Preparation of 2-Phenyl-2-hydroxymethyl-4-oxo-1,2,3,4-Tetrahydroquinazoline and 2-Methyl-4-oxo-3,4-Dihydroquinazoline Derivatives Formation

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Received Novemeber 29, 1999

Dedicated to the memory of Professor Raymond N. Castle

The cyclization of phenacyl anthranilate has been studied with the aim to develop the synthesis of 2-(2'-aminophenyl)-4-phenyloxazole. However, a different course of the reaction than expected was observed. 2-Phenyl-2-hydroxymethyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**3a**) was formed by the reaction of phenacyl anthranilate (**2**) with ammonium acetate under various conditions.

3-Hydroxy-2-phenyl-4(1*H*)-quinolinone (**4**) arose by heating compound **3a** in acetic acid. The same compound was obtained by melting compound **3a**, but the yield was lower.

Different types of products resulted in the reaction of compound **3a** with acetic anhydride. Under mild conditions acetylated products 2-acetoxymethyl-2-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**7a**) and 2-acetoxymethyl-3-acetyl-2-phenyl-4-oxo-1,2,3,4-tetrahydroquinazoline (**8**) were prepared. If the reaction was carried out under reflux of the reaction mixture, molecular rearrangement took place to give *cis* and *trans* 2-methyl-4-oxo-3-(1-phenyl-2-acetoxy)vinyl-3,4-dihydroquinazolines (**9a** and **9b**). All prepared compounds have been characterised by their ^{1}H, ^{13}C and ^{15}N NMR spectra, IR spectra and MS.

J. Heterocyclic Chem., **37**, 831 (2000).

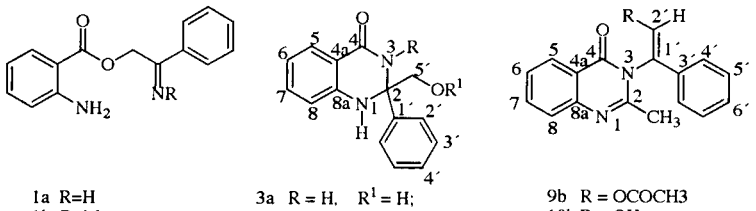
Phenacyl anthranilates are interesting molecules of considerable potential as synthetic intermediates [1,2]. They were used for the preparation of 3- hydroxy-2-aryl-4(1H)-quinolinones.[1] The potential applicability of using phenacyl anthranilate in order to prepare some derivatives of 2-(2'-aminophenyl)-oxazole, which have not been described yet, was also studied.

We applied the same conditions as those used for the reaction of 2-hydroxyketones with ammonium acetate in boiling acetic acid [3,4] by which phenacyl benzoate afforded 2,4-diphenyloxazole [5].

Results and Discusion.

Reaction of phenacyl anthranilate (**2**) with ammonium acetate and acetic acid gave 3-hydroxy-2-phenyl-4(1*H*)-quinolinone (**4**) as a main product at the boiling point of the reaction mixture. If lower temperature (90°C) was used, the formation of a different compound was preferred. The same compound, but with lower yield, is formed by melting phenacyl anthranilate (**2**) and ammonium acetate. Based on the elemental analysis and MS, we first supposed that 2-imino-2-phenyl-ethyl anthranilate (**1a**) arose (Figure 1). However ^{1}H and ^{13}C NMR did not correspond to this structure.

As a result of our doubt regarding the structure of **1a** we prepared its *N*-methyl analogue **1b**. Based on ^{1}H, ^{13}C and ^{15}N NMR results, we proposed structures **3a** and **3b** with *N*-methylamonium acetate (Figure 1) (Scheme 1) were elucidated as reaction products. The possible mechanism of their formation is formulated (Scheme 2).



1a R=H
1b R=Me

3a R = H, R^1 = H;
3b R = Me, R^1 = H;
7a R = H, R^1 = $COCH_3$
7b R = Me, R^1 = $COCH_3$
8 R = $COCH_3$, R^1 = $COCH_3$

9b R = OCOCH3
10b R = OH
11 R = NH2

Figure 1

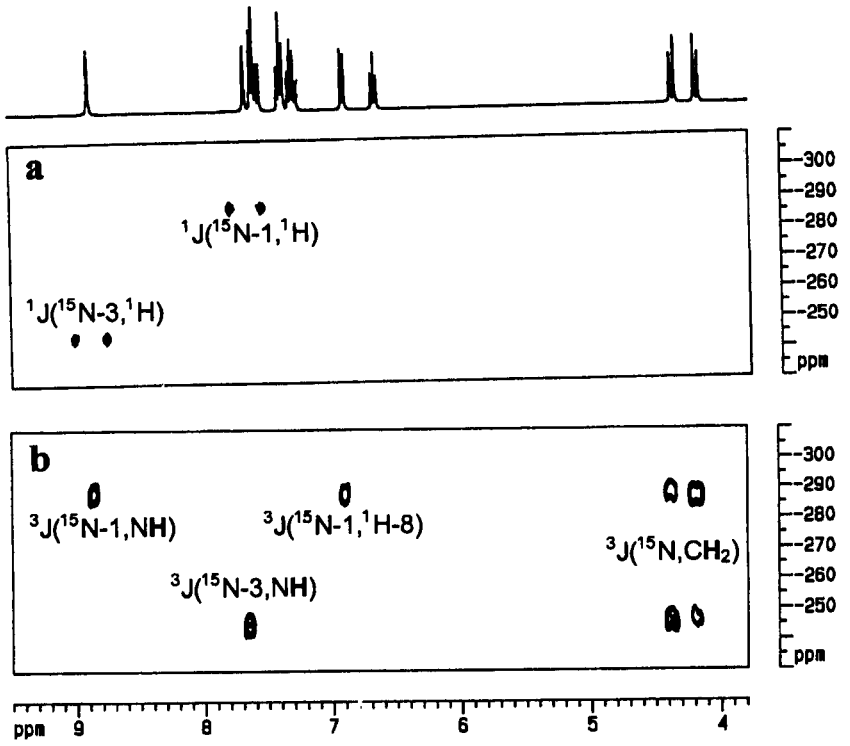


Figure 2. GHNMQC spectrum of compound **7a** optimized for a 90 Hz $J(^{15}N, ^1H)$ coupling constant (a) and for a 6 Hz $J(^{15}N, ^1H)$ coupling constant (b).

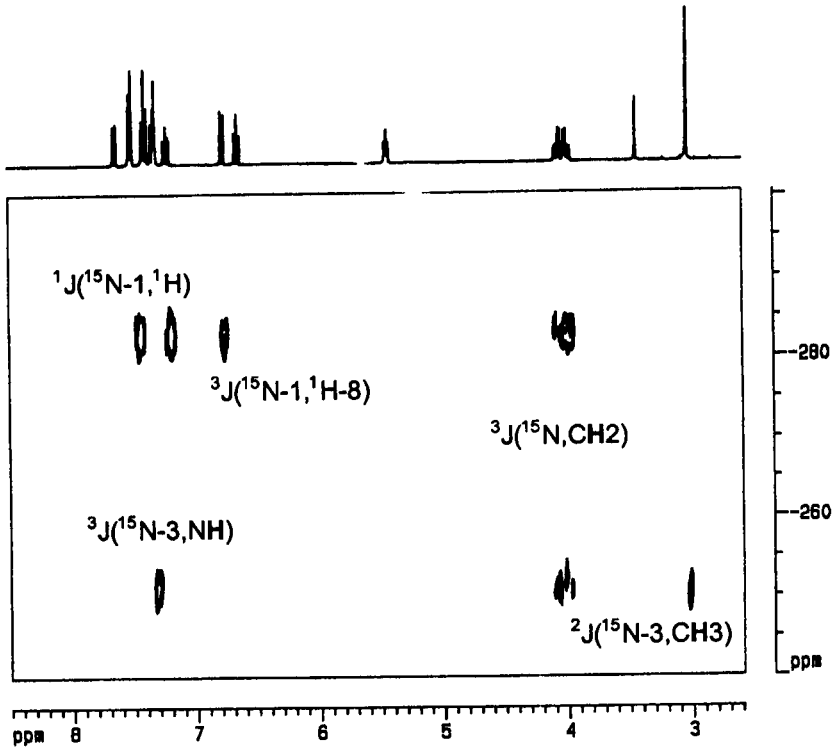
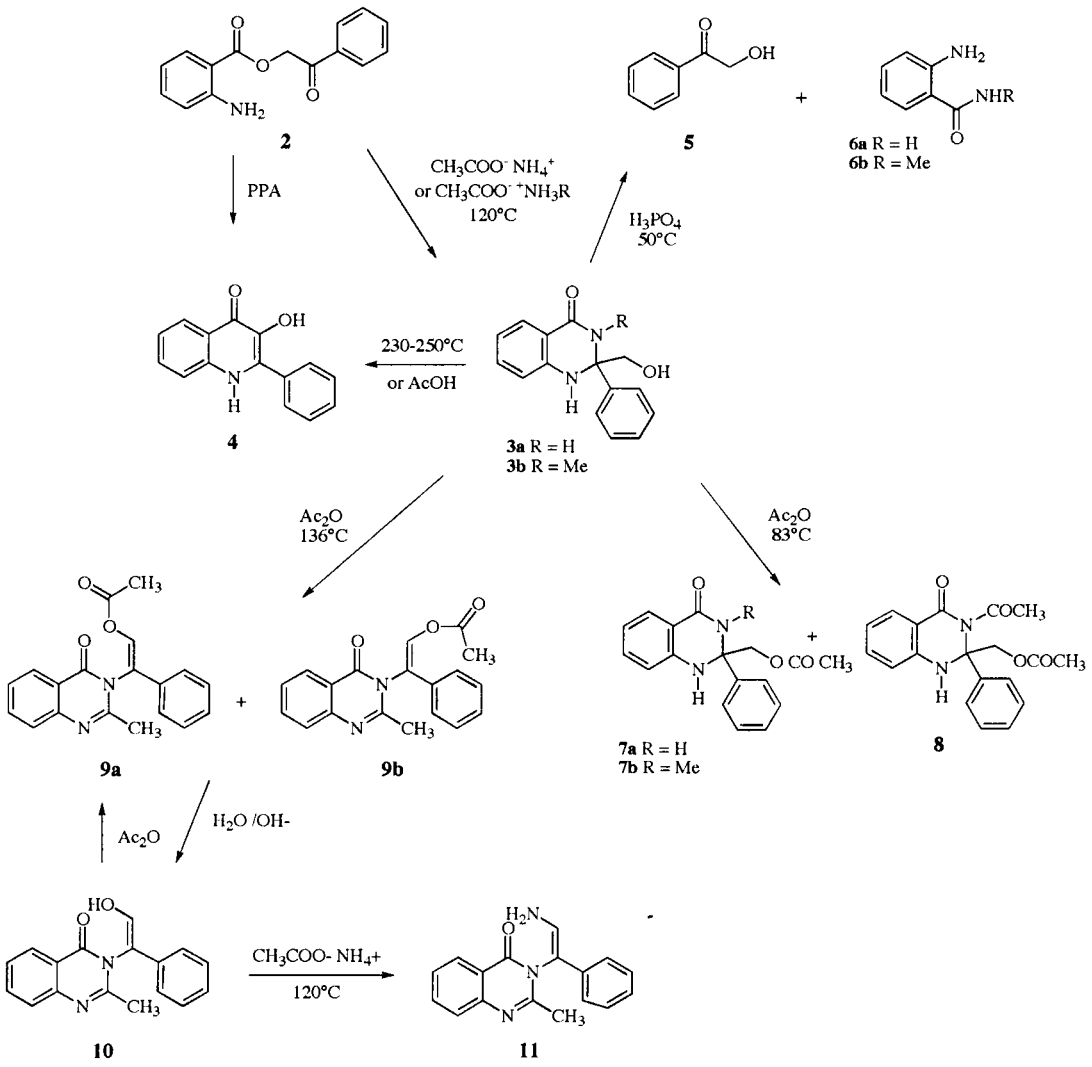


Figure 3. GHNMQC spectrum of compound **3b** optimized for a 6 Hz $J(^{15}N, ^1H)$ coupling constant.

Scheme 1

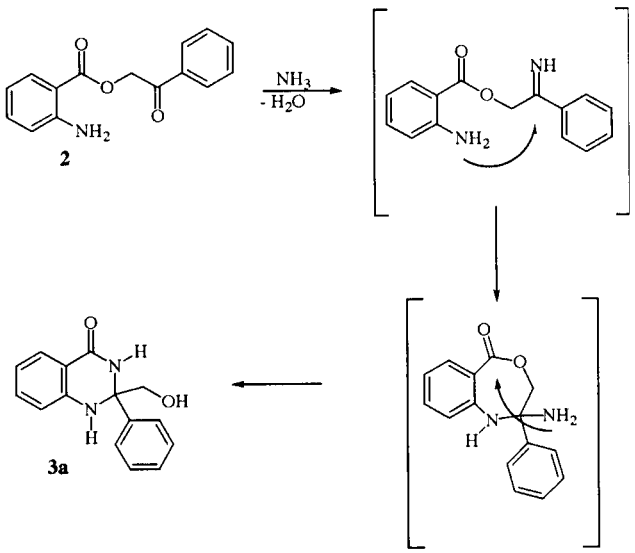


The reactivity of the compound **3a** was interesting. We attempted to cyclize this new compound **3a**, as in the case of phenacyl anthranilate (**2**) [1] by heating at 230-250°C. A molecule of ammonia was evolved and quinolinone **4** arose as we supposed. The yield was low and the reaction mixture contained a lot of unidentified by-products. The higher yield of quinolinone **4** was obtained when compound **3a** was heated with acetic acid. Anthranilate (**2**) afforded only *N*-acetyl derivative under the same conditions. We also tried to perform a reaction of compound **3a** in polyphosphoric acid (PPA). That method was successfully used for cyclization of anthranilate **2** and for the preparation of 3- hydroxy-2-phenyl- 4(1*H*)-quinolinone (**4**).[1] Hydrolysis of the molecule **3a** was observed. The reaction mixture contained 2-hydroxyacetophenone (**5**) and anthranilamide (**6a**) instead of anthranilic acid. The same result was obtained in the reaction of **3a** using diluted hydrochloric acid or phosphoric acid. Using the same conditions, compound **3b** afforded *N*-methyl anthranilamide (**6b**) and 2-hydroxyacetophenone (**5**). These compounds have not been isolated, but they were identified by comparison with standard sample in GC-MS analysis.

Interesting results were obtained in the following acetylation reactions of **3a**. If the reaction was performed with acetic anhydride in ethyl acetate, mono acetyl derivative **7a** is formed as a main product together with a small amount of the diacetyl derivative **8**. The structures of these compounds were also identified by NMR (*vide infra*).

If the reaction of **3a** is carried out without solvent at the boiling point of acetic anhydride, water elimination occurred during the rearrangement of the molecule. A mixture of *cis* and *trans* isomers **9a** and **9b** is formed. The exact mechanism of this rearrangement is not known. A possible way of generating compounds **9a** and **9b** is *via* compound **8**. The presence of this compound was observed after reaction with acetic anhydride at 83°C. The new ring should be formed

Scheme 2



turned back to the acetyl derivative by heating with acetic anhydride. In this case only one isomer is formed. Based on NMR analysis, we suppose that it is the *cis* isomer **9a**. Compound **3b** under the same conditions afforded only the monoacetyl derivative **7b**. In the phase sensitivite NOESY spectra of compounds **9 – 11**, negative cross-peaks were observed giving an evidence for the through-space proximity of protons C(2')H and C(4')H. From this fact the trans geometry on C(1')= C(2') double bond was determined.

We tested the behaviour of diacetyl derivative **8** in phosphoric acid. A mixture of compounds was formed in this reaction. 2-Methyl-4(3*H*)-quinazolinone was present as well as anthranilamide and 2-hydroxy-acetophenone. These compounds were identified by GC-MS. The formation of monoacetyl derivative **7** as an intermediate of the hydrolysis was observed by TLC. Compound **7** was isolated when the reaction was done in polyphosphoric acid.

We tried to cyclize the compound **10** by melting with ammonium acetate to prepare the imidazoquinazoline.

Table 1

^{1}H, ^{13}C and ^{15}N chemical shifts for compounds **3a,b**, **7a,b** and **8** in DMSO-D_6

H/C	**3a** [a]		**7a**		**8**		**3b** [e]		**7b**	
No	δ(^{1}H)	δ(^{13}C)	δ(^{1}H)	δ(^{13}C)	δ(^{1}H)	δ(^{13}C)	δ(^{1}H)	δ(^{13}C)	δ(^{1}H)	δ(^{13}C)
1	8.57	-288.0[b]	8.87	-289.3[b]	8.21	-280.7[b]	7.31	-283.5[b]	7.43	-285.3[b]
2	-	73.7	-	72.1	-	78.4	-	77.6	-	64.8
3	7.52	-245.1[b]	7.66	-246.1[b]	-	-198.1[b]	-	-251.9[b]	-	-253.0[b]
4	-	163.8	-	163.6	-	164.5	-	163.3	-	162.9
4a	-	147.4	-	146.8	-	140.5	-	114.2	-	113.9
5	7.58	127.3	7.56	127.3	7.69	128.1	7.63	127.4	7.66	127.3
6	6.63	116.8	6.67	117.2	6.74	118.0	6.65	114.3	6.71	114.0
7	7.26	133.4	7.31	133.6	7.40	135.5	7.22	133.0	7.26	133.3
8	6.98	114.8	6.91	114.7	6.92	115.2	6.76	116.8	6.71	117.1
8a	-	114.8	-	114.6	-	113.3	-	146.3	-	145.9
1'	-	144.8	-	143.3	-	147.3	-	142.0	-	140.6
2'	7.58	126.5	7.62	126.3	7.54	126.6	7.50	126.8	7.57	126.8
3'	7.34	127.9	7.40	128.2	7.40	128.5	7.40	128.2	7.47	128.6
4'	7.26	127.4	7.31	128.0	7.33	128.7	7.33	128.0	7.43	128.7
5'	3.72	68.0	4.19	67.7	4.57	65.5	3.96	64.5	4.66	64.8
5b'	3.76	68.0	4.38	67.7	4.74	65.5	4.06	64.5	4.80	64.8
CO	-	-	-	170.1	-	169.8[c]	-	-	-	169.9[c]
					-	176.3[d]				
CH_3	-	-	2.06	20.8	2.10[c]	20.5[c]	3.03	29.5	2.88[c]	29.6[c]
					2.53[d]	27.9[d]			1.96[f]	20.5[f]

[a] δ(^{1}H) of OH = 5.17 ; [b] δ(^{15}N); [c] $NCOCH_3$; [d] $OOCCH_3$;[e] δ(^{1}H) of OH = 5.43; [f] CH_3

between N-1 and C in carbonyl group of acetyl at N-3 and the simultaneous break of the bond between N-1 and C2 for compound **8** at higher temperature. Compounds **9a** and **9b** should be formed after elimination of water from this intermediate.

These acetyl derivatives are not too stable and easily hydrolyzed to the compound **10**. This compound can be The cyclization did not go and only intermediate **11** was formed.

The unambiguous assignment of the ^{1}H, ^{13}C and ^{15}N signals of the synthesized compounds was carried out by the analysis of the standard one-dimensional spectra and two-dimensional gradient-selected H,H-COSY, NOESY, ^{1}H-^{13}C HMQC (heteronuclear multiple quantum coherence) and

Table 2

^1H, ^{13}C and ^{15}N chemical shifts for compounds **9-11** in DMSO-D_6

H/C	**9a**[a,b]		**10**		**11**[d]	
No	δ(^1H)	δ(^{13}C)	δ(^1H)	δ(^{13}C)	δ(^1H)	δ(^{13}C)
1	-	-127.5 [c]	-	-115.3[c]	-	-110.[c]
2	-	161.0	-	162.5	-	146.4
3	-	-238.5[c]	-	-225.0[c]	-	-192.2[c]
4	-	168.8	-	168.2	-	167.9
5	-	119.2	-	119.4	-	135.5
6	8.37	128.4	8.14	127.3	7.73	128.7
7	7.43	126.0	7.49	116.6	7.59	129.2
8	7.56	133.9	7.70	134.1	7.54	130.9
9	7.13	115.5	7.28	125.8	7.18	129.7
10	-	140.3	-	141.0	-	134.6
1'	-	122.6	-	113.8	-	133.7
2'	8.30	133.8	7.90	143.8	7.11	126.0
3'	-	131.1	-	134.0	-	130.3
4'	7.37	124.0	7.28	124.8	7.22	127.2
5'	7.26	129.6	7.28	129.3	7.22	128.3
6'	7.37	124.0	7.28	127.3	7.22	126.8
CH_3	2.07	22.9	2.35	22.4	7.22	13.7

[a] In DCl_3; [b] CH_3CO: δ(^1H) = 2.41. δ(^{13}C) = 20.3 (CH_3). 168.8 (C=O); [c] δ(^{15}N); [d] δ(^{15}N) of NH_2 = -256.3.

HMBC (heteronuclear multiple bond coherence) [8,9] and two-dimensional GHNMQC (gradient-enhanced hydrogen-nitrogen multiple quantum coherence) [10] techniques.

The GHNMQC spectra played a key role in structure elucidation of compounds **3** – **11**. GHNMQC spectrum of **3a** gave two NH doublets

(δ(N-1) = -288.0, ^1J(NH) = 89.5 Hz, δ(N-3) = -245.1, ^1J(NH) = 90.6 Hz) in an experiment optimized for 90 Hz. Both nitrogens correlate with methylene group protons, but only N-1 correlates with proton H-8 in GHNMQC long-range correlation *via* ^3J(NH). The same results were observed for compound **7a** (Figure 2a). In Figure 2a, two NH doublets can be seen (δ(N-1) = -289.3, ^1J(NH) = 89.4 Hz, δ(N-3) = -246.1, ^1J(NH) = 90.4 Hz) while GHNMQC long-range correlation *via* ^nJ(NH) is depicted in Figure 2b. The proton at position 1 correlates with N-3 and the proton at position 3 correlates with N-1. From these facts it follows that the CH_2OH group (and not NH group) was acetylated first. In the diacetylated compound **8**, the N-1 nitrogen gave a doublet with ^1J(NH) = 90.2 Hz and correlates with proton H-8 in GHNMQC long-range correlation *via* ^3J(NH) and, hence, the acetylation had to occur on the N-3 nitrogen of compound **3** (^1H-^{13}C HMBC spectrum of **8** provided an independent evidence for the above mentioned fact showing the correlation of N-1 proton with C-8 *via* ^3J(CH)). The GHNMQC spectra of compounds **3b** and **7b** were analysed analously. Figure 3 shows the GHNMQC spectrum of compound **3b** providing the correlation of N-3 with protons of the methyl group. Signal of N-1 nitrogen is shifted considerably to lower frequency in compounds **9-11** in line with the fact that signals of nitrogens on double bond are commonly shifted in this direction [11]. The stereo-chemistry on the a C-1'= C-2'couble bond in compounds **9-11** was determined using NOESY [12] spectra.

In addition to the ^1H-^{13}C HMQC spectra, long-range ^1H-^{13}C HMBC experiments were performed for the purpose of providing direct attachment between protons and carbons, setting the ^nJ(CH) value to 8 Hz, to assign the quatenary carbons. Quarternary carbons, mainly to assign carbons C(4), C(4a) and C(8a). In ^1H-^{13}C HMBC spectra of compounds 3,7 and 8 the weak connectivity of NH protons with C(2) were observede as well as protons of methyl group with the same carbon in compounds **9-11**. The ^1H, ^{13}C and ^{15}N chemical shifts are collected in Tables 1 and 2.

EXPERIMENTAL

The IR spectra were measured in KBr pellets using the diffuse reflectance and scanned on an ATI UNICAM Genesis FT IR instrument. The ^1H (360.13 MHz), ^{13}C (90.56 MHz) and ^{15}N (36.50 MHz) NMR spectra were measured in hexadeuteriodimethyl sulfoxide on a Bruker AMX-360 spectrometer. The ^1H and ^{13}C chemical shifts were referred to the respective solvent signals and recalculated to the δ-scale ((δ(^1H) /δ(^{13}C) = 2.55 / 39.60, $(CD_3)_2SO$) and 7.25 / 77.00 ($CDCl_3$)). The ^{15}N chemical shifts were referenced to the external nitromethane placed in a co-axial capillary (δ(^{15}N) = 0.0). The coupling constants J are given in Hz. The unambiguous assignment of the ^1H, ^{13}C and ^{15}N signals was carried out by the analysis of standard one-dimensional spectra and gradient selected two-dimensional H,H-COSY, ^1H -^{13}C HMQC and HMBC and GHNMBC experiments. CHN analyses were performed using an EA 1108

Elemental Analyser (Fison Instrument). TLC was performed on Polygram Sil G/UV$_{254}$ with UV light detection. Melting points were measured in the Kofler apparatus and are uncorrected. The mass spectra (MS) was measured on LCQ (Finnigan Mat) equipped with an ionization electrospray in positive mode. GC-MS was measured on GCD system (Hewlett Packard).

2-Hydroxymethyl-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazoline (**3a**) and 3-Methyl Derivative (**3b**).

Method A.

Compound **2** (2.55 g, 10 mmol) was added to melted ammonium or methyl ammonium acetate (0.14 mol) at 70°C. The clear solution was obtained and the temperature was gradually increased to 120°C and kept at this temperature for 20 minutes in the first case and 90 minutes in the second case. Then the reaction mixture was poured into a mixture of water (50 ml) and ethyl acetate (7 ml) and stirred at ambient temperature for 10 minutes The precipitated solid was collected by suction and thoroughly washed with a mixture of water (20 ml) and ethyl acetate (10 ml) and dried at 60°C in a drying oven. The solid was recrystallized from acetone for **3a** and from ethanol for **3b**. Compound **3a** was isolated in the yield of 1.55 g; (61%), mp 226-230°C; ms: (M+1) 255.1; ir: 3404, 3341 (NH_2), 3062 (ArH), 2907, 2869 (CH_2), 1649 (CO), 1390 (CH_2).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$ (254.1): C, 70.85; H, 5.55; N, 11,02. Found: C, 70.60; H, 5.91; N, 10.96.

Compound **3b** was isolated in the yield of 1.3 g (48%), mp 207-211°C; ms: (M+1) 269.3; ir: 3304, 3284 (NH), 3060 (ArH), 1623 (CO), 1382 (CH_2).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.02; N, 10.44. Found: C, 71.95; H, 6.38; N, 10.44.

Method B.

The compound **2** (2.55 g, 10 mmol) was added to the solution of ammonium or methyl ammonium acetate (0.1 mol) in acetic acid (12 ml) at temperature 50°C and gradually heated. After reaching 90°C, the stirred mixture was kept at this temperature for 90 minutes The starting material was not present on the TLC after 90 minutes for **3a** or 150 minutes for **3b** of the reaction at this temperature. The reaction mixture was left cool to room temperature. The solid compound was precipitated by the addition of water (40 ml) and collected by suction. Isolated product was dried and crystallized from acetone for **3a** or ethanol for **3b**.

Compound **3a** was isolated in the yield of 2.05 g (81%), mp 226-230°C.

Compound **3b** was isolated in the yield of 2.03 g (76%), mp 206-210°C.

3-Hydroxy-2-phenyl-4(1H)-quinolinone (**4**).

Method A.

Compound **2** (1 g, 3.92 mmol) was dissolved in acetic acid (20 ml) and ammonium acetate (4.8 g) was added. The reaction mixture was refluxed for 2 hours Then the reaction mixture was poured into water (150 ml). The solid was collected by suction. This compound was identified by TLC and IR as quinolinone **4**. The solid was recrystallized from the mixture of dimethylformamide and acetone to give 0.52 g (56%), mp 278-280 °C, (lit.[1] mp 278 -281°C).

Method B.

Compound **3a** (1.08 g, 4.25 mmol) was melted and heated at 230 to 250 °C for 45 minutes After ammonia escaped from the reaction mixture, it was cooled and dissolved in boiling ethyl acetate. The resulting solution was cooled and the precipitated solid was filtered off. The isolated product was identified by TLC and IR as compound **4**. The yield 0.15 g (15%), mp 276 - 281°C (lit.[1] mp 278 -281°C). (The product from the mother liquor was not isolated.)

Method C.

Compound **3a** (0.51 g, 2 mmol) was dissolved at acetic acid and refluxed for 2 hours At which time the starting material was not observed by the TLC. The reaction mixture was cooled a bit and diluted by water (50 ml). The precipitated compound was filtered off and carefully washed with water. After drying the isolated product was dissolved in dimethylformamide and precipitated with ethanol. The yield 0.31 g (65%) of product **4**, mp 279-283°C (lit. [1] mp 278 -281°C). (The product from the mother liquor was not isolated.) Compound **4** was identified comparing TLC and IR with that of the standard.

Decomposition of Compound **3a** in Phosphoric Acid

Compound **3a** (0.66 g, 2.60 mmol) was dissolved in 85% phosphoric acid (10 ml) and heated at 60°C. The reaction mixture was stirred at this temperature for 10 minutes at which time the starting material was not detectable by TLC. Only two compounds were identified by TLC in the reaction mixture. The reaction mixture was poured into water (50 ml) and the water layer was extracted with ethyl acetate (3 x 25 ml). The organic layer was washed with water, dried with sodium sulfate and evaporated *in vacuo*. The residual oil was dissolved in a small amount of toluene and precipitated with petroleum ether. The crystalline part was identified by HPLC as compound **5** by comparison with a standard. The inclusive yield of the product from the mother liquor was 0.18 g, (51%), mp 81-85,5°C (lit. [7] 86-87°C).

The water layer was neutralized with $NaHCO_3$ and extracted with ethyl acetate (3 x 25 ml). The ethyl acetate portion was washed with water and dried with sodium sulfate. The filtered solution was evaporated *in vacuo* and the solid was recrystallized using a mixture of toluene and hexane. The crystalline part was identified by HPLC as compound **6** by comparisonwith a standard. The inclusive yield of the product from the mother liquor was 0.18 g (50%), mp 108.5-111°C (lit.[7] mp 109-111.5°C).

2-Acetoxymethyl-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazoline (**7a**) and 2-acetoxymethyl-3-acetyl-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazoline (**8**).

Compound **3a** (0.51 g, 2 mmol) was added to the mixture of ethyl acetate (15 ml) and acetic anhydride (10 ml). The reaction mixture was heated at 83°C for 2 hours Then the reaction mixture was evaporated *in vacuo* and chromatographed on a silica gel column in toluene : ethyl acetate = 1 :1. Two compounds were isolated. The first was identified as **7a**. The yield was 0.37 g (62%), mp 143.5 – 145.5°C; ms: (M+1) 297.2; ir: 3362 (NH), 3057 (ArH), 2942 (CH_2), 1725 (CO), 1383 (CH_2).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$ (296.1): C, 68.91; H, 5.44; N, 9.45. Found: C, 68.65; H, 5.92; N, 9.28.

The second compound was identified as **8** in the yield of 0.1 g, (15%), mp 159-164°C; ms: (M+1) 339.1; ir: 3330 (NH), 3039 (ArH), 2948 (CH_2), 1748, 1727 (CO), 1341 (CH_2).

Anal. Calcd. for $C_{19}H_{18}N_2O_4$ (338.1): C, 67.45; H, 5.36; N, 8.28. Found: C, 67.67; H, 5.39; N, 8.37.

2-Acetoxymethyl-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazoline (**7a**).

Compound **8** (0.5 g, 1.48 mmol) was stirred with polyphosphoric acid (4 g) and the reaction mixture was heated at 70°C. After 5 minutes the reaction mixture became homogenous and no starting material was detected. Compound **7a** was identified by TLC. The reaction mixture was poured into a solution of sodium hydrogen carbonate (10 g) in water (50 ml) and the water layer was extracted with ethyl acetate (3 x 25 ml). The organic layer was washed with water, dried with sodium sulfate and evaporated *in vacuo*. The residual oil was purified on a silicagel column with toluene : ethyl acetate 1:1. The yield of the product **7a** was 0.16 g (36%), mp 143-145°C.

2-Acetoxymethyl-3-methyl-4-oxo-2-phenyl -1,2,3,4-tetrahydroquinazoline (**7b**).

Compound **3b** (0.7 g, 2.6 mmol) was added to a mixture of acetic anhydride (4.75 ml) and acetic acid (0.25 ml). The yellow solution was stirred and heated under the reflux for 30 minutes The reaction mixture was evaporated *in vacuo*, and rest was diluted by diethyl ether (10 ml). The precipitated white solid was filtered off, washed with diethyl ether and crystallized from ethanol to give **7b** in a yield of 0.75 g (81%), mp 156-9°C; ms: (M+1) 311.3; ir: 3296 (NH), 3060 (ArH), 2942 (CH_2), 1629, 1748 (CO), 1372 (CH_2).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$ (310.4): C, 69.70; H, 5.80; N, 9.06. Found: C, 69.76; H, 6.19; N, 8.87.

Mixture of *cis* and *trans* 2-Methyl-4-oxo-3-(1-phenyl-2-acetoxy)vinyl-3,4-dihydroquinazoline (**9a** and **9b**).

Compound **3a** (0.66 g, 2.6 mmol) was added to a mixture of acetic anhydride containing 2% of acetic acid (5 ml). The resulting suspension was heated under intensive reflux for 40 minutes The solid compound was dissolved below the boiling point. Then the solution was evaporated *in vacuo*. The residual acetic anhydride was removed by evaporation of the remaining oil with ethyl acetate several times. The honey-like residue was dissolved in ethanol and the solid was precipitated by addition of diethyl ether. The solid compound was filtered off and recrystallized from a mixture of ethanol and diethyl ether. This compound was identified as a mixture **9a** and **9b**. The yield was 0.34 g (41%), mp 185 -190°C; ms: (M+1) 321.1; ir:3069 (ArH), 1771, 1645 (CO), 1392 (CH_3), 1196 (C-N), 776 (ArH).

Anal. Calcd. for $C_{19}H_{16}N_2O_3$ (320.3): C, 71.24; H, 5.03; N, 8.74. Found: C, 71.17; H, 5.03; N, 8.44.

Cis 2-methyl-4-oxo-3-(1-phenyl-2-acetoxy)vinyl-3,4-dihydroquinazoline (**9a**).

Compound **10** (0.36 g, 1.29 mmol) was boiled under reflux with acetic anhydride (5 ml) for 45 minutes Then the solution was evaporated *in vacuo* and the honey-like residue was dissolved in ethyl acetate (5 ml) and solid **9b** was precipitated by the addition of diethyl ether (30 ml). The solid compound was filtered off and dried at 60°C. The yield was 0.28 g (67%), mp 180-187°C. ms: (M+1) 321.1.

2-Methyl-4-oxo-3-(1-phenyl-2-hydroxy)vinyl-3,4-dihydroquinazoline (**10**).

A mixture of compound **9a** and **9b** (0.525 g, 1.6 mmol) was dissolved in a mixture of ethanol (15 ml) and water (10 ml) and refluxed for 4 hours Then the reaction mixture was checked by TLC and the solution was evaporated *in vacuo*. The mixture was diluted with distilled water (30 ml). After cooling to an ambient temperature, the precipitated solid was filtered. The solid compound was crystallized from ethanol to give **10** in a yield of 0.35 g (77%), mp 209-212°C; ms: (M+1) 279.1; ir: 1666 (NH), 1456, 1404 (CH_3).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$ (278.3): C, 73.37; H, 5.07; N, 10.07. Found: C, 72.98; H, 5.17; N, 9.88.

2-Methyl-4-oxo-3-(1-phenyl-2-amino)vinyl-3,4-dihydroquinazoline (**11**).

Compound **10** (0.497 g, 1.8 mmol) was melted with ammonium acetate (3.3 g) at 140°C for 90 minutes Then the reaction mixture was diluted with water (25 ml) and extracted with ethyl acetate (3 x 25 ml). The organic layer was dried over sodium sulfate and filtered with charcoal (0.2 g). The solution was evaporated *in vacuo*. The honey-like residue (0.45 g) was dissolved in diethyl ether. After staying overnight a yellow crystalline material precipitated. The solid was filtered off, washed with ether and dried in the vacuum drier at 60°C. The product from mother liquor was not isolated. The yield was 0.17 g, (34%), mp 174-176°C; ms: (M+1) 278.3; ir: 3325 (N-H), 3060 (ArH), 1683 (CO), 1628 (C=C), 1391 (CH_3).

Anal. Calcd. for $C_{17}H_{15}N_3O$ (277.3): C, 73.63; H, 5.45; N, 15.15. Found: C, 73.20; H, 5.62; N, 14.77.

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