STEREOSELECTIVE SYNTHESIS OF A 2,3-DISUBSTITUTED 5-PYRROLIDINONE DERIVATIVE OF QUINAZOLIN-4(3*H*)-ONE

Mónika Szabó[a], József Kökösi*[a], Attila Kovács[b], Zsolt Böcskei[c], and István Hermecz*[c]

Institute for Pharmaceutical Chemistry, Semmelweis University of Medicine, Hõgyes E. u. 9, H-1092 Budapest, Hungary; [b] Department of General and Analytical Chemistry, Technical University, Gellért tér 4, H-1114 Budapest, HUNGARY; [c] CHINOIN Pharmaceutical and Chemical Works Ltd., P.O.Box 110, H-1325 Budapest, Hungary

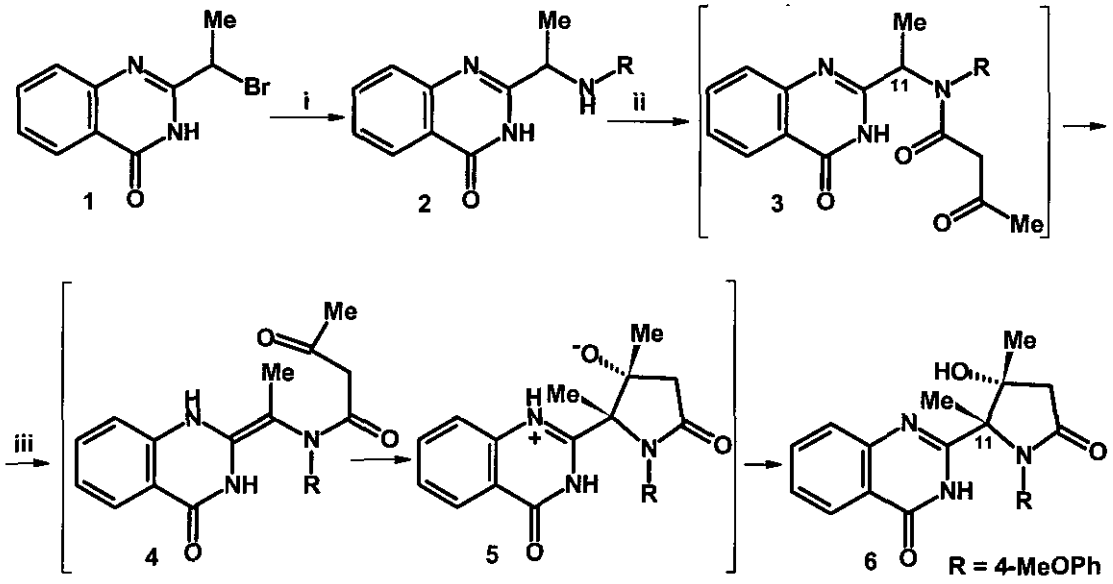
Abstract- Thermal cyclization of acetoacetamide (**3**), prepared from 2-[1'-(*p*-methoxyphenylaminoethyl]quinazolin-4(3*H*)-one (**2**) and ethyl acetoacetate, resulted in the formation of 2-(5-oxopyrrolidin-2-yl)quinazolin-4(3*H*)-one (**6**) with high selectivity in excellent yield. The stereostructure of **6** was investigated by NMR spectroscopy, and determined by X-Ray investigations.

5-Pyrrolidones, five-membered ring analogues of substituted lactams, constitute an important area of synthetic organic, medicinal and pharmacological chemistry[1]. Hydroxylated 2-substituted pyrrolin-5-ones have recently attracted much attention, in consequence of their selective glycosidase inhibitory activity, with a variety of therapeutic effects[2]. The wide range of biological activity of quinazolones[3] prompted us to synthesize pyrrolylquinazolone, a combination of the two structures, as a new potential pharmacological agent.

Most of the synthetic strategies directed towards the preparation of 2-substituted 5-pyrrolidones involve the use of naturally occurring hydroxylated compounds[4], the ring transformation of furanones with amines[5], the cyclization of γ-substituted carboxylic acid derivatives[6], or the photocyclization of a β-oxoamide[7].

Several pyrrolylquinazolones are known,[8] but 5-pyrrolidone derivatives of quinazolones have not yet been described. We set out to prepare such a compound via the synthetic route shown in Scheme 1. Nucleophilic substitution of the bromine atom of 2-(1'-bromoethyl)quinazolone (**1**)[9] by reaction with *p*-

anisidine in *N,N*-dimethylformamide at 100 °C for 2.5 h afforded 2-[1'(p-methoxyphenylamino)-ethyl]quinazolone (**2**) in 67% yield. Thermal acylation of **2** with ethyl acetoacetate at 180 °C for 3 h resulted in the acetoacetamide (**3**), as an oily product. This was converted directly to a pyrrolidone derivative of quinazolone (**6**) by cyclization of the β-oxo group to the α-methylene group of the side-chain at 240 °C for 1 h. Under heating condition, **6** is surprisingly stable, and colorless crystals were isolated in 85% yield by simple crystallization.



Scheme 1. *Reagents and conditions*: i, p-anisidine (2.5 equiv), DMF, 100 °C, 2.5 h; ii, ethyl acetoacetate (10 equiv), 180 °C, 3 h; iii, 240 °C, 1 h.

Clear evidence of the cyclic nature of this compound was provided by the NMR spectra in DMSO-d_6. There was no signal of H-11 in the ^{1}H NMR spectrum of **6**, and APT measurement revealed that C-11 had been converted from tertiary to a quaternary C atom. Only two C=O groups could be identified in the ^{13}C NMR spectra. The keto group of the acetoacetic ester was converted to a tertiary alcohol and a peak at around 75 ppm was tentatively assigned as OH-bond carbon. The structure of (5-oxopyrrol-2-yl)quinazolone (**6**) was confirmed by X-Ray crystallographic analysis.

The crystal structure of **6** (Figure 1) was determined to establish the stereochemistry around the two chiral centres (C11 and C15). These were shown to have the same configurations. Compound (**6**) is a racemic one, i.e. the individual crystals contain both enantiomers. As shown in Figure 1, the two methyl groups

(C16 and C27) are in a *cis* arrangement, the former being in a pseudo-equatorial, and the latter in a pseudo-axial position. A somewhat unusual feature of the structure of **6** is that N3 does not form hydrogen-bonds with potential acceptors available in the crystal structure. However, the presence of the intermolecular hydrogen-bond O26_$1-H26_$1...O25 (where $1 is a symmetry operator, x, y, z-1, to generate the neighbouring molecule) was proved. Since this is a fairly strong hydrogen-bond, the O26_$1..O25 bridgehead distance being 2.708(9) Å, it may well make a significant contribution to the experimentally observed solid-state stability of **6**.

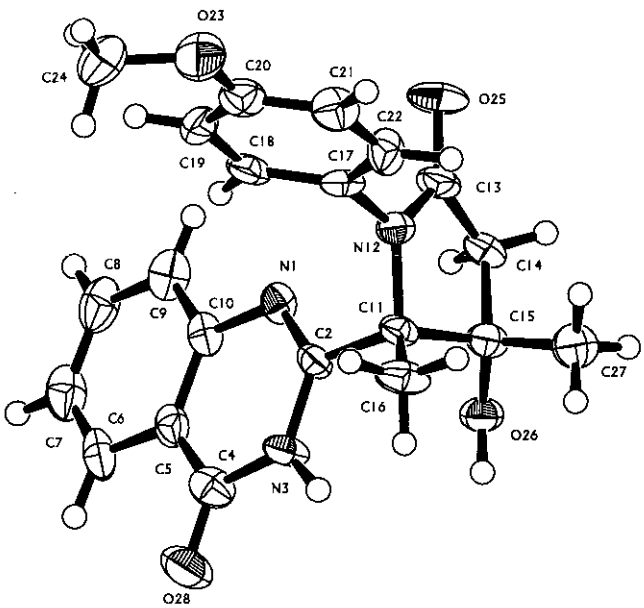


Figure 1. ORTEP drawing of **6** with atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. A few characteristic geometrical parameters are enumerated in Table 1.

The intramolecular enamine addition to the keto carbonyl group took place with complete *syn* selectivity and afforded the hydroxylated pyrrolidone (**6**) in 85% yield. The interesting selectivity of the cyclization can be explained in terms of the exo-trig mode[10] of the cyclization of **4**, a pre-equilibrated tautomeric form of **3**, *via* intermediate (**5**). The formation of **6** with high selectivity is a consequence of the minimized steric interactions between the pyrrolidone ring and its abutting substituents.

EXPERIMENTAL:

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-400 spectrometer at 400.13 and 100.62 MHz, respecively, in $CDCl_3$. Internal TMS was used as the chemical shift reference. The yields were not maximized. Melting points were determined on a Boetius apparatus and are uncorrected.

2-[1'-(*p*-Methoxyphenylamino)ethyl]quinazolin-4(3*H*)-ones (2). A mixture of 2-(1'-bromoethyl)-quinazolin-4-(3*H*)-one (1) (253 mg, 1.00 mmol), *p*-anisidine (307 mg, 2.50 mmol) and *N*,*N*-dimethyl-formamide (5 mL) was stirred for 2.5 h at 100 °C. The reaction mixture was poured into ice water and the precipitated solid was filtered off, washed with water. The dried crystals were recrystallized from ethanol to give **2** in 67% yield (198 mg), mp 191 - 195 °C. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 71.56; H, 6.01; N, 14.73. Found: C, 71.64; H, 5.94; N, 14.89.

Table 1. Selected bond lengths (pm), angles (°) and torsion angles (°) for **6**.

O(23)-C(20)	1.374(10)	C(20)-O(23)-C(24)	117.9(7)	C(13)-N(12)-C(11)-C(15)	24.9(9)
O(23)-C(24)	1.427(10)	C(2)-N(1)-C(10)	117.3(7)	C(17)-N(12)-C(11)-C(15)	-163.3(7)
O(25)-C(13)	1.236(10)	C(2)-N(3)-C(4)	123.30(7)	N(1)-C(2)-C(11)-N(12)	26.1(10)
O(26)-C(15)	1.411(9)	C(13)-N(12)-C(17)	122.0(7)	N(1)-C(2)-C(11)-C(15)	-82.3(9)
O(28)-C(4)	1.204(11)	C(13)-N(12)-C(11)	112.5(7)	C(11)-N(12)-C(13)-C(14)	-6.3(10)
N(1)-C(2)	1.283(10)	C(17)-N(12)-C(11)	125.0(7)	N(12)-C(13)-C(14)-C(15)	-16.1(10)
N(1)-C(10)	1.403(9)			C(13)-C(14)-C(15)-C(11)	29.9(8)
N(3)-C(2)	1.374(10)			C(2)-C(11)-C(15)-C(26)	-34.2(9)
N(3)-C(4)	1.405(11)			N(12)-C(11)-C(15)-C(14)	-32.6(7)
N(12)-C(13)	1.340(11)			N(12)-C(11)-C(15)-C(27)	87.4(8)
N(12)-C(17)	1.435(10)			C(16)-C(11)-C(15)-C(27)	-31.1(10)
N(12)-C(11)	1.477(10)			C(2)-C(11)-C(15)-C(27)	-158.3(7)
C(11)-C(15)	1.576(11)			C(11)-N(12)-C(17)-C(18)	-78.7(10)

2-[2',3'-Dimethyl-3'-hydroxy-1'-(*p*-methoxyphenyl)-5'-oxopyrrolidin-2'-yl]quinazolin-4(3*H*)-one (6). A mixture of **2** (295 mg, 1.00 mmol) and ethyl acetoacetate (1.3 g, 10 mmol) was heated for 3 h at 180 °C. The reaction mixture was evaporated to dryness, and the oily residue was heated at 240 °C for 1 h. The white crystals were recrystallized from ethyl acetate to give **6** in 85 % yield (323 mg), mp 236 - 240 °C. ^{1}H NMR: δ 1.41 (3H, s), 1.55 (3H, s), 2.33 (1H, J = 16.3 Hz, d), 2.78 (1H, J = 16.3 Hz, d), 3.69 (3H, s), 5.38 (1H, br s), 6.82 (2H, J = 8.9 Hz, d), 7.18 (2H, J = 8.9 Hz, d), 7.3-7.9 (3H, m), 8.11 (1H, J = 7.8 Hz, d),. ^{13}C NMR: δ 17.7 (s), 24.2 (s), 44.7 (d), 55.1 (s), 73.5 (s), 76.1 (s), 113.8 (d), 121.0 (s),

125.6 (s), 126.6 (s), 127.3 (s), 129.1 (s), 129.6 (s), 134.2 (s), 147.7 (s), 156.3 (s), 157.9 (s),161.4 (s), 172.6 (s). Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.53; N, 11.08. Found: C, 66.41; H, 5.64; N, 10.97.

X-Ray Crystal Structure Determination.

Data on **6**: Crystal data: $C_{21}H_{21}O_4N_3$, orthorhombic, $Pna2_1$, a = 14.147(7), b = 18.62(5), c = 6.964(8) Å, V = 1834(5) $Å^3$, D_x = 1.374 $g.cm^{-3}$, Z = 4, μ = 7.95 cm^{-1}, T = 293(2) K, crystal dimensions 0.35 x 0.08 x 0.08 mm, 2041 independent reflections, R_1 = 0.053 for reflections with $I > 2\sigma(I)$, wR_2 = 0.1828 for all data, maximum final ΔF peak 0.29 $eÅ^{-3}$, Figaku AFC6S diffractometer, wavelength: 1.5418 Å, θ_{max} = 75.18°. The structure was solved by using the TEXSAN program package [TEXSAN: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992)], while the full-matrix leastsquares (on F^2) refiniment was performed with SHELXL-93 (G. M. Sheldrick, SHELXL-93 Program for the prefinement of Crystal Structures, University of Göttingen, 1993) running on a Silicon Graphics R-3000 workstation. No absorption correction was applied. Hydrogen atoms with known geometry were generated. Atomic coordinates, bond lengths and bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

References

1. C. M. Marson and A. Fallah, *Tetrahedron Lett.*, 1994, **35**, 293.
2. (a) G. Casiraghi, F. Zanardi, G. Rassu, and P. Spanu, *Chem. Rev.*, 1995, **95**, 1677; and references cited therein. (b) G. W. J. Fleet, *Top. Med. Chem.*, 1988, **65**, 149. (c) G. Legler, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 319. (d) B. Winchester and G. W. J. Fleet, *Glycobiology*, 1992, **2**, 199.
3. S. Sinha and M. Srivastava, *Progress in Drug Research*, 1994, **43**, 143 (Birkhauser Verlag, Basel, Switzerland).
4. (a) F. Merchau, P. Merino, and T. Tejero, *Tetrahedron Lett.*, 1995, **36**, 6949. (b) P. Spanu, G. Rassu, F.Ulgheri, F. Zanardi, L. Battistini, and G. Casiraghi, *Tetrahedron*, 1996, **52**, 4829.
5. (a) B. Chantegrel and S. Gelin, *J. Heterocycl. Chem.*, 1978, **15**, 1215. (b) O. S. Andrejchikov and B. O. Kozminikh, *Zh. Org. Chem.*, 1989, **25**, 616. (c) M. Weigele, J. P. Tengi, S. De Bernardo, R. Czajkowski, and W. Leimgruber, *J. Org. Chem.*, 1976, **41**, 388.
6. (a) H. Takahata, T. Takamatsu, and T. Yamazaki, *J. Org. Chem.*, 1989, **54**, 4812. (b) T. Kato and M. Sato, *Yakugaku Zasshi*, 1972, **92**, 1507. (c) H. Plieninger and M. Decker, *Liebigs Ann. Chem.*, 1955, **598**, 198.
7. (a) T. Hasegawa, H. Aoyama, and Y. Omote, *J. Chem. Soc., Perkin Trans. 1*, 1979, 963. (b) T. Hasegawa, H. Aoyama, and Y. Omote, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2054.

8. (a) A. R. Katritzky and J. W. Suwinski, *Tetrahedron,* 1975, **31**, 1549. (b) T. L. Gilchrist, C. W. Rees, and E. Stanton, *J. Chem. Soc. C,* 1971, 3036. (c) T. L. Gilchrist, C. W. Rees, and E. Stanton, *J. Chem. Soc. C,* 1971, 988. (d) E. P. Papadopoulos, *J. Org. Chem.,* 1973, **38**, 667. (e) V. Looney-Dean, B. S. Lindamood, and E. P. Papadopoulos, *Synthesis,* 1984, **1**, 68. (f) J. M. Dickinson and J. A. Murphy, *J. Chem. Soc., Chem. Comm.,* 1990, 434.

9. J. Kökösi, L. Örfi, M. Szabó, K. Takács-Novák, and Gy. Szász, *Magy. Kém. Folyóirat,* 1991, **97**, 185 (*Chem. Abstr.,* 1991, **115**, 159501).

10. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.,* 1976, 734.

Received, 30th June, 1997