NOVEL HETEROCYCLES. 11[1]. SYNTHESIS OF THE SPIRO[PYRROLIDINE-3,2'(1'H)-QUINAZOLINE]RING SYSTEM

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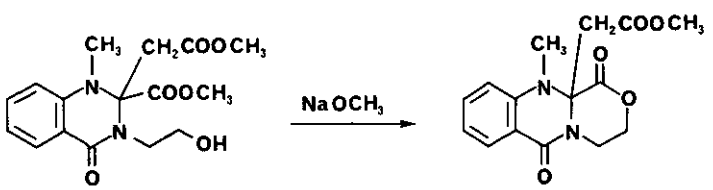
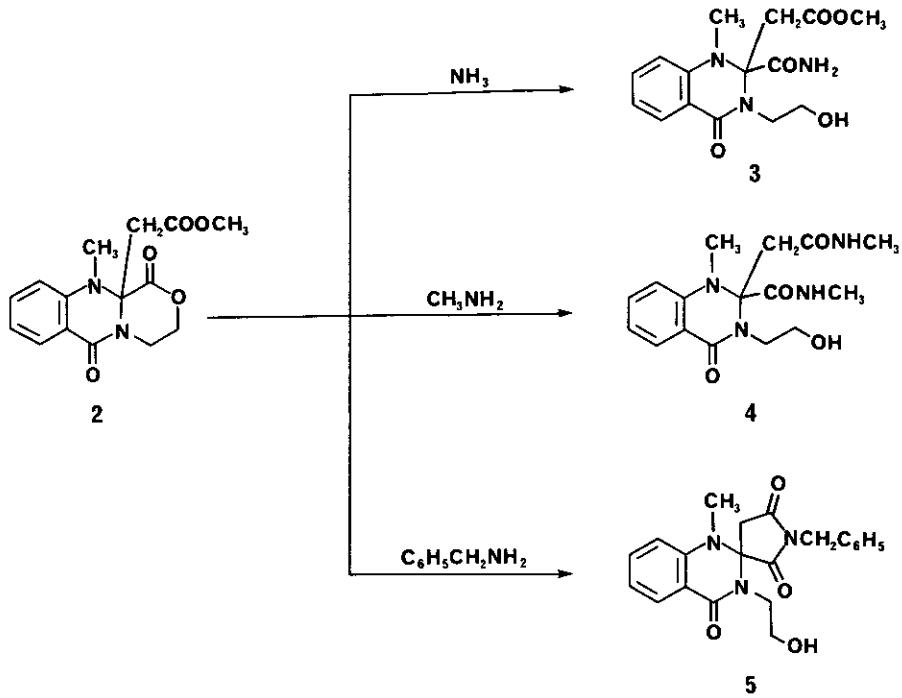
Abstract - The reaction of amines with 1 and 2 was investigated. When 1 or 2 was treated with ammonia only the monoamide 3 was formed. An analogous reaction of 2 with methylamine produced the diamide 4 whereas 1 yielded the spiro imide 6 contaminated with minor amounts of 4. Compound 6 was also obtained from the alkylation of 3 with methyl iodide. The reaction of equimolar amounts of 2 and benzylamine furnished the spiro imide 5. Some spectral data, including carbon-13 assigments, are also discussed.

In a previous report[2] we described the synthesis of some lactone fused quinazolines. In one such preparation, the cyclization of the hydroxy-diester 1 formed the 6-membered lactone 2.[2,3]



1 2

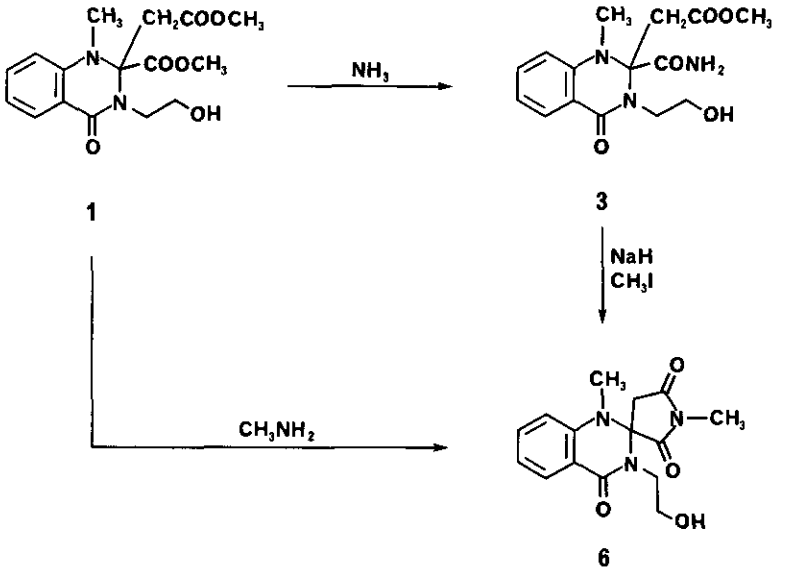
It was of interest to us to investigate the reaction of 2 with amines because of potential lactam formation which would yield a novel ring system. Our initial reaction was performed with ammonia. When 2 was treated with gaseous ammonia for 2 h and then kept at room temperature for an additional 18 h, the starting material was consumed. Analysis of the crystalline product (isolated in 84% yield) indicated that the amine did indeed open the lactone but recyclization to the lactam did not take place and compound 3 was produced as the sole isolable product.



When the bacisity of the amine was increased and the reaction was performed with gaseous methylamine, attack at both lactone and ester sites occurred (due to the excess of the amine) and the diamide 4 was isolated in 90% yield. The use of a higher boiling amine made stoichiometric measurements more manageable. When equimolar quantities of 2 and benzylamine were allowed to stir at 60°C for 24 h complete consumption of the reactants occurred. Spectral analysis of the product revealed infrared absorptions at 3420 (OH), 1725 (CONCO), and 1650 cm^{-1} (amide CO). Its proton spectrum lacked an ester OCH_3 signal and exhibited a two proton singlet at δ4.78 (N-benzyl CH_2) and an AB quartet at δ3.2 and 2.9 (J=18Hz). Data such as this suggest the spiro structure 5. In addition, the mass spectrum of the product gave a molecular ion at m/z 379 which corresponds to the proper molecular weight expected for 5.

It was subsequently found, however, that the lactone 2 is not required for the execution of the reactions just discussed. When 1 was reacted with gaseous ammonia (analogous to that of 2), the monoamide 3 was isolated in 60% yield. Its physical characteristics are identical to that obtained from the reaction of 2

with ammonia. In a similar reaction with methylamine, careful monitoring of the progress of the reaction indicated that 30 min was required for the consumption of 1. The resulting mixture was composed of one major and one minor product which were readily separated by column chromatography. The major component was determined to be the spiro compound 6 by comparison of its spectral features with those of 5, whereas the minor component proved to be the diamide 4. This result is interesting being that virtually none of the spiro compound 6 was formed in the reaction of 2 with methylamine. Formation of 6 was also accomplished by the alkylation of 3 with methyl iodide in the presence of sodium hydride.



Further structure confirmation of compounds 3, 4, and 5, was provided from analysis of their carbon-13 nmr spectra. The method of deuterium isotope induced shifts[4] proved valuable in the assignment of structure 3.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on Varian T-60, EM-360, and Varian XL-100 spectrometers using Me_4Si as an internal reference. Chemical shifts are quoted

in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on LKB 9000 or AEI MS-30 spectrometers.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Varian XL-100-12 spectrometer system equipped with a Varian 620/L computer with 16K memory. The spectra were obtained at an observing frequency of 25.159 MHz. Sample concentrations were ca. 0.5 molar (in deuteriochloroform for **4** and **5**, and DMSO-d_6 for **3**) in 10 mm (od) sample tubes. General NMR spectral and instrumental parameters employed were: Internal deuterium lock to the solvent; spectral width of 5120 Hz, a pulse width of 25 μs corresponding to a 43° pulse angle; and a pulse repetition time of 1.8 sec. For all spectra, 8K time-domain points were used. All shifts reported are referenced to internal Me_4Si and are estimated to be accurate to ± 0.05 ppm.

2-Aminocarbonyl-3-(2-hydroxyethyl)-1-methyl-4-oxo-2-quinazolineacetic Acid Methyl Ester (**3**). Into a solution of 2.5g of **2**[2] in 50 ml of dry tetrahydrofuran was bubble anhydrous ammonia for 2 h. The mixture was then allowed to continue stirring at room temperature for 18 h. The mixture was concentrated to one-half volume and the resulting precipitate was filtered to give 2.2g (84%) of **3**. An analytical sample was crystallized from acetone/chloroform, mp 206-208°C (dec); IR (KBr): 3435, 3350, 3240, 1740, 1700, 1655 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ8.15 (s, broad, 1H, exchangeable), 7.75 (s, broad, 1H, exchangeable), 7.8-7.2 (m, 2H), 6.9-6.6 (m, 2H), 4.68 (t, broad, 1H, exchangeable), 3.9-3.1 (m, 4H), 2.9 (s, 3H), 2.8 (s, 2H), 2.75 (s, 3H). Anal. Calcd. for $C_{15}H_{19}N_3O_5$: C, 56.1; H, 6.0; N, 13.1. Found: C, 56.1; H, 6.2; N, 13.0.

When the above reaction was performed using **1** in place of **2**, the amide **3** was isolated in 60% yield. An analytical sample was crystallized from acetone/chloroform, mp 206-208°C (dec). All spectral data were identical to that described above.

3-(2-Hydroxyethyl)-2-methylaminocarbonyl-1-methyl-4-oxo-2-quinazolineacetic Acid N-Methylamide (**4**). Into a solution of 0.5g of **2** in 15 ml of dry tetrahydrofuran was bubbled anhydrous methylamine for 1 h. The mixture was then allowed to continue stirring at room temperature for 18 h. The solvent was removed under reduced pressure giving 0.55g (90%) of **4** as a foam; IR ($CHCl_3$): 3405, 3310, 1690-1620 (broad) cm^{-1}, ^{1}H-NMR: δ7.8-6.5 (m, 6H, contains 2 exchangeable

protons), 4.55 (t, broad, 1H), 4.05-3.2 (m, 4H), 2.85 (d, 3H, J=5Hz) 2.8 (s, 2H), 2.75 (s, 3H), 2.25 (d, 3H, J=5Hz); MS: Calcd. for $C_{16}H_{22}N_4O_4$: M, 334.1641. Found: m/z:M^+, 334.1654.

1-Benzyl-3'-(2-hydroxyethyl)-1'-methyl-spiro[pyrrolidine-3,2'(1'H)-quinazoline]-2,4',5(3'H)-trione (5). A solution of 2.2 g of 2 and 0.8 g of benzylamine in 50 ml of dry tetrahydrofuran was stirred at 60°C for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 2.1 g (76%) of 5. An analytical sample was crystallized from ether/pentane, mp 126-129°C; IR ($CHCl_3$): 3420, 1725, 1650, 1490, 1395, cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ7.95 (dd, 1H, J=8 Hz and 2 Hz), 7.6-6.6 (m, 8H), 4.78 (s, 2H), 4.0-3.35 (m, 4H), 3.2, 2.9 (ABq, 2H, J=18Hz), 2.95 (m, 1H, exchangeable), 2.57 (s, 3H); MS: Calcd. for $C_{21}H_{21}N_3O_4$: M, 379.1531. Found: m/z:M^+, 379.1501.

1,1'-Dimethyl-3'-(2-hydroxyethyl)spiro[pyrrolidine-3,2'(1'H)-quinazoline]-2,4',5(3'H)-trione (6). Into a solution of 0.5g of 1 in 20 ml of dry tetrahydrofuran was bubbled methylamine for 30 min. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 2% methanol/chloroform to elute the product, 0.19 g (42%) of 6 as a foam. IR (KBr): 3440, 1720, 1640, 1485, 1440, 1380 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ7.95 (dd, 1H, J = 8 Hz and 2 Hz), 7.65-7.3 (m, 1H), 7.17-6.66 (m, 2H), 4.05-3.5 (m, 4H), 3.3 (m, 1H, exchangeable), 3.2, 2.9 (ABq, 2H, J=18 Hz), 3.14 (s, 3H), 2.8 (s, 3H); MS: Calcd. for $C_{15}H_{17}N_3O_4$: M, 303.1218. Found: m/z:M^+, 303.1224.

To a solution of 350 mg of 3 and 155 mg of methyl iodide in 10 ml of dimethylacetamide was added 50 mg of sodium hydride (50% in mineral oil, pentane washed) and the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using ethyl acetate to elute the product, 150 mg (45%) of 6.

ACKNOWLEDGEMENT

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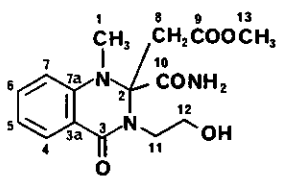
TABLE ^{13}C NMR Assignments for Compounds 3, 4, and 5.



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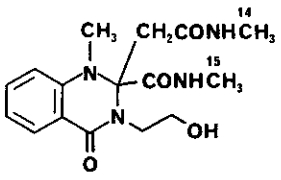

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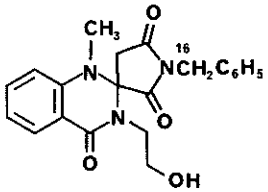

5

Carbon			
1	33.4	34.2	33.2
2	82.6	83.6	81.6
3	161.9	164.6	163.9
3a	114.2	115.4	117.1
4	127.2	127.9	128.8
5	117.4	119.1	120.8
6	134.0	134.7	134.7
7	111.5	112.4	114.0
7a	146.6	146.8	146.8
8	35.7	38.6	39.4
9	170.8	169.7	172.5*
10	171.2	170.9	172.9*
11	47.0	48.9	47.4
12	58.3	60.8	61.2
13	51.1	-	-
14	-	26.2*	-
15	-	26.9*	-
16	-	-	43.2

*Assignments are interchangeable

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