

## SOME REACTIONS OF 2-( $\alpha$ -NAPHTHYL METHYL)-(4H)-3, 1-BENZOXAZIN-4-ONE

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Synthesis and reactions of 2-( $\alpha$ -naphthyl methyl)-4(3H)quinazolone (2) with benzamide and succinimide was considered. Alkylation with ethyl chloroacetate, benzoylation and the effect of  $P_2S_5$  on compound (2) were investigated. Reactions of the titled compound (1) with ethyl chloroacetate and active methylene compounds were studied. Beside the effect of aromatic hydrocarbons under Friedel-Crafts condition and Grignard's reagents on compound (1) were also considered.

**Key words:** Benzoxazin-4-one, Quinazol-4-ones, Active methylene compounds.

### Introduction

(4H)-3, 1-Benzoxazin-4-ones have become very important owing to their vast biological activity [1,2]. On the other hand 4-(3H)-quinazolones have been applied for different biological and pharmacological purposes such as diuretic [3], antihistaminic [4], anticonvulsant [5] and long active sedative agent [6]. This promoted us to prepare and study the reactions of these compounds.

### Experimental

Melting points reported are uncorrected. IR spectra in KBr were run on a Pye-Unicam No. 641749 spectrophotometer and PMR spectra on a Biumberg No. 4032 instrument.

*Action of formamide on 1; Formation of 2.* A mixture of (1) (0.01 mole) and formamide (0.015 mole) was heated at 180° in oil bath for 3 hrs. The product obtained after cooling was crystallized from ethanol (Tables 1 and 2).

*Formation of mannich bases (3 a & b).* A mixture of (2) (0.01 mole), formaldehyde (5 ml), few drops of conc. HCl and amide or imide namely benzamide and succinimide in (30 ml) ethanol was heated under reflux for 3 hrs. The product obtained after cooling was crystallized from ethanol (Tables 1 and 2).

*Action of ethyl chloroacetate on quinazolinone 2: Formation of (4).* A solution of (2) (0.01 mole) and ethyl chloroacetate (0.01 mole) in (30 ml) ethanol was heated under reflux for 6 hrs. The product obtained after cooling was crystallized from ethanol (Tables 1 and 2).

*Benzoylation of quinazolinone (2): Formation of (5).* A mixture of (2) (0.01 mole) and benzoyl chloride (0.01 mole) in (30 ml) dry benzene was heated under reflux for 3 hrs. The product obtained after cooling was crystallized from isopropyl alcohol (Tables 1 and 2).

*Action of phosphorus pentasulphide on (2): Formation of (6).* A mixture of (2) (0.01 mole) and phosphorous pentasulphide (0.05 mole) in (40 ml) dry exylene was heated

under reflux for 3 hrs. The product obtained after cooling was crystallized from acetic acid (Tables 1 and 2).

*Reaction of benzoxazinone (1) with active methylene compounds: Formation of (7).* A solution of (1) (0.01 mole) and active methylene compounds namely ethyl acetoacetate, diethyl malonate or ethyl cyanoacetate (0.02 mole) in (40 ml) pyridine was heated under reflux for 12 hrs., the reaction mixture was poured into ice-cold dil. HCl to give product which was crystallized from ethanol (Tables 1 and 2).

*Reaction of benzoxazinone (1) with acetyl acetone and or malononitrile: Formation of (8 & 9).* A mixture of (1) (0.01 mole), sodium ethoxide and acetyl acetone or malononitrile (0.01 mole) in (50 ml) ethanol was heated under reflux for 18 hrs., the reaction mixture was poured into ice-cold dil-HCl. The product was crystallized from ethanol and acetic acid respectively (Table 1 and 2).

*Iodoform reaction: Formation of (10).* A mixture of (8) (0.01 mole), alkaline solution of methanol and iodines solution was heated on water bath, the iodoform was separated and the filtrate was acidified by dil-HCl. The product obtained was crystallized form isopropyl alcohol (Tables 1 and 2).

*Action of hydrazine hydrate on (8): Formation of (II).* A solution of (8) (0.01 mole) and hydrazin hydrate (0.02 mole) in (30 ml) isopropanol was heated under reflux for 6 hrs. The product obtained after cooling was crystallized from isopropyl alcohol (Tables 1 and 2).

*Friedel-Crafts reaction with benzoxazinone (1): formation of (12).* A solution of (1) (0.01 mole) in toluene, *m* xylene or cumene (50 ml),  $AlCl_3$  (0.04 mole) was added with stirring, a vigorous evolution of hydrogen chloride took place. Stirring was continued for 8 hrs. at room temperature acid ice-cold dil-HCl was added. The organic layer was washed with  $H_2O$ , dried by anhydrous  $MgSO_4$  and excess solvent was removed by steam distillation. The solid obtained was crystallized from toluene (Tables 1 and 2).

*Action of Grignard reagent on the benzoxazone (1): Formation of (13).* A solution of (1) (0.01 mole) in (40 ml) dry toluene was treated with an ethereal solution of ethylmagnesium iodide or phenylmagnesium bromide (0.03 mole) in the course of 30 mins. The reaction mixture was heated under reflux for 5 hrs left overnight at room temperature and then decomposed in the usual way. The oil obtained was solidified with light petrol (40-60) and recrystallized from toluene (Tables 1 and 2).

TABLE 1. DATA FOR THE PREPARED COMPOUNDS.

Compd. No.	m.p. (°C)	Yield %	Mol. formula (mol. wt.)	Analysis calcd./found		
				C	H	N
1	126	68	C <sub>19</sub> H <sub>13</sub> NO <sub>2</sub> (287.30)	79.40 79.20	4.56 4.32	4.90 4.60
2	250	80	C <sub>19</sub> H <sub>14</sub> N <sub>2</sub> O (286.30)	79.70 79.40	4.93 4.59	9.80 9.70
3a	160	70	C <sub>27</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub> (419.50)	77.30 77.10	5.05 4.71	10.00 9.60
3b	200	65	C <sub>24</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub> (397.40)	72.50 72.10	4.82 4.49	10.60 10.50
4	225	48	C <sub>21</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> (326.40)	77.30 77.00	4.32 4.11	8.60 8.30
5	180	67	C <sub>26</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub> (390.40)	80.00 79.80	4.65 4.36	7.20 6.80
6	210	45	C <sub>19</sub> H <sub>14</sub> N <sub>2</sub> S (302.40)	75.50 75.20	4.67 4.41	9.30 9.00
7	190	58	C <sub>23</sub> H <sub>19</sub> NO <sub>3</sub> (357.40)	77.30 77.10	5.36 5.12	3.90 3.60
8	220	69	C <sub>22</sub> H <sub>17</sub> NO <sub>2</sub> (327.40)	80.70 80.50	5.23 4.95	4.30 4.20
9	215	46	C <sub>21</sub> H <sub>14</sub> N <sub>2</sub> O (310.40)	81.30 81.00	4.55 4.29	9.00 8.80
10	240	57	C <sub>21</sub> H <sub>15</sub> NO <sub>3</sub> (329.40)	76.60 76.50	4.60 4.37	4.30 3.90
11	145	66	C <sub>22</sub> H <sub>17</sub> N <sub>3</sub> (323.40)	81.70 81.40	5.30 5.18	13.00 12.90
12a	243	48	C <sub>26</sub> H <sub>21</sub> NO <sub>2</sub> (379.50)	82.30 82.10	5.58 5.38	3.70 3.40
12b	280	45	C <sub>27</sub> H <sub>23</sub> NO <sub>2</sub> (393.50)	82.40 82.20	5.89 5.66	3.60 3.30
12c	296	60	C <sub>28</sub> H <sub>25</sub> NO <sub>2</sub> (407.50)	82.50 82.10	6.18 5.99	3.40 3.10
13a	100	65	C <sub>21</sub> H <sub>19</sub> NO <sub>2</sub> (317.40)	79.50 79.40	6.03 5.78	4.40 4.20
13b	208	55	C <sub>25</sub> H <sub>19</sub> NO <sub>2</sub> (365.40)	82.20 81.90	5.24 5.03	3.80 3.50

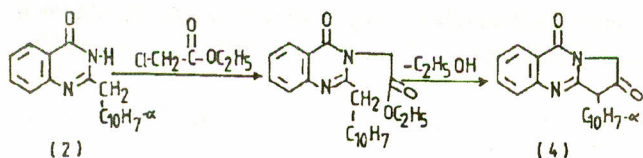
## Results and Discussion

Thus fusion of 2-( $\alpha$ -naphthyl methyl (-4H)-3, 1-benzoxazin-4-one (1) with formamide [7-8] at 170°, yielded 2-( $\alpha$ -naphthylmethyl)-4 (3H) quinazolone (2). The quinazolone (2) reacted with benzamide or succinimide in presence of formaldehyde in boiling ethanol to give the corresponding Mannich bases; 2, 3-disubstituted quinazolin-4 (3H)-ones (3a & b). The

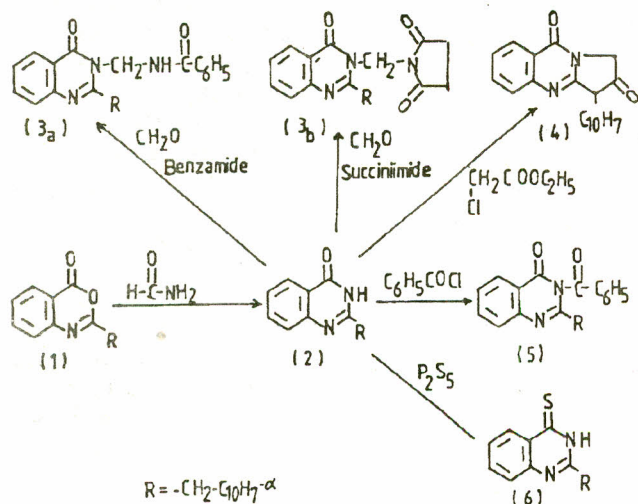
TABLE 2. SPECTRAL DATA OF THE PREPARED COMPOUNDS.

Compd. No.	IR in KBr ( $\nu$ in cm <sup>-1</sup> )	H1 nmr (CDCl <sub>3</sub> solvent, TMS reference, $\delta$ ppm)
1	1710 (C=O), 1615 (C=N) and 980 (C-O-C)	8.34-7.62(m, 11H; arom-H) and 4.12(s, 2H, -CH <sub>2</sub> )
2	3450(O-H), 3240(N-H), 1670 (C=O) and 1620 (C=N)	8.35-7.35(m, 11H, arom-H), 6.50 (br, 1H, OH) and 4.43 (s, 2H, CH <sub>2</sub> )
3a	3290 (N-H), 1670 (C=O) & 1610 (C=N)	8.35-7.60 (m, 20H, arom-H), 6.55 (br, s, 1H, NH), 4.42 (s, 2H, -CH <sub>2</sub> -NH) and 4.10 (s, 2H, CH <sub>2</sub> ).
4	1740 (C=O), 1670 (C=O) and 1615 (C=N)	8.34-7.62 (m, 11H, arom-H), 5.11 (s, 1H, CH) and 4.65 (s, 2H, CH <sub>2</sub> )
5	1685 (C=O) and 1620 (C=N)	8.40-7.50 (m, 16H, arom-H), and 4.10 (s, 2H, -CH <sub>2</sub> )
6	3210 (N-H), 1610 (C=N) and 1090 (C=S)	7.89-7.34 (m, 11H, arom-H), 6.08 (br, s, 1H, -NH) and 3.87 (s, 2H, CH <sub>2</sub> )
7	1735 (C=O) ester), 1710 (C=O cyclic), 1610 (C=N) and 1200 (C-O)	8.25-7.50 (m, 11H, arom-H), 6.22 (br, 1H, OH), 4.12 (s, 2H, CH <sub>2</sub> ), 3.80 (q, 2H, CH <sub>2</sub> ) and 1.83 (t, 3H, CH <sub>3</sub> ).
8	3300 (OH enol form) 1710 (C=O), 1615 (C=N and 1200 (C-O)	7.88-7.45 (m, 11H, arom-H) 4.34 (s, 2H, CH <sub>2</sub> ) and 3.01 (s, 3H, CH <sub>3</sub> )
9	2260 (C=N), 1700 (C=O) and 1615 (C=N)	8.10-7.30 (m, 11H, arom-H), 6.20 (br, 1H, -OH) and 4.10 (s, 2H, CH <sub>2</sub> )
10	3400-3000 (O-H acid), 1710 (C=O) and 1590 (C=N)	11.20 (br, 1H, -COH), 8.30-7.50 (m, 11H, arom-H), 6.10 (br, 1H -OH) and 4.15 (s, 2H, CH <sub>2</sub> )
11	1615 (C=N)	7.82-7.34 (m, 11H, arom-H) 4.09 (s, 2H, -CH <sub>2</sub> ) and 2.73 (s, 3H, CH <sub>3</sub> )
12a	3340 (N-H), 1750 (C=O) and 1685 (C=O amide)	10.11 (br, s, 1H, -NH-CO) 8.37-7.69 (m, 15H, arom-H), 4.49 (s, 2H, -COCH <sub>2</sub> ) and 1.90 (s, 3H, -CH <sub>3</sub> )
12b	3350 (N-H), 1705 (C=O) and 1680 (C=O amide)	10.12 (br, s, 1H, NH), 8.35-7.30 (m, 14H, arom-H), 4.49 (s, 2H, CH <sub>2</sub> ) and 1.85 (s, 6H, CH <sub>3</sub> )
13b	3350 (N-H), 1700 (C=O) and 1670 (C=O amide)	10.12 (br, s, 1H, -NH-CO), 8.35-7.50 (m, 16H, arom-H) and 4.80 (s, 2H, CH <sub>2</sub> )

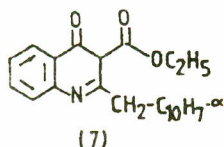
alkylation of compound (2) with ethylchloroacetate in boiling ethanol yielded the fused heterocyclic system 3-naphthyl-4-oxo-pyrrolo (2, 1-b)-quinazolin-4-one (4). This reaction may be proceeded according to the following steps.



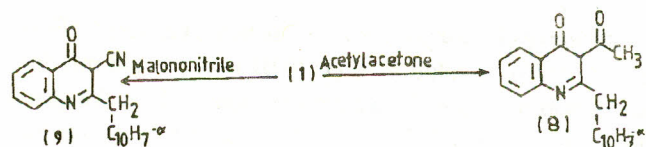
Also benzoylation of (2) in dry benzene gave 3-benzoyl-2-( $\alpha$ -naphthyl methyl)-quinazolin-4-one (5). On the other hand, when quinazolone (2) was reacted with  $P_2S_5$  in boiling xylene, the corresponding thioxoquinazolone derivative (6) was obtained. (Tables 1, 2 and Chart I).



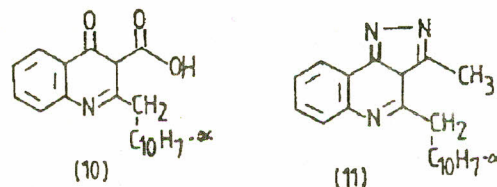
In a recent series of publications [9-11], it has been reported that, the reaction of 3, 1-benzoxazin-4-ones with active methylene compounds in basic medium gave the corresponding 3-substituted quinoline. In the present investigation, the reaction of benzoxazin (1) with ethyl acetoacetate, diethyl malonate or ethyl cyanoacetate in boiling pyridine yielded one and the same product; 2-( $\alpha$ -naphthyl methyl)-3-carboethoxy quinolin-4-one (7).



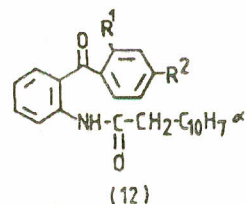
Extending the reaction to include acetylacetone or malononitrile using sodium ethoxide as a catalyst, 3-acetyl-2-( $\alpha$ -naphthyl methyl)-quinoline-4-one (8) and 3-cyano-2-( $\alpha$ -naphthyl methyl)-quinolin-4-one (9) were obtained in good yields (C.f. Tables 1 and 2).



The presence of 3-acetyl group in compound (8) was established chemically by the haloform reaction to yield 3-carboxy-2-( $\alpha$ -naphthyl methyl)-quinolin-4-one (10), (ii) condensation of (8) with hydrazine hydrate in boiling isopropanol gave 3-methyl-4-1-( $\alpha$ -naphthyl methyl)-pyrazolo (3,4-c) quinoline (11). (C.f. Tables 1 and 2).

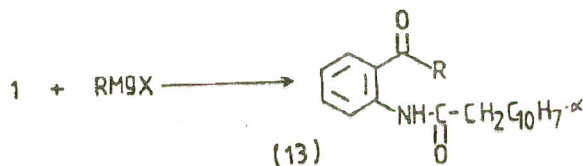


It has been reported that, benzoxazin-4-ones react with aromatic hydrocarbons in the presence of  $AlCl_3$  under Friedel-Crafts conditions to give 2-arylimidobenzophenones [11-13]. In the present investigation the reaction of 1 with toluene, *m*-xylene and cumene in the presence of  $AlCl_3$  yielded the corresponding 4-methyl, 2,4-dimethyl-4-isopropyl-2-( $\alpha$ -naphthyl)-acetamidobenzophenones (12 a-c) (C.f. Tables 1 and 2).



- a:  $R_1 = H$        $R_2 = CH_3$   
 b:  $R_1 = CH_3$      $R_2 = CH_3$   
 c:  $R_1 = H$        $R_2 = CH(CH_3)_2$

The reaction of 2-substituted-(4H)-3, 1-benzoxazin-4-ones with Grignard reagents has been reported [11, 13, 14]. In the present investigation treatment of compound (1) with ethylmagnesium bromide or phenylmagnesium bromide, gave 2-( $\alpha$ -naphthyl acetamido)-propiophenone (13 a) and 2-( $\alpha$ -naphthyl acetamido)-benzophenone (13 b). (C.f. Tables 1 and 2).



- a:  $R = C_2H_5$   
 b:  $R = -C_6H_5$

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