, Reactions, Triazole thiol.

### Introduction

Diverse pharmacological properties have been found to be associated with triazole derivatives [1-8]. These include anti-inflammatory, anticholinergic, antidepressant, analgesic, sedative, antihypertensive, antiasthmatic and tranquilizing properties.

Similar to what has been reported earlier [9] in the present study anthranilic acid reacted with phenylisocyanate in the presence of acetone to give N-phenyl-2-amino-4H-3, 1-benzoxazin-4-one (1) as a key starting material for the preparation of heterocyclic compounds containing triazole thiol and quinazolinone moieties. Such compounds are expected to show pharmacological activity.

### Results and Discussion

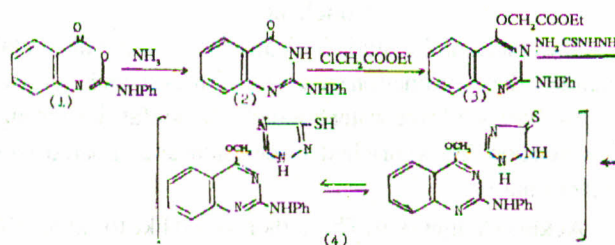
Aminolysis of N-phenyl-2-amino-4H-3, 1 benzoxazin-4-one (1) with ammonia from ammonium acetate or formamide by fusion at 150°, gave the corresponding N-phenyl-2-amino-4(3H)-quinazolinone (2, Scheme 1). Their IR spectra showed stretching frequencies at 3440, 3290 and 1680 cm<sup>-1</sup> for OH, NH and CO functions, respectively. These IR data infer that quinazolinone 2 exists in a lactam  $\rightleftharpoons$  lactim tautomeric equilibrium.

5-(N-phenyl-2-amino quinazolinone-4-yloxomethyl)-1,2,4-triazole-3-thiol (4) was prepared by a route shown in Scheme 1. It involved alkylation of N-phenyl-2-amino-4(3H)-quinazolinone (2) with ethylchloroacetate yielding 4-carbomethoxymethoxy-2N-phenylamino-quinazolinone (3), followed by condensation of 3 with thiosemicarbazide. The structures of 3 and 4 were supported by their spectral data. The IR spectrum of 3 showed bands due to ester CO (1745), ether linkage (1220 and 1210) and NH (3270 cm<sup>-1</sup>), while that of 4 exhibited bands due to C=N (1630), C=C (1610), 1250 (C=S),

SH (2650) and 3200 – 3280 cm<sup>-1</sup> (NH). This indicates that compound 4 exists in thiol  $\rightleftharpoons$  thione equilibrium. This dynamic equilibrium was more elucidated by the PMR spectrum showing signals at  $\delta$  4.3 (s, 2H, -O-CH<sub>2</sub>-), 6.8-8.1 (m, 10H, Ar-H and NH), 9.9 (br's, ~0.6 H of -NH-C=S), 4.6 (br,s, ~0.4 H of SH) and 10.4 (s, 1H, NH).

This tautomeric equilibrium in 4 was further established by chemical reaction. Thus, compound 4 reacted as a thiol with nitrogen nucleophiles [10] such as hydrazine hydrate and cyanoacetylhydrazine to give the corresponding 5-(N-phenyl-2-amino-quinazolinone-4-yloxomethyl)-3-hydrazino derivatives-1,2,4-triazole (5 a,b; Scheme 2). Their IR spectra showed bands attributable to CO, C $\equiv$ N, C=N, C=C and NH functions at 1680, 2240, 1630, 1610 and 3280,-3210 cm<sup>-1</sup> respectively. The PMR spectrum of 5b in (CF<sub>3</sub> COOD) showed signals at  $\delta$  2.4 (s, 2H, -CH<sub>2</sub>CN), 4.2 (s, 2H, -O-CH<sub>2</sub>-), 6.6-8.1 (m, 11 H, Ar-H, NH) and 10.2-10.4 (br s, 2H, NH).

Condensation of this hydrazine 5a with aromatic aldehydes, namely 4-hydroxybenzaldehyde or 3-nitrobenzaldehyde resulted in the formation 5-(N-phenyl-2-aminoquinazolinone-4-yloxomethyl)-3-arylidenehydrazino-1,2,4-triazole (6 a, b; Scheme 2). The IR spectrum of 6 showed bands at 1630 (C=N), 1610 (C=C), 3280 (NH) and 3605 cm<sup>-1</sup> (OH). The



Scheme 1.

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PMR ( $\text{CF}_3\text{COOD}$ ) spectrum of **6b** showed signals at  $\delta$  4.2 (s, 2H, -O-CH<sub>2</sub>-), 6.6-8.3 (m, 15 H, Ar - H and NH) and 10.3 (s, 1H, NH).

The ethanolic solution of **5b** with 3-nitrobenzaldehyde in the presence of drops piperidine afforded the corresponding N- ( $\beta$ - cyano-3-nitrocinnamoyl) -N' [5-(N-phenyl -2-aminoquinazoline-4-yloxomethyl)-1,2,4-triazole-3-yl]-hydrazine (**7**, Scheme 2). The IR spectrum of **7** showed bands at 1680 (CO), 1630 (C=N), 1605 (C=C), 2235 (C=N) and 3282-3200  $\text{cm}^{-1}$  (NH).

Alkylation of **4** with alkyl halides, namely methyl iodide or ethyl iodide in the presence of sodium ethoxide solution afforded the corresponding 5-(N-phenyl-2-aminoquinazoline -4-yloxomethyl)- 1,2,4-triazole-3-ylthioalkyl (**8a,b**, scheme2). The IR spectrum of **8** showed characteristic absorption bands due to C=N, C=C and NH functions at 1630, 1605 and 3280 - 3240  $\text{cm}^{-1}$  respectively. The PMR ( $\text{CF}_3\text{COOD}$ ) spectrum of **8a** showed signals at  $\delta$  2.1 (s, 3H, -SCH<sub>3</sub>), 4.2 (s, 2H, -OCH<sub>2</sub>-), 6.7-8.1 (m, 10 H, Ar-H and NH) and 10.2 (s, 1H, NH).

Compound **4** reacted with aromatic aldehydes [11] such as 4-N, N-dimethylaminobenzaldehyde and 4-hydroxybenzaldehyde in the presence of piperidine under fusion ( $150^\circ$ ) yielded  $\alpha$ -arylidene- 5-(N-phenyl -2-amino-quinazoline-4-yloxomethyl)-1,2,4-triazole-3- thiol (**9a,b**; Scheme 2). The IR spectrum of **9** showed strong absorption bands at 1630 (C=N), C=C (1610), 1255 (C=S), 2555 (SH) and 3550-3200  $\text{cm}^{-1}$  (NH and OH). The PMR spectrum of **9a** in ( $\text{CDCl}_3$ ) showed signals at  $\delta$  2.8-3.0 (br s, 6H, 2x CH<sub>3</sub>-N) 6.6. - 8.1 (m, 11H, Ar- H, olefinic proton and NH), 9.8 (br,s,-0.6H of NH-C=S), 4.6 (br,s, 0.4 H of SH) and 10.3 (s, 1H, NH).

The ethanolic solution of **9b** with hydrazine hydrate afforded the corresponding  $\alpha$ -4-hydroxybenzylidene-5-(N-

phenyl -2- aminoquinazoline-4-yloxomethyl)-1,2,4-triazole-3-hydrazine (**10**, Scheme 2). The IR spectra of **10** showed strong absorption bands at 1630 (C=N), 1605 (C=C) and 3390-3240 (NH and NH<sub>2</sub>).

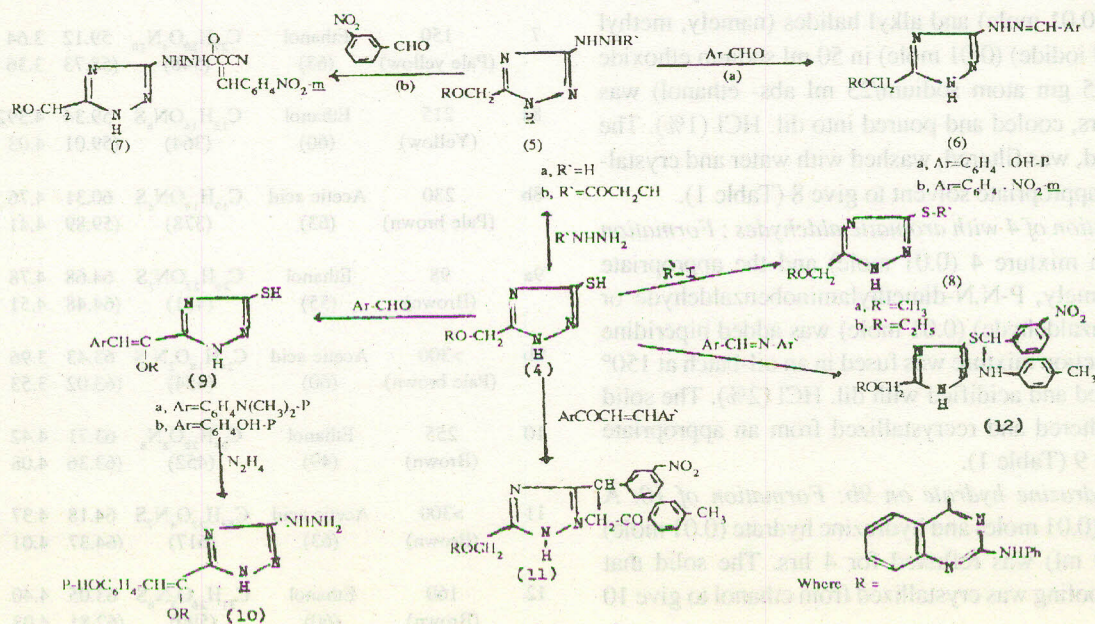
However, the reaction of **4** with activated olefinic compounds [12] such as  $\beta$ -(4-methyl benzoyl)-3-nitrostyrene and 3- nitrobenzylidene-4-methylaniline under Michael reaction conditions in the presence of sodium ethoxide afforded the corresponding Michael adducts (**11**, **12**; Scheme 2). The IR spectrum of **11** and **12**; showed absorptions characteristic of ketonic CO, C=N, C=C, NH and NO<sub>2</sub> functions at 1695, 1630, 1610, 3290-3220 and 1560 11350  $\text{cm}^{-1}$ , respectively. The PMR spectrum of **11** in ( $\text{CF}_3\text{COOD}$ ) showed signals at  $\delta$  2.1 (s, 3H, -CH<sub>3</sub>), 2.4 (d, 2H, -CH<sub>2</sub>CO-), 3.4 (t, 1H, S-CH-), 4.3 (s, 2H, -OCH<sub>2</sub>-), 6.6-3.2 (m, 18H, Ar-H and NH) and 10.3 (s, 1H, NH).

### Experimental

IR spectra were recorded in KBr on a Unicam SP 1200 spectrometer and PMR spectra on a Varian EM-360-60 MHz NMR spectrometer. All m.p. reported are uncorrected.

*N*-phenyl 2-amino-4H-3, 1-benzoxazin-4-one (**1**). A mixture of anthranilic acid (0.01 mole) and phenyl isocyanate (0.01 mole) in acetone (70 ml) was refluxed for 4 hrs. The reaction mixture was cooled, the solid obtained, was filtered, washed with water, air dried and crystallized from a proper solvent to give **1** (Table 1).

*Aminolysis of 1: Formation of 2*. A mixture of **1** (0.01 mole) and formamide or ammonium acetate (0.03 mole) was fused in an oilbath at  $150^\circ$  for 3 hrs, and poured into water. The solid obtained was crystallized from an appropriate solvent to give **2** (Table 1).



Scheme 2.

*Alkylation of 2 with ethyl chloroacetate: Formation of 3.* A mixture of 2 (23.7 gm; 0.01 mole), ethyl chloro acetate (11.4 ml, 0.01 mole) and anhydrous potassium carbonate (15 gm) in dry acetone (200 ml) was refluxed on a water-bath for 24 hrs. The reaction mixture was cooled and poured into water. The resultant solid was filtered and crystallized from appropriate solvent to give 3 (Table 1).

*Condensation of 3 with thiosemicarbazide: Formation of 4.* A mixture of 3 (0.01 mole) and thiosemicarbazide (0.01 mole) in 50 ml sodium ethoxide solution (0.005 gm atom sodium/25 ml abs. ethanol) was heated for 6 hrs cooled and poured into dil. HCl (1%). The solid, thus separated, was filtered, washed with water and crystallized from a proper solvent to give 4 (Table 1).

*Action of hydrazines on 4: Formation of 5 a,b.* A solution of 4 (0.01 mole) and the hydrazine derivative (namely, hydrazine hydrate or cyanoacetyl hydrazide) (0.01 mole) in ethanol (70 ml) was refluxed for 6 hrs. The solid that separated on cooling was crystallized from an appropriate solvent to give 5 (Table 1).

*Condensation of 5a with aromatic aldehydes: Formation of 6 a,b.* A solution of 5a (0.01 mole) with aromatic aldehydes (namely, hydroxy benzaldehyde or m-nitro benzaldehyde) (0.01 mole) in acetic acid (50 ml) was refluxed for 4 hrs. The solid that separated on cooling was crystallized from an appropriate solvent to give 6 (Table 1).

*Reaction of 5 b with 3-nitrobenzaldehyde: Formation of 7.* A mixture of 5 b (0.01 mole), 3-nitrobenzaldehyde (0.01 mole) and piperidine (1 ml) was refluxed for 6 hrs, cooled and acidified with dil. HCl (2%). The solid formed was filtered and recrystallized from a proper solvent to give 7 (Table 1).

*Alkylation of 4 with alkyl halides: Formation of 8 a,b.* A mixture of 4 (0.01 mole) and alkyl halides (namely, methyl iodide or ethyl iodide) (0.01 mole) in 50 ml sodium ethoxide solution (0.005 gm atom sodium/25 ml abs- ethanol) was heated for 4 hrs, cooled and poured into dil. HCl (1%). The solid, separated, was filtered, washed with water and crystallized from an appropriate solvent to give 8 (Table 1).

*Condensation of 4 with aromatic aldehydes: Formation of 9 a,b.* To a mixture 4 (0.01 mole) and the appropriate aldehydes (namely, P,N,N-dimethylaminobenzaldehyde or P-hydroxy benzaldehyde) (0.01 mole) was added piperidine (1 ml). The reaction mixture was fused in an oil-bath at 150° for 6 hrs, cooled and acidified with dil. HCl (2%). The solid formed was filtered and recrystallized from an appropriate solvent to give 9 (Table 1).

*Action hydrazine hydrate on 9b: Formation of 10.* A solution of 9b (0.01 mole) and hydrazine hydrate (0.01 mole) in ethanol (50 ml) was refluxed for 4 hrs. The solid that separated on cooling was crystallized from ethanol to give 10 (Table 1),

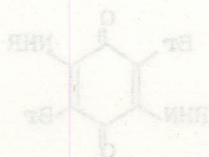
*Reaction of 4 with active olefinic compounds: Formation of 11 and 12.* A mixture of 4 (0.01 mole) and the active olefinic compound, namely  $\beta$ -(4-methylbenzoyl)-3-nitrostyrene or 3-nitrobenzylidene-4-methylaniline (0.01 mole) in 50 ml sodium ethoxide (0.005 gm atom sodium/25 ml ethanol) was refluxed for 6 hrs, cooled and poured into dil. HCl (1%). The solid, thus separated was filtered, washed with water and crystallized from a proper solvent to give 11 and 12 (Table 1).

TABLE 1. CHARACTERISATION DATA OF THE COMPOUNDS 1-12.

Compd	M.P. °C (colour)	Crystallized from (yield %)	Mol. formula (m.wt)	Microanalyses % Calcd / (Found)			
				C	H	N	S
1	185 (Colourless)	Acetone (85)	C <sub>14</sub> H <sub>10</sub> O <sub>2</sub> N <sub>2</sub> (238)	70.58 (70.21)	4.2 4.0	11.76 11.41	- -
2	260 (Pale yellow)	Ethanol (50)	C <sub>14</sub> H <sub>11</sub> ON <sub>3</sub> (237)	70.88 (70.50)	4.64 4.31	17.72 17.41	- -
3	147 (Colourless)	Acetone (63)	C <sub>18</sub> H <sub>17</sub> O <sub>3</sub> N <sub>3</sub> (323)	66.87 (66.42)	5.26 4.98	13.00 12.81	- -
4	188 (Yellow)	Acetic acid (60)	C <sub>17</sub> H <sub>14</sub> ON <sub>6</sub> S (350)	58.28 (58.01)	4.0 3.76	24.00 23.70	9.14 9.00
5a	204 (Colourless)	Acetic acid (65)	C <sub>17</sub> H <sub>16</sub> ON <sub>8</sub> (348)	58.62 (58.20)	4.59 4.31	32.18 31.92	- -
5b	207 (Brown)	Ethanol (63)	C <sub>20</sub> H <sub>17</sub> O <sub>2</sub> N <sub>9</sub> (415)	57.83 (57.42)	3.85 3.51	30.36 29.96	- -
6a	260 (Yellow)	Acetic acid (65)	C <sub>24</sub> H <sub>20</sub> O <sub>2</sub> N <sub>8</sub> (452)	63.71 (63.33)	4.42 4.21	24.77 24.46	- -
6b	180 (Pale yellow)	Ethanol (55)	C <sub>24</sub> H <sub>19</sub> O <sub>3</sub> N <sub>9</sub> (481)	59.87 (59.47)	3.95 3.56	26.19 25.88	- -
7	150 (Pale yellow)	Ethanol (63)	C <sub>27</sub> H <sub>20</sub> O <sub>4</sub> N <sub>10</sub> (548)	59.12 (58.73)	3.64 3.36	25.54 25.21	- -
8a	215 (Yellow)	Ethanol (60)	C <sub>18</sub> H <sub>16</sub> ON <sub>6</sub> S (364)	59.34 (59.01)	4.39 4.03	23.07 22.79	8.79 8.51
8b	230 (Pale brown)	Acetic acid (63)	C <sub>19</sub> H <sub>18</sub> ON <sub>6</sub> S (378)	60.31 (59.89)	4.76 4.41	22.22 22.00	8.46 8.07
9a	98 (Brown)	Ethanol (55)	C <sub>26</sub> H <sub>23</sub> ON <sub>7</sub> S (481)	64.68 (64.48)	4.78 4.51	20.37 19.88	6.65 6.30
9b	>300 (Pale brown)	Acetic acid (60)	C <sub>24</sub> H <sub>18</sub> O <sub>2</sub> N <sub>6</sub> S (454)	63.43 (63.02)	3.96 3.53	18.50 18.20	7.04 6.83
10	255 (Brown)	Ethanol (49)	C <sub>24</sub> H <sub>20</sub> O <sub>2</sub> N <sub>8</sub> (452)	63.71 (63.36)	4.42 4.08	24.77 24.50	- -
11	>300 (Brown)	Acetic acid (63)	C <sub>33</sub> H <sub>27</sub> O <sub>4</sub> N <sub>7</sub> S (617)	64.18 (64.37)	4.37 4.01	15.88 15.49	5.18 5.00
12	160 (Brown)	Ethanol (60)	C <sub>31</sub> H <sub>26</sub> O <sub>3</sub> N <sub>8</sub> S (590)	63.05 (62.81)	4.40 4.03	18.89 18.57	5.42 5.01

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and Br contains (Table I). The compounds have the general structure:

where R = C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub>, C<sub>4</sub>H<sub>9</sub>, C<sub>6</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>4</sub>OH, C<sub>6</sub>H<sub>4</sub>Cl, C<sub>6</sub>H<sub>4</sub>Br, C<sub>6</sub>H<sub>4</sub>NO<sub>2</sub>.

The solvents used were all of spectral grade (BDH or B. Merck products). Stock solutions were prepared by dissolving the accurate weight of each compound in the appropriate volume of the required solvent. Solutions of four concentrations were obtained by accurate dilution. The absorption spectra in the UV and visible regions were recorded with the aid of Shimadzu UV 200 S recording spectrophotometer using 1 cm matched silica cells.

Results and Discussion

The electronic spectra of the parent compound 2, 2-diamino-3, 4-dihydro-1, 4-benzodiazepine was studied in chloroform, ethanol and ether by Issa et al. [6]. In chloroform only one band is observed at 338 nm, while in ethanol and ether two bands are observed, the first at 245 nm and the second at 338 nm in ethanol, and at 355 nm in ether. The bands at 335 nm and 338 nm are assigned to π-π\* transition of the quinoid

TABLE I. ANALYTICAL DATA ON PREPARED COMPOUNDS I.

Compound	Color	mp, °C	Analytical Calc'd (found)		
			C, %	H, %	N, %
C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	Dark	170	74.09 (74.08)	4.41 (4.37)	1.91 (1.85)
C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	Yellowish	173	74.35 (74.31)	4.19 (4.15)	1.81 (1.76)
C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	Brown	198	74.10 (74.05)	4.20 (4.15)	1.82 (1.76)
C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub>	Deep orange	183	74.40 (74.30)	3.88 (3.82)	1.78 (1.72)

Introduction

The electronic absorption spectra of quinones with condensed ring system and with heterocyclic nucleus have been studied by several authors [1-6]. The effect of substituents, solvents and pH on the electronic spectral behaviour of p-benzoquinone and some of its derivatives have been reported [7-12]. Haseeb [9] has found that the spectra of p-benzoquinone derivatives commonly comprised two sets of bands. The first one at shorter wavelength due to π-π\* transition within a benzoid structure (phenyl ring of the quinoid structure). The second set at longer wavelength corresponds to the π-π\* transition within the quinoid structure (carbonyl and ethylenic systems). These bands displayed some changes in position and intensity on changing the substituents on the quinone nucleus or the polarity of the medium. The charge transfer bands shift to red with increasing polarity. The compounds 2, 2-dihydroxy-1, 4-benzodiazepine-1, 4-benzodiazepine were used as reagents for detection of some drugs spectrophotometrically [13]. Very recently, the electronic absorption spectra of some new substituted diamine-diazepine-1, 4-benzodiazepine were investigated [12].

In this paper, the effect of ethanol, methanol, dioxane and chloroform on spectral behaviour of some 2, 2-dihydroxy-1, 4-benzodiazepine-1, 4-benzodiazepine compounds was studied.

Experimental

The compounds I were prepared [10] as follows: A mixture of tetraamino-1, 4-benzodiazepine [17] (0.02 mole) and relevant aluminium (0.1 mole) was refluxed in excess of absolute ethanol for varying periods (0.5-10 hr) until brownish red precipitate and a highly coloured solution or solid was formed. The reaction mixture was then cooled and the precipitated product was collected and recrystallized from appropriate solvent. The compounds were analysed for their C, H,