Synthesis and Characterisation of Some 3-Amino-2-Alkyl/Aryl-3,4-Dihydro-4-Oxoquinazolines and Their Acyl Derivatives

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In the present paper we describe the synthesis and characterisation of some 3-amino-2-alkyl/aryl-3,4-dihydro-4-oxoquinazoline (I–VI). Various acyl derivatives of these 4-oxoquinazolines (VII, VIII) were prepared and their structure established by various physico-chemical methods.

INTRODUCTION

A large variety of quinazolines were synthesised due to various possible and synthetic approaches. Some of the naturally occurring and synthetic quinazolines were found to possess physiological activity[1–6]. The physiological activity in the naturally occurring quinazoline[7] as also in most of the synthetic compounds was found to be due to the 4-oxo structure present in them. The 4-oxoquinazolines, therefore, assume special significance and lead us to be interested in synthesising these compounds.

3-Amino-2-alkyl/aryl-3,4-dihydro-4-oxoquinazolines are quite interesting compounds as these have three reactive sites $C_{(2)}$-methyl or methylene group, $N_{(3)}$-amino and 4-oxo group in only pyrimidine part of the quinazoline ring system.

Our main aim was to introduce a third ring on to the pyrimidine part of the 4-oxo-quinazoline ring by using the reactivity of these active sites.

For the projected synthetic work we prepared a number of 4-oxoquinazolines having $N_{(3)}$-amino and $C_{(2)}$-methyl or methylene group and their various acyl derivatives were prepared by two routes. By directly acylating the precursors 3-amino-4-alkyl/aryl-3,4-dihydro-4-oxoquinazolines with acyl halide in pyridine in appropriate acid anhydrides and secondly treating 3,1,4-benzoxazones (acyl anthranils) with appropriate acid hydrazides. The pioneering work of this excellent route goes to Josef Klosa[8], whose method was employed by us with slight modification. 3-Amino-2-methyl-3,4-dihydro-4-oxoquinazoline was first prepared by Bogert and Seil[9].

EXPERIMENTAL

Melting points were determined in sulphuric acid bath in open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer-577 spectrophotometer.

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3-Acetamido-2-methyl-3,4-dihydro-4-oxoquinazoline (VII) (R′ = —CH_3)

First Method: 3-Amino-2-methyl-3,4-dihydro-4-oxoquinazoline (III) (2.8 g), acetic anhydride (12 mL) and freshly fused sodium acelate (3 g) were mixed together and heated under reflux for 2.5 h. The reaction mixture was poured into crushed ice (150 g) when a thick oil was separated. Water was decanted away and the oil was washed 2–3 times with ice water. The oil was left in ice chest where it solidified after 3 days. The solid was collected by filtration and recrystallised from aqueous ethanol to furnish the pure acetamido compound as white plates (2.4 g; 70%), m.p. 175°C.

Second Method: (a) *Acetic acid hydrazide:* A mixture of ethyl acetate (10 mL) and hydrazine hydrate (5 mL; 99%) was heated under reflux for 2 h to give a homogeneous solution. The white solid hydrazide was obtained by distilling the solution to half its volume followed by chilling in ice (m.p. 66°C, 3.1 g).

(b) *Reaction of acetic acid hydrazide with acetanthranil*: Acetanthranil (3.2 g) and acetic acid hydrazide (1.6 g) were taken in a small round bottomed flask and the reaction mixture was heated in an oil bath at 160–170°C for 3.5 h. The neck of the flask was kept plugged with cotton wool. The reaction mixture was cooled and treated with excess of liquor ammonia to dissolve the product. The solution was filtered, cooled and neutralised with glacial acetic acid. The solution was cooled in ice water to deposit white solid. Recrystallisation from water gave the pure acetamido compound (VII, R = —CH_3) (2.7 g, 65%), m.p. 175°C, as white plates.

Identity of this product with that obtained by the earlier process was established by mixed m.p. which was undepressed.

3-Benzamido-2-methyl-3,4-dihydro-4-oxoquinazoline (VII; R′ = —CH_2Ph)

3-Amino-2-methyl-3,4-dihydro-4-oxoquinazoline (2.5 g) was dissolved in a mixture of dry benzene (40 mL) and dry pyridine (10 mL). To this mixture redistilled benzoyl chloride (2.5 mL) was added dropwise. The mixture was heated under reflux on a water bath maintained at 60–70°C for 1 h and then left at room temperature overnight. After 24 h, the solution was poured into water and the seperated benzene layer was removed. The aqueous layer was extracted with benzene. The benzene extracts were combined and washed successively with aqueous sodium carbonate and water and then dried over anhydrous magnesium sulphate. Benzene was distilled off and the remaining liquid was triturated with light petroleum when the solid was obtained. This was recrystallised from acetic acid to furnish the pure benzamidoquinazolone as white needles (1.75 g; 70%), m.p. 181°C. Analysis: found, N: 15.26%; calculated for $C_{16}H_{13}N_3O_2$, N: 14.30%. I.R.: ν_{max} (KBr) 1670 cm^{-1} (quinazolone carbonyl), 1710 cm^{-1} (open chain carbonyl), 3370 cm^{-1} (N—H bonded).

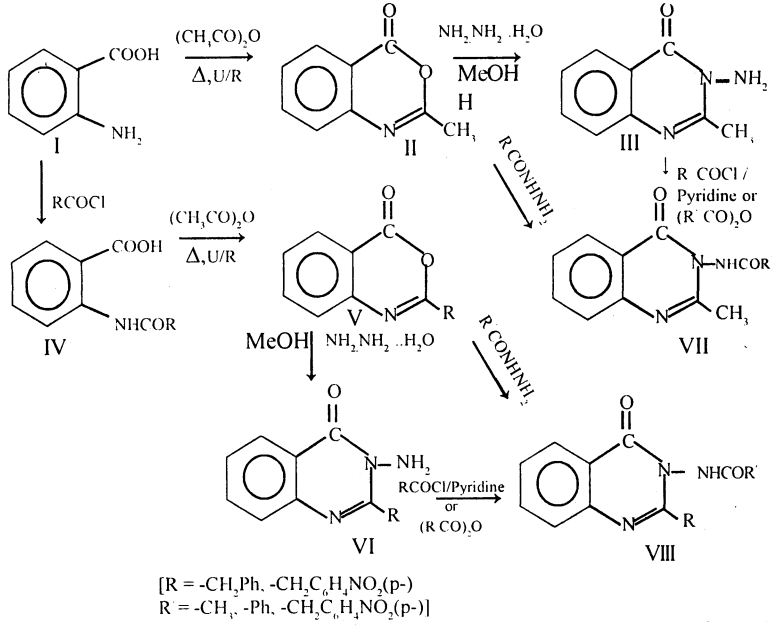
3-Benzamido-2-benzyl-3,4-dihydro-4-oxoqinazoline (VIII, R = —CH_2Ph, R′ = —Ph)

3-Amino-2-benzyl-3,4-dihydro-4-oxoquinazoline (5.0 g) was reacted with benzoyl chloride (5.0 mL) in benzene/pyridine solution following the method

described earlier. Working up as before resulted in solid product which was recrystallised from acetic acid to furnish the pure benzamidoquinazolone (4.0 g, 60%), m.p. 235°C. (Found, C: 74.10%, H; 4.28%, N: 12.16%; calculated for $C_{22}H_{17}N_3O_2$, C: 74.366%, H: 4.789%, N: 11.83%; ν_{max} (KBr) 1660 cm^{-1} (quinazolone carbonyl), 1710 cm^{-1} (open chain carbonyl), 3380 cm^{-1} (N—H bonded).

RESULTS AND DISCUSSION

The full Scheme of preparative work is shown below:



3-Amino-2-methyl-3,4-dihydro-4-oxoquinazoline (III) was prepared by the Klosa's method[8] with some modification. The compound gave correct m.p. (148–150°C) and analytical results. [Found (%), C: 61.47, H: 5.32, N: 23.82; $C_9H_9N_3O$ requires (%), C: 61.71, H: 5.14, N: 24.00]

ν_{max} (KBr) 1670 cm^{-1} (quinazolone carbonyl structure), 3330 and 3230 cm^{-1} (N—H bonded hydrazide str.), 3-amino-2-benzyl-3, 4-dihydro-4-oxoquinazoline (VI; R = —CH_2Ph) and 3-amino-2-*p*-nitrobenzyl-3,4-dihydro-4-oxoquinazoline [VI; R = —$CH_2C_6H_4NO_2(p$-)] were prepared by converting to anilide, then to 3,1,4-benzoxazones and finally to the 4-oxoquinazolines. [VI; R = —CH_2Ph] and [VI: R = —$CH_2C_6H_4NO_2(p$-)] analysed correctly and also gave characteristic IR absorptions which were consistent with their structure.

3-Acetamido, 3-benzamido, 3-phenyl acetemido and 3-*p*-nitrophenyl acetamido derivatives of III and VI [R = —CH_2Ph, —$CH_2C_6H_4NO_2(p$-)] were prepared by direct acylation as well as by condensation of 3,1,4-benzoxazones (V) with appropriate acid hydrazides. These products gave correct analysis and characteristic IR absorptions. Their identity was established by determining mixed

m.p.s which were undepressed. For example, 3-benazamido-2-benzyl-3,4-dihydro-4-oxoquinazoline furnished the following results. [Found (%), C: 74.10, H: 4.28%, N: 12.16; calculated for $C_{22}H_{17}N_3O_2$ (%), C: 74.366, H: 4.789, N: 11.83; ν_{max} (KBr) 1660 cm^{-1} (quinazolone carbonyl); 1710 cm^{-1} (open chain carbonyl); 3380 (N—H bonded).

Following table shows the nitrogen (%) and m.p.s of various 4-oxoquinazolines and their acyl derivatives.

3-Amino-2-alkyl/aryl-3,4-dihydro-4-oxoquinazoline		Acyl derivatives			
		3-Acetamido	3-benzamido	3-Phenyl acetamido	3-*p*-Nitrophenyl acetamido
(III)					
N (%)	28.82 (F)	19.60 (f)	15.26 (F)	14.62 (F/)	16.32 (F)
	24.00 (Cal)	19.355 (Cal)	15.054 (Cal)	14.30 (Cal)	1656 (Cal)
m.p. (°C)	148–150	175	181	161–61	192–193
VII R = (—CH_2Ph)					
N (%)	16.41 (F)	14.71 (F)	12.16 (F)	11.20 (f)	13.24 (F)
	16.37 (Cal)	14.33 (Cal)	11.83 (Cal)	11.38 (Cal)	13.52 (Cal)
m.p. (°C)	120	164	235	173–74	192–93
(VI) R = (—$CH_2C_6H_4NO_2$(-p-)					
N (%)	18.64 (F)	16.82 (F)	13.96 (F)	13.60 (F)	15.10 (F)
	18.92 (Cal)	16.57 (Cal)	14.00 (Cal)	13.53 (Cal)	15.25 (Cal)
m.p. (°C)	186	161–62	185–86	172–73	215–16

F = Found; Cal = Calculated

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