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

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A number of 3-amino-2-alkyl/aryl-3,4-dihydro-4-oxoquinazolines (Scheme I-VI) were prepared and characterised. Their 2,4-DNP derivatives were also prepared and characterised.

INTRODUCTION

Amongst the various quinazoline derivatives, 3-amino-2-alkyl/aryl-3,4-dihydro-4-oxoquinozolines appeared to be of particular interest to us in view of their physiological and medicinal activities. They possess three reactive sites at $C_{(2)}$-alkyl/aryl, $N_{(3)}$-NH_2 and 4-oxo groups in pyrimidine moiety itself. Our interest in quinazolines was directed mainly toward preparation of tricyclic compounds from the 4-oxo-quinazolines, especially those in which a third heterocyclic ring is fused on to the pyrimidine part of the 4-oxoquinazolines ring system.

For the above projected synthesis we have to choose suitable 3-amino-2-alkyl/aryl-3,4-dihydro-4-oxoquinazolines having reactive methyl or methylene group at $C_{(2)}$ as starting materials, which have to be prepared in bulk. The commonly employed methods start with some derivatives of anthranilic acid which was cyclised to quinazolones on reaction with hydrazine. For example, *o*-amidobenzoic acids or their esters have been converted into 4-oxoquinazolines on reaction with hydrazine[8–10].

In a variation of above method, cyclisation of *o*-amino benzoyl hydrazines has been effected by the action of an acylating agent[11].

In these methods anthranilic acid has first to be converted into a suitable derivative for its subsequent transformation into 4-oxoquinazolines.

Compared to these methods, Klosa's method[12] of preparing 3-amino-2-methyl-3,4-dihydro-4-oxoquinazoline from benzoxazinones appeared more attractive to us, owing to its simplicity and convenience of not isolating the intermediates. Furthermore mechanistic investigation of this reaction by Errede *et al.*[13–16] prevented any pitfalls for us.

This method was used with some modification to prepare a number of 3-amino-2-alkyl/aryl-3,4-dihydro-4-oxoquinazolines. Following a reported

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method[17] with slight modification, 2,4-DNP derivatives of these 4-oxoquinazolines were prepared and characterised by various physico-chemical methods.

EXPERIMENTAL

Melting points of the compounds were determined in sulphuric acid bath, and those of high melting solids in an electrical apparatus, and are uncorrected. IR spectra were recorded on a potassium bromide discs using a Perkin-Elmer-577 spectrophotometer.

3-Amino-2-methyl-3,4-dihydro-4-oxoquinazoline (III)

Anthranilic acid (20 g) was mixed with freshly distilled acetic anhydride (70 mL) over phosphorus pentoxide, and heated under reflux for 3 h. The excess of acetic anhydride was removed by direct distillation and its last traces were distilled off under reduced pressure. The residual brown solid, acetanthranil, was washed 2–3 times with light petroleum. A solution of hydrazine hydrate (90%, 20 mL) in methyl alcohol (25 mL) was then added to the solid and the mixture was heated for 30 min. When a clear solution was obtained, the solution on cooling yielded a white solid. This was collected by filtration. The filtrate was concentrated and cooled to deposit a second crop of crystals. The solids were combined and recrystallised from water to furnish pure 3-amino-2-methyl-3,4-dihydro-4-oxoquinazoline as white needles (16.81 g, 60% yield), m.p. 148–150°C.

Analysis: 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 structure).

2,4-Dinitrophenylhydrazone of 3-amino-2-methyl-3,4-dihydro-4-oxoquinazoline (VII)

A mixture of 3-amino-2-methyl-3,4-dihydro-4-oxoquinazoline (8.75 g), 2,4-dinitrophenyl hydrazine (10.0 g), ethanol (40 mL) and a few drops of concentrated sulphuric acid were heated under reflux for 8 h. The solution was cooled in ice, when reddish brown solid separated from it. This was collected by filtration and recrystallised from ethanol to furnish yellow crystals of the pure 2,4-DNP derivative, m.p. 242–44°C.

Analysis: Found N: 27.38%; calculated for $C_{15}H_{13}N_7O_4$, N: 27.60% ν_{max}(KBr) 1600 cm^{-1} (substituted aromatic ring); 1520, 1350 cm^{-1} (aromatic —NO_2); 3270 cm^{-1} (bonded N—H). There was no absorption in the region 1600–1800 cm^{-1} showing absence of quinazoline carbonyl structure.

3-Amino-2-benzyl-3,4-dihydro-4-oxoquinoline (VI) [R = —CH_2Ph]

(a) *Preparation of phenylacetyl chloride from phenyl acetic acid*

Dry phenyl acetic acid (10 g) and thionyl chloride (25 mL) were mixed together and heated under reflux for nearly 5 h. When hydrogen chloride ceased to be evolved, a red coloured liquid was obtained in the reaction vessel, from which excess of thionyl chloride were removed by distillation and subsequently traces of thionyl chloride was removed by the azeotropic distillation with benzene followed by prolonged suction. This left almost pure phenylacetyl chloride as a red liquid.

(b) *Reaction of phenylacetyl chloride with anthranilic acid*

A solution of anthranilic acid (10 g) in a mixture of acetone (25 mL) and dry pyridine (6 mL) was added dropwise to phenylacetyl chloride (10 mL) and the mixture was left overnight. Next day acetone was distilled off and ice cold water added to the residual liquid. A solid speparated out, which was filtered out and recrystallised from acetic acid to yield anilide (IV; R = CH_2Ph) as light brown needles (7 g); m.p. 185°C.

(c) *Cyclisation of above anilide to the anthranil* [V; R = —CH_2Ph]

Dried acetic anhydride (50 mL) was added to dry anilide (10 g) in a mixture of acetone (25 mL) and dry pyridine (6 mL) was added dropwise to phenylacetyl chloride (10 mL) and the mixture was left overnight. After 24 h, acetone was distilled off and ice cold water was added to the residual liquid when a solid separated out, which was filtered out and recrystallised from acetic acid to yield the anilide [IV: R = —CH_2Ph] as light brown needles (7 g) m.p. 185°C.

(d) *Conversion of anthranil* [V; R = —CH_2Ph] *into 3-amino-2-benzyl-3,4-dihydro-4-oxoquinazoline* {[*VI*; *R*=CH_2Ph]

A solution of hydrazine hydrate [20 mL; 90%] in dry methanol was added to the solid anthranil obtained above and the mixture was heated under reflux for 2.5 h. The solution was filtered while hot. The filtrate on cooling deposited a grey solid, which was collected by filtration. On reducing the volume of filtrate a second crop of crystals was obtained. The solid were combined and recrystallised. from ethanol to furnish the benzyl quinazolone [VI; R = —CH_2Ph) (6.8 g) as light grey needles; m.p. 120°C.

Analysis: Found (%), C: 71.71, H: 5.40, N: 16.41; calculated for $C_{15}H_{13}N_3O$ (%), C: 71.71, H: 5.18, N: 16.37.

I.R. ν_{max}(KBr) 1660 cm^{-1} quinazoline carbonyl, 3325, 3230 cm^{-1} (N—H bonded)

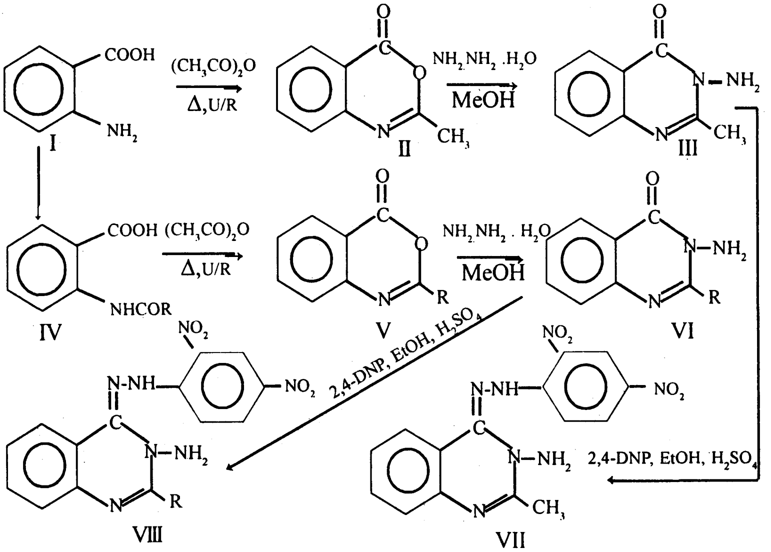
2.4-Dinitrophenylhydrazone of 3-amino-2-benzyl-3, 4-dihydro-4-oxoquinazoline [VIII; R= —CH_2Ph]

The reaction of 2,4-dinitrophenylhydrazine with 3-amino-2-benzyl-3,4-dihydro-4-oxoquinazoline was carried out as above. The 2,4-DNP derivative was obtained as yellowish red crystals; m.p. 252–254°C.

RESULTS AND DISCUSSION

The full scheme of preparative work is shown on the next page.

3-Amino-2-methyl-3,4-dihydro-4-oxoquinazoline(III) was prepared by the Klosa's method[12] with some modification. The compound gave correct m.p. (148–150°C) and elemental analyses. Its 2,4-DNP derivative was also prepared



$[R = -CH_2Ph,\ -CH_2C_6H_4NO_2(p\text{-})]$

by prolonged heating under reflux with 2,4-DNP in ethanol in presence of few drops of conc. $H_2\ SO_4$. 3,4-dihydro-4-oxoquinazoline exists in tautomeric form, which was recognised as early as 1887. Since the tautomerism is due to the presence of mobile hydrogen at $N_{(1)}$,or $N_{(3)}$, the presence of substituents in these places prevents tautomerism. Amino group at $N_{(3)}$ in (III) hinders the tautomerism which enabled us to prepare its 2,4-DNP derivative (VIII). It analysed correctly for nitrogen [found, N: 27.38%; calculated for $C_{15}H_{13}N_7O_4$, N: 27.60%]. Its IR spectra did not show any absorption in the region 1800–1600 cm^{-1} which proved that 4-oxo-group had reacted with 2,4-DNP. [ν_{max}(KBr) 1600 cm^{-1} (substituted aromatic ring); 1520–1350 cm^{-1} (aromatic —NO_2); 3270 cm^{-1} (bonded N—H). 3-amino-2-benzyl-3,4-dihydro-4-oxoquinazoline [VI; R = —$CH_2C_6H_4NO_2$ (-*p*-)] were prepared by I to IV (Anilide)-V (Benzoxazinone)-VI (4-oxoquinazoline) route in high yield (*ca.* 70%). VI [R = —CH_2Ph] gave correct analysis for elements [Found (%), C: 71.42, H: 5.40, N: 16.35; calculated for $C_{15}H_{13}N_3O$ (%), C: 71.71, H: 5.18, N: 16.37) and it also showed characteristic IR absorptions at 1670 cm^{-1} (quinazolone carbonyl); 3320 and 3240 cm^{-1} (N—H-primary and bonded), which was consistent with its structure, VI [R = (*p*-)$O_2N{\cdot}C_6H_4{\cdot}CH_2$—] also gave correct analysis for nitrogen (found, N: 18.64%; calculated for $C_{15}H_{12}N_4O_3$, N: 18.92%) and also showed characteristic IR absorptions at 1670 cm^{-1} (quinazolone carbonyl), 1560 and 1330 cm^{-1} (aromatic —NO_2), 3370 and 3020 cm^{-1} (bonded N—H) which were consistent with its structure. 2,4-DNP derivatives of these compounds were also prepared as high melling solids.

The following Table shows the % of nitrogen and m.p. of various 4-oxoquinazolines and their 2,4-DNP derivatives.

3 amino-2-alkyl/aryl-3,4-dihydro-4-oxoquinazoline				2,4-DNP derivative			
	(%) Nitrogen		m.p. (°C)		(%) Nitrogen		m.p. (°C)
	Found	Calc.			Found	Calc.	
III	23.82	24.00	148–150	VII	28.38	27.60	242–44
VI (R = $—CH_2Ph$)	16.41	16.37	120	VIII (R = $—CH_4Ph$)	22.90	22.74	252–44
VI [R = $—CH_2C_6H_4NO_2$(-p)-]	18.64	18.92	186	VI (R =$—CH_2C_6H_4NO_2$(-p)-]	24.16	23.63	61–62

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