A Facile Synthesis of 2,3-Disubstituted 4-Oxo-3,4-dihydroquinazolines

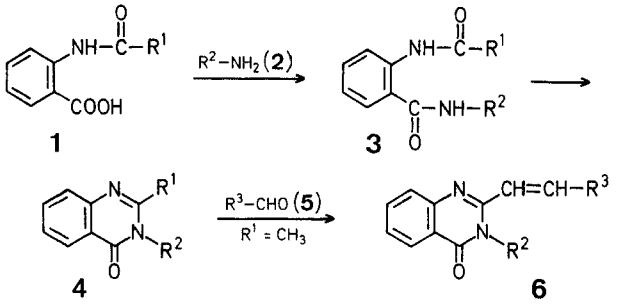
Raafat SOLIMAN*, Farid S. G. SOLIMAN

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, Egypt

Several substituted 4-oxo-3,4-dihydroquinazolines [4(3*H*)-quinazolinones] are known to possess biological activities. In addition, the 4-quinazolinone moiety is found in several quinazoline alkaloids.

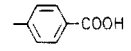
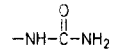
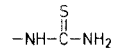
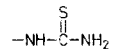
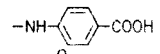
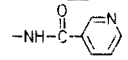
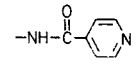
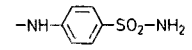
Different methods are known for the synthesis of substituted 4(3*H*)-quinazolinones. However, the largest number of 2,3-disubstituted 4(3*H*)-quinazolinones (**4**) have been synthesized by reacting an *N*-acylanthranilic acids with a primary amine in a suitable solvent in the presence of a catalyst, by reacting 3,1,4-benzoxazones with amines, or by thermal cyclization of *o*-acylaminobenzamides[1]. In our previous communication[2], we reported the synthesis of 2-methyl-3-(2-methylphenyl)-4-oxo-3,4-dihydroquinazoline (**4d**) by refluxing *N*-acetylanthranilic acid with *o*-toluidine in a high-boiling solvent as bromobenzene.

We now describe the facile synthesis of 2,3-disubstituted 4-oxo-3,4-dihydroquinazolines (**4**) by the fusion of equimolar amounts of *N*-acylanthranilic acids (**1**) with primary amino compounds (**2**) such as amines, hydrazine and derivatives, semicarbazide, and thiosemicarbazide at 150–190° for 30–60 min. The yields are good. The structure of products **4** was confirmed by mixed melting points with authentic specimen, comparison of T.L.C. and spectral data, and (for new compounds) microanalyses. A further proof of the structure was obtained by conversion of compounds **4a–d** to the 2-styryl derivatives (**6**) by refluxing with substituted



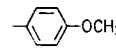
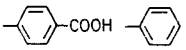
0039-7881/79/1032-0803 $ 03.00

Table 1. 2,3-Disubstituted 4-Oxo-3,4-dihydroquinazolines (**4**)

4	R^1	R^2	Yield [%]	m.p.	Molecular formula[a] or Lit. m.p.
a	CH_3	$-CH_2-COOH$	57	259° (dec)	263° (dec)[3]
b	CH_3		54	248° (dec)	246–247°[4]
c	CH_3		53	276–277°	276°[4]
d	CH_3		60	112.5–113°	112.5–113°[2]
e	CH_3	$-NH_2$	46	148–149°	148–149°[5]
f	C_2H_5	$-NH_2$	52	152–153°[b]	$C_{10}H_{11}N_3O_6$ (189.2)
g	CH_3		55	231–232°	231–232°[6]
h	CH_3		75	183–185°	183–184°[6]
i	C_2H_5		55	280–281°[b]	$C_{11}H_{12}N_4OS$ (248.3)
j	CH_3		56	237–238°[c]	$C_{16}H_{13}N_3O_3$ (295.3)
k	CH_3		52	210–212°	210–212°[7]
l	CH_3		50	214–216°	214–216°[7]
m	CH_3		76	254–255°[d]	$C_{15}H_{14}N_4O_3S$ (330.3)

[a] The microanalyses of the new compounds were in satisfactory agreement with the calculated values: C, ±0.40; H, ±0.20; N, ±0.40; S (**4m**), −0.10.
[b] Recrystallized from ethanol.
[c] Recrystallized from aqueous ethanol.
[d] Recrystallized from aqueous acetic acid.
M.S.: $m/e = 330$ (M^+, 100%).
^{1}H-N.M.R. (DMSO-d_6): $\delta = 2.40$ (s, 3H); 6.6–8.5 (m, H_{arom}); 9.40 ppm (s, NH).

Table 2. 4-Oxo-2-styryl-3,4-dihydroquinazolines (**6**)

6	R^2	R^3	Yield [%]	m.p. (solvent)	Molecular formula[a]
a	$-CH_2-COOH$		36	209–211° (H_2O/CH_3OH)	$C_{19}H_{16}N_2O_4$ (336.3)
b			67	206–207° (CH_3OH)	$C_{24}H_{18}N_2O_5$ (414.4)
c			60	287–288° (AcOH)	$C_{23}H_{16}N_2O_3$ (368.4)
d			52	161–162° (CH_3OH)	$C_{23}H_{18}N_2O$ (338.4)

[a] The microanalyses were in agreement with the calculated values.

benzaldehydes (**5**) in glacial acetic acid in the presence of concentrated sulfuric acid.

The I.R. (nujol) spectra of compounds **4** showed the C=O absorption at 1670–1680 cm^{-1}, whereas the 2-styryl derivatives **6** showed this absorption at 1650 cm^{-1}. An additional carbonyl band appeared at 1700 cm^{-1} in spectra of the acids **6a** and **6c**.

The assumption that the cyclocondensation proceeds via the *o*-acylaminobenzamides **3** as intermediates was proven by the thermal cyclization of separately prepared **3** to give the quinazoline derivatives **4**.

All melting points were determined in open glass capillaries and are uncorrected.

2,3-Disubstituted 4-Oxo-3,4-dihydroquinazolines (4); General Procedure:

An intimate mixture of the *N*-acylanthranilic acid **1** (0.01 mol) and the primary amine, hydrazine, acyl hydrazide, semicarbazide hydrochloride, or thiosemicarbazide (**2**; 0.01 mol) is fused at 150–190° for 30–60 min; the crude product obtained after cooling is recrystallized from a suitable solvent.

3-Substituted 4-Oxo-2-styryl-3,4-dihydroquinazolines (6a–d); General Procedure:

A solution of the 3-substituted 2-methyl-4-oxo-3,4-dihydroquinazoline (**4a–d**; 5 mmol) and a substituted benzaldehyde (**5**; 5 mmol) in glacial acid (25 ml) containing concentrated sulfuric acid (5 drops) is refluxed for 3 h and then allowed to cool. The crystalline product is isolated by suction and recrystallized from a suitable solvent.

Received: January 15, 1979
(Revised form: March 2, 1979)

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