QUINAZOLINONES DERIVED FROM N-(1,1-DIMETHYLPROPIO-2-NYL)-BENZAMIDE

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ABSTRACT

*The ring opening of isatoic anhydride with 1,1-dimethylpropio-2-inylamine at 45°C in dimethylformamide gave 2-amino-N-(1,1-dimethylprop-2-inyl)-benzamide **3** while refluxing isatoic anhydride with 1,1-dimethylprop-2-inylamine at 100°C in water afforded 2-amino-N-(1,1-dimethylpropio-2nyl)-benzamide **4**. When **3** was refluxed in formic acid-water mixture, **4** was also obtained which on cyclization with triphosgene and triethylorthoacetate yielded the quinazolinones **5** and **6** respectively.*

INTRODUCTION

The use of isatoic anhydride in synthetic chemistry cannot be over-emphasised. Isatoic anhydride has been used in the construction of various heterocyclic ring systems including quinazolines in dyes and agrochemicals[1]. The quinazoline heterocyclic systems has continued to receive unprecedented research attention since the discovery of Febrifugine[2]. This is not unconnected with the interesting and important pharmacological activities exhibited by quinazolines. Quinazoline derivatives[3] have been used as anticonvulsants, antihypertensives, diuretics, antimicrobial agents to mention a few. The reports on the synthesis of oxazoloquinazolinones and various quinazolines using acetylenic amides as intermediates are documented[4]. Acetylenic amides[5] have been condensed with orthoesters to give various quinazolinones depending on the substitution pattern. The necessity to transform the acetylene moiety to a ketonic moiety became necessary as the envisaged corresponding quinazolinones **5** and **6** are presumed to have anticonvulsant activity. The management of epilepsy which plagues more than 20 million people world-wide is a dynamic process and the control of seizures may vary from time to time[6]. There is an increasing need for new anticonvulsants with fewer toxic and more selective action[7].

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage microscope and were reported uncorrected. The reactions and purity of the products were monitored by thin layer chromatography (tlc) using precoated silica gel plate[8]. Silica gel[8] (70-230 mesh) was used for column chromatography. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Varian Gemini 200 (TMS); infrared spectra were measured on a Perkin-Elmer type 457 and the mass spectra were determined using a Varian MAT 44S, EI: 70 eV.

2-Amino-N-(1,1-dimethylprop-2-inyl)-benzamide 3

1,1-dimethylprop-2-inylamine 2 (4.98g, 0.06mole) was added to isatoic anhydride (6.52g, 0.04 mole) in dimethylformamide (20ml) at 45°C and stirred under nitrogen for 4h. The reaction mixture was poured into 100ml water and extracted with ethyl acetate (3x40ml). The combined organic phase was washed with brine, dried (anhydrous sodium sulphate) and evaporated in vacuo to give a crude product which on recrystallisation from dichloromethane-hexane gave **3** as needles 5.80g (72%) m.p. 121-122°C [Lit[4] 121-123°C]: IR (KBr): 3490, 3400, 3390 (NH_2, NH), 3000, 1645 (C=O), 1600, 1260, 760, 700cm^{-1}. ^1H NMR: ($CDCl_3$) δ = 1.72 (s, 6H, 2 x CH_3), 2.38 (s, 1H, 3'-H), 5.34 (brs, 2H, NH_2), 6.14 (brs, 1H, NH), 6.61 (t, J=7.9Hz, 1H, 5-H), 6.67 (d, J=8.0 Hz, 1H, 3-H), 7.18 (ddd, J=1.2, 7.1, 7.4 Hz, 1H,4-H), 7.77 (dd, J=1.6, 7.9 Hz, 6-H). ^{13}C NMR: ($CDCl_3$) δ = 29.3, 47.9, 69.5, 87.6, 116.6, 116.8, 117.8, 127.6, 132.7, 149.3, 169.4. MS: m/z = 202 [M^+] (55), 174 (13), 136 (20), 119 (100), 105 (30), 92 (50), 65 (42).

Synthesis 2-amino-N-(1,1-dimethylpropio-2-nyl)-benzamide 4

Method A

A mixture of isatoic anhydride (3.26g, 0.02 mole) and 1,1-dimethylprop-2-inylamine (2.49g,

0.03mole) in water (30ml) was refluxed for 3h. The reaction mixture was allowed to cool to room temperature and extracted with dichloromethane (3 x 30ml). The combined organic phase was dried over anhydrous sodium sulphate, evaporated in vacuo to give a crude product which could be recrystallised from dichloromethane-hexane gave **4** as colourless needles 1.0g (30%), m.p. 95-96°C. IR (KBr): 3490, 3400, 3380 (NH_2, NH), 3000, 1705 (C=O), 1640, (C=O, amide), 1620, 1240, 760, 700cm^{-1}. ^{1}H NMR: ($CDCl_3$) δ = 1.55 (s, 6H, 2 x CH_3), 2.23 (s, 3H, $COCH_3$), 5.50 (brs, 2H, NH_2), 6.65 (t, J = 7.5Hz, 1H, 5-H), 6.66 (d, J = 8.0Hz, 1H, 3-H), 6.87 (brs, 1H, NH), 7.22 (ddd, J=1.1, 7.3, 8.1Hz, 1H, 4-H), 7.40 (dd, J=1.4, 8.4Hz, 1H, 6-H),. ^{13}C NMR ($CDCl_3$): δ = 23.5, 23.8, 115.9, 116.9, 117.8, 127.8, 132.0, 149.5, 169.4, 209.3. MS: m/z (%) = 220 [M$^+$] (8), 177 (22), 120 (100), 92 (22), 65 (18). Analysis C_{12} $H_{16}N_2O_2$, Cal. C 65.41 H 7.33 N 12.72. Found C 65.22 H 7.17 N 12.56.

Method B

2-amino-N-(1,1-dimethylprop-2-inyl)-benzamide **3** (3.0g, 0.015mole) was refluxed in 20ml water-formic acid (6:1) mixture for 4h. The reaction mixture was cooled to room temperature and extracted with dichloromethane (3 x 20ml). The combined organic phase washed with 5% $NaHCO_3$ water, dried (anhydrous sodium sulphate) and evaporated in vacuo. Recrystallisation from dichloromethane-hexane afforded 2-amino-N-(1,1-dimethylpropio-2-nyl)-benzamide **4** as colourless needles. 2.12g (65%) m.p. 95-96°C.

3-(1,1-Dimethylacetonyl)-quinazolin-2,4-(1H)-dione ***5***

To 2-amino-N-(1,1-dimethylpropio-2-nyl)-benzamide **4** (1.0g, 4.55mole) in dioxane (20ml) and triethylamine (3ml) stirred under nitrogen at 0°C was added triphosgene (0.5g, 5.0mole). The reaction mixture was allowed to warm up to room temperature and then gradually heated to reflux and maintained at reflux for 6h. The volatile solvents were removed in vacuo and water (40ml) added and extracted into ethylacetate (3 x 30 ml). The combined organic phase was washed with brine, dried (anhydrous sodium sulphate) and evaporated to give a crude product which was purified by column chromatography (dichloromethane-ethylacetate 3:1) to give **5** which was recrystallised from methanol as colourless plates 0.78g (70%) m.p. 162-164°C. IR (KBr): 3420, 3000, 1740, 1720, 1680, 1605, 1600, 1280, 960, 750, 700cm^{-1}. ^{1}H NMR: (DMSO-d_6) δ = 1.78 (s, 6H, 2 x CH_3), 2.22 (s, 3H, 3'-H), 7.24 (ddd, J=1.3, 6.8, 7.1Hz, 1H, 7-H), 7.48 (dd, J=1.4, 7.1 1H, 8-H), 7.66 (ddd, J=1.5, 6.8, 7.1Hz, 1H, 6-H), 7.90 (dd, J=1.4, 8.0 Hz, 1H, 5-H).. ^{13}C NMR: (DMSO d_6) δ = 23.8, 24.4, 68.8, 113.6, 115.8, 123.2, 128.5, 136.2, 140.1, 150.0, 162.4, 202.8. MS: m/z (%) = 246 [M$^+$] (20), 204 (100), 163 (60), 146 (50), 120 (40), 120 (40), 104 (40), 92 (20), 65 (20), 51 (10). Analysis C_{13} $H_{14}N_2O_3$ (246.27) Cal. C 63.40 H 5.73 N 11.38. Found C 63.28 H 5.70 N 11.28.

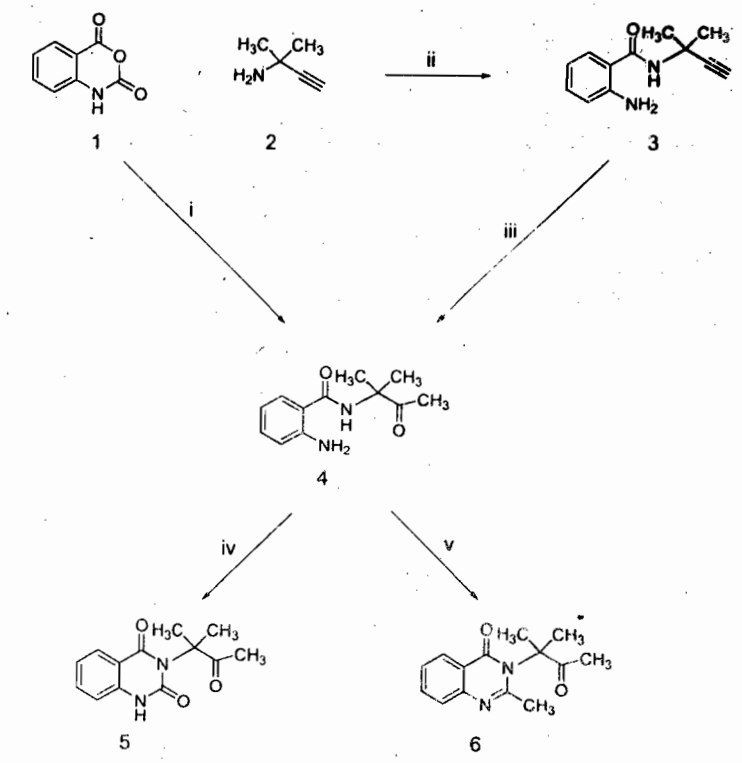
3-(1,1-Dimethylacetonyl)-2-methyl-quinazolin-4-(3H)-one ***6***

The benzamide **4** (1.32g, 6.0mmole), glacial acetic acid (1.0ml) and triethylorthoacetate (1.0g, 6.0mmole) were refluxed in ethanol (20ml) for 5h. The volatile solvents were evaporated and water (10ml) was added and brought to pH8 with 5% sodium hydroxide and extracted with dichloromethane (3 x 20ml). The combined organic phase was dried (anhydrous sodium sulphate), evaporated to give a crude product which was purified by column chromatography (dichloromethane). Recrystallisation from dichloromethane-hexane afforded **6** as colourless plates 1.20g (80%) m.p. 109-110°C [Lit[5] 108-110°C]. IR (KBr): 3000, 2990, 1710, 1690 (C=O), 1640, 1600, 1140, 760, 700cm^{-1}. ^{1}H NMR: ($CDCl_3$) δ = 1.75 (s, 6H, 2 x CH_3), 2.15 (s, 3H, 3'-H), 2.78 (s, 3H, C_2 - CH_3), 7.45 (ddd, J=1.3, 6.9, 7.1 Hz, 1H, 7-H), 7.62 (dd, J=0.6, 7.1, 1H, 8-H), 7.73 (ddd, J=1.6, 6.7, 7.1 Hz, 1H, 6-H), 8.14-8.20(dd, J=0.7, 8.0 Hz, 1H, 5-H). ^{13}C NMR: ($CDCl_3$) δ = 23.8, 24.7, 26.8, 69.2, 120.8, 126.7, 127.1, 127.3, 135.1, 147.1, 154.0, 164.2, 202.6. MS: m/z (%) = 224 [M$^+$] (28%), 229 (4), 202 (83), 160 (100), 143 (95), 118 (21), 102 (12), 91 (29), 76 (34), 65 (13). Analysis $C_{12}H_{16}N_2O_2$, Cal. C 68.83 H 6.60 N 11.47. Found C 68.68 H 6.58 N 11.40.

DISCUSSION

The ring opening of **1** with **2** gave the benzamides **3** and **4** under different reaction conditions. The benzamide **4** was obtained in low

Scheme



i: H_2O, 100°C, 3h; ii: DMF, 45°C, 4h; iii: H_2O-HCOOH (6:1), reflux, 4h;

iv: Triphosgene-dioxane, 6h: v: Triethylorthoacetate, CH_3COOH, 5h.

yield. An attempt was made to obtain **4** from **3** by boiling in water. After over 10h, only **3** can be identified from tlc with no formation of **4** or any other breakdown product. On refluxing **3** in water-formic acid (6:1) mixture, the benzamide **4** was formed in good yield. This indicates that hydration of the benzamide occurs under acid-catalysis.

With a better alternative route to the benzamide **4**, it became reasonable to cyclise **4** with triphosgene in dioxane in the presence of triethylamine at reflux for 6h to provide the quinazolinone **5**. The quinazolinone **6** was obtained in good yield on refluxing **4** in triethylorthoacetate. This new synthetic approach to the quinazolinone **6** is a preferred route compared to an earlier reported procedure where **6** was obtained as a side product[5]. The benzamides and quinazolinones were unequivocably characterised by their spectroscopic data and elemental analysis.

The strong carbonyl bands of **4** at 1705cm^{-1} and 1640cm^{-1} were attributed to the propio-2-onyl moiety and the amide respectively while the amino (NH_2) group and amide NH were clearly centered at 3490, 3400 and 3380 in the IR spectrum. The proton NMR showed the presence of three methyl groups with two centered at 1.55 ppm and the third at 2.23 ppm and the absence of acetylene proton.

The IR spectrum of the quinazolinone **5** revealed three carbonyl groups which were confirmed by the ^{13}C NMR. All spectra data, including melting point of the quinazolinone **6** were identical to what was earlier reported for quinazolinone[5].

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