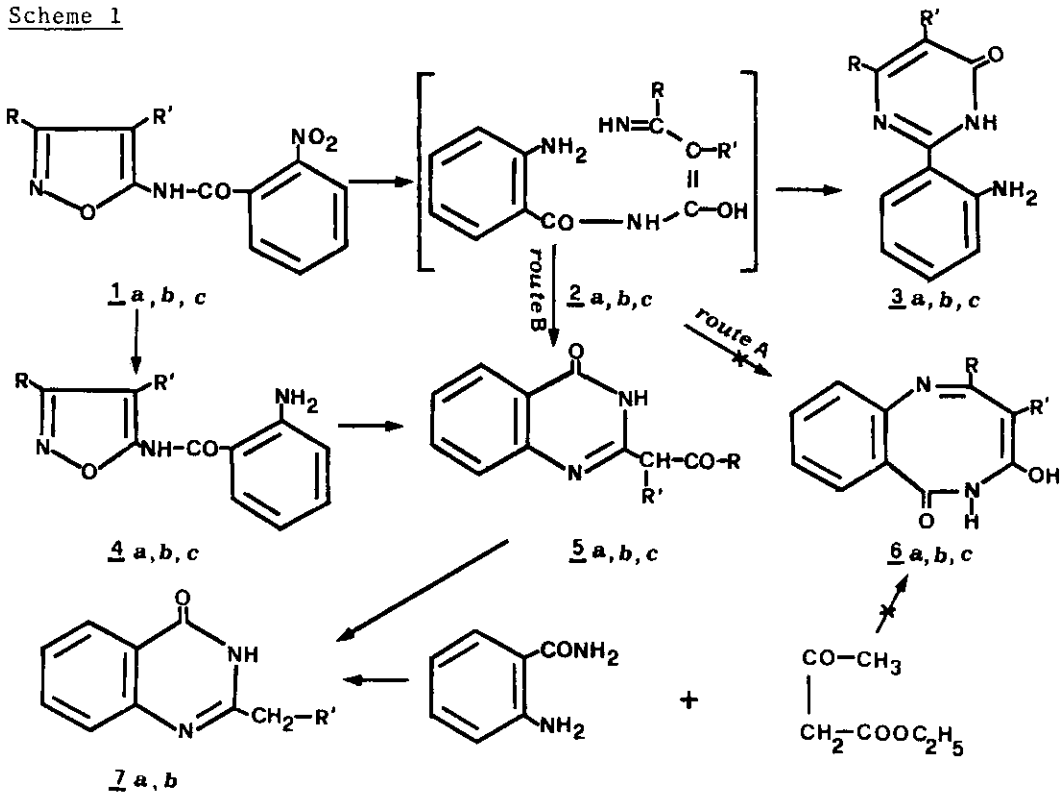
STUDIES ON THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS. PART XI. A NOVEL ACCESS TO SOME 2-SUBSTITUTED 4(3H)-QUINAZOLINONES

Maria Luisa Bajardi, Giuseppe Daidone, Demetrio Raffa, and Salvatore Plescia*
Istituto di Chimica Farmaceutica e Tossicologica dell'Università, Via Archirafi 32, 90123 Palermo, Italy

Abstract — Hydrogenolysis of N-(3-R-4-R'-isoxazol-5-yl)-2-nitrobenzamides 1a,b,c with iron powder in acetic acid afforded directly the 2-substituted 4(3H)-quinazolinones 5a,b,c. Additionally, the structure of the methylation product of 2-acetonyl-4(3H)-quinazolinone is elucidated. An attempt devoted to achieve an alternative synthesis of compound 6a by reaction of anthranilamide with ethyl acetoacetate failed to give the desired benzodiazocine but only 2-methyl-4(3H)-quinazolinone 7a was obtained. Products 5a and 9 were evaluated for their antimicrobial activity.

Previously[1], we described a synthesis of 2-o-aminophenylpyrimidin-4(3H)-ones 3a,b,c by applying reductive isoxazole ring opening of some readly available N-(3-R-4-R'-isoxazol-5-yl)-2-nitrobenzamides 1a,b,c in the presence of W-2 Raney-Nickel (Scheme 1). Furthermore, as a part of a medicinal chemistry program[2] it was of interest to obtain some N-(3-R-4-R'-isoxazol-5-yl)-2-aminobenzamides 4a,b,c (Scheme 1), as a starting material for the synthesis of 4(3H)-quinazolinones and benzo-1,2,3-triazin-4(3H)-ones, bearing 5-isoxazolyl substituent. A general method for the preparation of compounds 4a,b,c is the reduction of the nitro group of the precursors 1a,b,c to the amino group with stannous chloride in aqueous concentrated hydrochloric acid. In connection with the previous studies[1,2], we now report the results obtained when N-(3-methyl-isoxazol-5-yl)-2-nitrobenzamide 1a was treated with iron powder in acetic acid as reducing agent. These reactions gave the different products from 3 in 15-20% yields together with the several by-products. The elemental analysis and molecular weight determined by mass spectroscopy indicated that the product 5 would be formed through reductive isoxazole ring to 2, reduction of the nitro group to the amino and successive dehydrative cyclization and deamination. The benzodiazocines 6 were not obtained under the present reaction conditions (Scheme 1, route A). The ^{1}H-NMR spectrum of 5a in dimethylsulfoxide (DMSO-d_6) exhibited methylene and vinyl proton signals due to the tautomers 5A and 5B (Scheme 2) at δ3.89 and 5.09 respectively, and integral ratio of the two signals was 1:2. Moreover, compound 5A has been reported to exist in a lactam-lactim tautomeric equilibrium on the

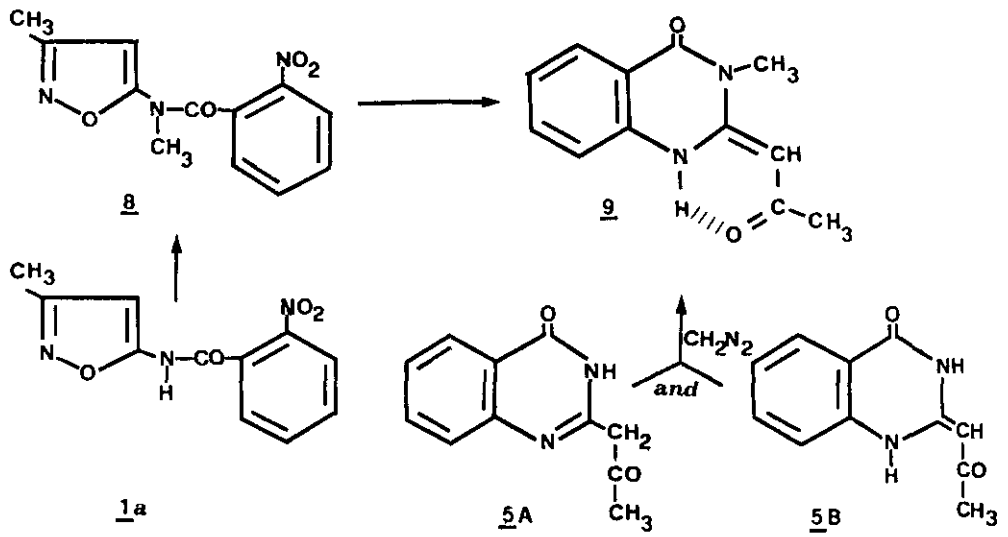
Scheme 1



	R	R'
a	CH_3	H
b	CH_3	C_6H_5
c	$-(CH_2)_4-$	

basis of ir spectral data[3]. Compound 5a was also obtained in comparable yield by reacting N-(3-methylisoxazol-5-yl)-2-aminobenzamide 4a with iron powder in acetic acid. When derivatives 1b,c were reduced under the conditions mentioned above, the new products 5b,c were obtained. The action of aqueous potassium hydroxide at room temperature led to conversion of 5a,b into the corresponding 2-alkyl-quinazolinones 7a,b (Scheme 1). Next, methylation of 2-acetonyl-4(3H)-quinazolinone with diazomethane was investigated: treatment of 5a with diazomethane at room temperature gave a product formulated as 9 in good yield. In order to confirm that the alkylation occurred at N(3) of quinazolinone nucleus we prepared 9 by an unequivocal synthetic route. In fact, treatment of 1a with methyl iodide in acetone gave N-methyl-(3-methylisoxazol-5-yl)-2-nitrobenzamide 8 in 87% yield, which, in turn, by hydrogenation with iron powder in acetic acid, afforded in poor yield 2-acetonylidine-3-methyl-4(1H)-quinazolinone 9 (Scheme 2). The structure of 9 was confirmed by its pro-

Scheme 2



ton magnetic resonance spectrum, which exhibited signals for a "single compound" due to vinyl proton at δ 5.14 (1H) and a broad absorption at δ 14.86 (1H) due to a "chelated" proton, exchangeable with deuterium oxide (Scheme 2). Lastly, an attempt to prepare benzodiazocine 6a by reaction of anthranilamide with ethyl acetoacetate at 140°C failed and this reaction gave 2-methyl-4(3H)-quinazolinone 7a, identified by comparison with an authentic sample[5]. This finding is in accordance with the recent reported behaviour of 2-aminobenzoic acid hydrazide toward benzoylacetone[6].

The product 5a and its methyl derivative 9 were evaluated in vitro for their antimicrobial properties. The results obtained indicate that compound 5 is more potent than 9, having a M.I.C. (minimum inhibitory concentration) of 25 μg/ml and 50 μg/ml against Candida Albicans and Cryptococcus Neoformans, respectively, while compound 9 shows a M.I.C. of 50 μg/ml and 100 μg/ml against the above test organism used. These preliminary results of the antimicrobial assay show clearly that the antimicrobial activity is considerably reduced when the secondary amidic group of 5a is methylated, as expected on the basis of the previous data[8].

EXPERIMENTAL

Melting points were measured with a Büchi-Tottoli apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in the indicated solvent on a Varian FT80A (80 MHz) spectrometer with TMS as an internal reference. A Jasco IR 810 spectrophotometer and Jeol JMS-01-SG-2 mass spectrometer were used to determine infrared (IR) and mass spectra (MS),

respectively.

General procedure for 2-substituted 4(3H)-quinazolinones 5a,b,c.

A solution of 1a[1], 1b[2], 1c[2] (30 mmoles) in glacial acetic acid (60 ml) was heated at 70°C, and iron powder (4.5 g) was added to the solution over a period of 1 h. After adding, the mixture was kept at 70°C for 2 h, and then poured into crushed ice. After standing overnight at room temperature, a solid precipitate was collected and refluxed in methanol (300 ml) for 3 h. After cooling, the insoluble material was filtered off and the filtrate was evaporated under vacuum to dryness to leave a residue, which was dissolved in aqueous KOH (10%). Addition of saturated aqueous ammonium sulfate precipitated the product, which was recrystallized from ethanol to give pure 5 as white needles.

2-Acetonyl-4(3H)-quinazolinone (5a).

Yield 15-20%. Mp 219°C (lit[4]. mp 212-213°C). IR ν (Nujol) 1690-1710 cm^{-1}(2xCO); NMR δ (DMSO-d_6) 2.00(s, CH_3), 2.25(s, CH_3), 3.89(s, CH_2), 5.09(s, CH), 7.24-7.96 (m, C_6H_4), 8.10(broad, exchangeable proton), 13.74(broad, exchangeable proton). MS m/z 202(M^+). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found, C, 65.35; H, 5.20; N, 13.73.

2-(α-Acetylbenzyl)-4(3H)-quinazolinone (5b).

Yield 24-26%. Mp 198-199°C. IR ν (Nujol) 1680-1690 cm^{-1} (2xCO); NMR δ (DMSO-d_6) 1.74(s, CH_3), 2.22(s, CH_3), 5.23(s, CH), 7.27-7.98(m, C_6H_4 and C_6H_5), 9.56(broad, exchangeable proton), 12.50(broad, exchangeable proton). MS m/z 278(M^+). Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found, C, 73.44; H, 5.19; N, 10.15. The presence of singlets at δ 1.74 and 2.22 attributable to two methyl groups suggests that the product 5b exsists in the DMSO solution as two tautomers of type 5A and 5B (see scheme 2).

2-(2-Oxocyclohexyl)-4(3H)-quinazolinone (5c).

Yield 12%. Mp 270-273°C. IR ν (Nujol) 1670-1690 cm^{-1}(2xCO); NMR δ (DMSO-d_6) 1.60-4.40(m, -$(CH_2)_4$-), 7.30-8.50(m, C_6H_4), 12.20(broad). MS m/z 242(M^+). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found, C, 69.54; H, 5.73; N, 11.64. The addition of D_2O to the solution resulted in the precipitation of compound.

Action of aqueous potassium hydroxide on 5a,b, 7a,b.

A solution of 5a,b (1.8 mmoles) in 10% aqueous potassium hydroxide (40 ml) was allowed to stand at room temperature for 5 days. The resultant mixture was filtered off, to the solution of which was added a saturated aqueous ammonium sulfate. The solid which was separated out, was collected and recrystallized from ethanol to give 2-alkylquinazolinones 7a,b in 45-50% yield. The products 7a,b were identified by comparison (mp, mixed mp, R_f, ir) with authentic samples of 2-methyl-4(3H)-quinazolinone and 2-benzyl-4(3H)-quinazolinone[7] respectively.

2-Acetonylidine-3-methyl-4(1H)-quinazolinone (9)

To a solution of 5a (1 mmole) in methanol (50 ml) was added an ethereal diazomethane and the mixture was allowed to stand overnight at room temperature. After the solvent was evaporated, the residue was crystallized from ethanol to give 9 as pale yellow needles; yield 65%. Mp 201-202°C. IR ν (Nujol) 1680 cm^{-1}(CO); NMR δ ($CDCl_3$) 2.19(s, 3H, CH_3), 3.41(s, 3H, CH_3), 5.14(s, 1H, CH), 7.09-8.15(m, 4H, C_6H_4), 14.08(broad, exchangeable proton). MS m/z 216(M^+). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C,

66.65; H, 5.59; N, 12.96. Found: C, 66.53; H, 5.53; N, 12.89.

N-Methyl-(3-methyl-isoxazol-5-yl)-2-nitrobenzamide (8)

To a solution of 1a (2.8 mmoles) in hot acetone (100 ml) was added powedered potassium hydroxide (6 g), followed by addition of methyl iodide (2.6 ml) in acetone (15 ml). The mixture was refluxed for 30 min. It was then filtered and the resultant solution was concentrated. The addition of water and cooling resulted in the precipitation of the product 8, which was recrystallized from ethyl acetate-petroleum ether to give 8 as pale yellow needles; yield 87%. Mp 87-88°C. IR ν (Nujol) 1675 cm^{-1} (CO); NMR δ ($CDCl_3$) 2.15(s, CH_3), 3.40(s, CH_3), 5.35(broad,isoxazole H-4), 6.50(broad, isoxazole H-4), 7.20-8.20(m, C_6H_4). The two broad absorptions observed at δ 5.35 and 6.50 (integral ratio c.a. 1:1) could be attributed to the presence of different isomers as a consequence of the partial double bond character of the amide group, according to the literature reported data[9]. MS m/z 261 (M^+). Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found, C, 54.97; H, 4.27; N, 16.14.

Action of iron powder in acetic acid on 8.

A solution of 8 (10 mmoles) in glacial acetic acid (30 ml) was heated at 70°C, and then iron powder (1.5 g) was added to the solution over a period of 1 h. After adding, the mixture was kept at 70°C for 2 h, and then poured on to crushed ice. After standing overnight at room temperature, the solid precipitate was filtered off and the mother liquor was extracted with chloroform (3x100 ml). The extract was dried over sodium sulfate and evaporated under reduced pressure to give a solid residue, which was crystallized from ethanol. Yield 9-10%. The product was identical in all the respects with a sample of 2-acetonylidine-3-methyl-4(1H)-quinazolinone 9 obtained by methylation of 5a.

Reaction of anthranilamide with ethyl acetoacetate. 7a

Anthranilamide and an equimolar amount of ethyl acetoacetate were heated at 140°C in an oil bath for 3 h to provide a product which was crystallized from petroleum ether-dioxane to give 7a in 25-26% yield. The product was identified by comparison with an authentic sample of 2-methyl-4(3H)-quinazolinone[5].

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* Author to whom correspondence should be addressed.

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