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Synthesis of New Quinazoline-4-One Compounds of Medicinal Importance

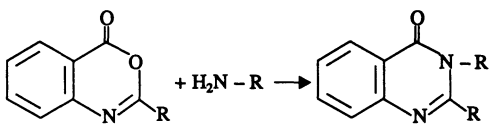
(Ms.) R.K. KAWADKAR and B.J. GHIYA*
Chemistry Department, Institute of Science
Nagpur-440 001, India

Some new quinazoline-4-ons (II–VII) have been synthesised using different amino compounds, *viz.*, ammonia, hydrazine hydrate, urea, thiourea, formamide, guanidine carbonate, etc., with different oxo-compounds. Further condensations of these quinazolines were carried out using piperazine formaldehyde or phenyl isothiocyanate. All the compounds were purified and the structure of the products has been established by elemental analysis and spectral data. (IR, ^{1}H NMR). Significant antimicrobial activities were observed for some members of the series.

INTRODUCTION

Heterocyclics possessing two nitrogen atoms are reported to posess physiological and pharmacological activities. Literature survey reveals that quinazoline derivatives are known to possess antimalarial, antiinflammatory[1], antileprotic and hypnotic[2] activities.

Our work deals with the synthesis of quinazoline-4-one and similar type of compounds[3]. Various methods have been used for the preparation of 2- and 3-substituted quinazoline. The most widely used method is by the exothermal reaction of 2-substituted benzoxazine-4-one with appropriate amino compound under non-aqueous condition[4]. Hence we carried out similar work with different amino compounds. When the reaction of benzoxazine-4-one is carried out with amino compound the following type of compound is reported in most of the cases[5, 6], with the exception of urea and thiourea.



During our study, the following observations were made:

Benzoxazine-4-one (I) on reaction with ammonia gives quinazoline-4-one (II). Same product is obtained on reaction of (I) with formamide[7]. It was confirmed from the melting point and TLC of products obtained by both the methods (ammonia/formamide) for their identity. The reaction of (I) with guanidine

carbonate in ethylene glycol leads to the formation of 3-N amino-imino-methyl-quinazoline-4-one-(III).

The reaction of (I) with hydrazine hydrate produces 3-amino-quinazoline-4-one. This 3-amino-quinazoline-4-one was condensed with piperazine and formaldehyde in presence of acidic alcohol to get 1-4-di-[2-aryl/alkyl-3-amino-quinazoline-4-one] 1,4-dimethyl piperazine[3].

(I) on reaction with phenyl isothiocyanate gave N-phenyl-N′-2-methyl/phenyl-4-oxoquinazoline-3yl thiourea. (I) on reaction with urea in alkaline ethanol brings about hydrolysis to get original starting material, the N-acetylated/benzoylated anthranilic acid. This is unusual.

Benzoxazine-4-one (I) on reaction with thiourea in alkaline ethanol was recovered unchanged.

The compounds thus synthesised are tested for their antimicrobial activities by cup-plate method[8] using DMF as solvent against *S aureus*, *B subtilis*, *E coli*, *Pr. mirabilis* at 100 μg/mL. Compounds (III a, b) and (VII a, b) showed significant antibacterial activities, while the rest of the compounds exhibited moderate antibacterial activities.

The physical data and yield of the compounds are illustrated in Table-1. The compounds have also been screened at TAACF for their antituberculosis activity and results are promising. Compounds VII a, b were screened for anti-AIDS activity and were confirmed negative.

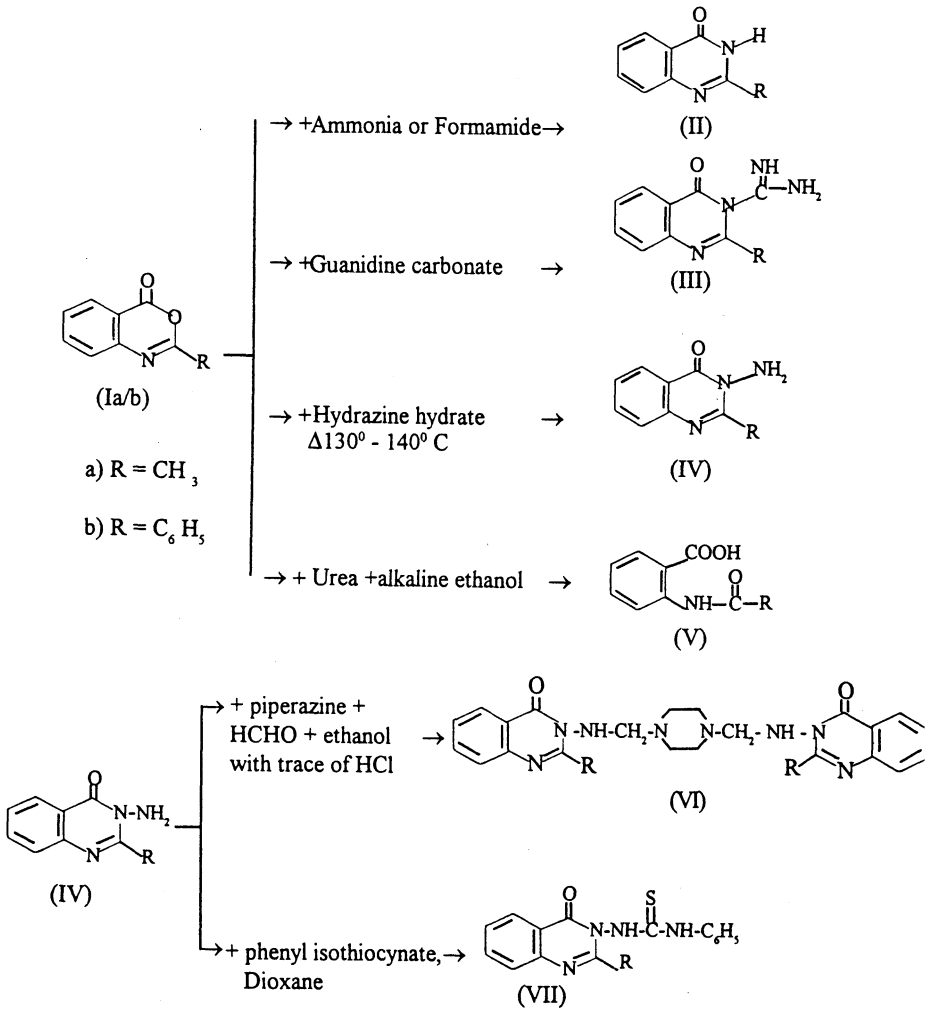
TABLE-1
PHYSICAL DATA AND YIELD (%) OF THE COMPOUNDS

S. No.	Compound	R	Molecular formula	Nitrogen percentage		Melting point (°C)	Yield (%)
				Calcd.	Found		
1.	IIa	CH_3	$C_9H_8N_2O$	17.50	17.20	190	80
2.	IIb	C_6H_5	$C_{14}H_{10}N_8O$	12.60	12.80	220	80
3.	IIIa	CH_3	$C_{10}H_{10}N_4O$	27.70	27.60	102	75
4.	IIIb	C_6H_5	$C_{15}H_{12}N_4O$	21.20	21.00	108	70
5.	VIa	CH_3	$C_{24}H_{28}N_8O_2$	24.30	24.00	220(d)	72
6.	VIb	C_6H_5	$C_{34}H_{32}N_8O_2$	19.17	19.20	250(d)	67
7.	VIIa	CH_3	$C_{16}H_{14}N_4O_2S$	18.00	18.30	181	70
8.	VIIb	C_6H_5	$C_{21}H_{16}N_4O_2S$	15.05	15.20	190	60

EXPERIMENTAL

All the melting points are uncorrected. The IR spectra are recorded on Perkin-Elmer spectrophotometer and NMR on Brucher AC 300 F NMR spectrometer (300 MHz).

(i) *Preparation of 2-alkyl/aryl quinazoline-4-one*: A mixture of benzoxazine (0.01 mol) and liquor ammonia in excess were taken in a round-bottom flask reaction mixture was heated on oil bath at 130°–140°C for 30 min.



Scheme

a white-coloured compound separated out which was filtered and was crystallised from ethanol, *e.g.*, IIb.

IR: ν_{max} (cm^{-1}): 3389 ν(N—H), 3188 (b Ar C—H streching), 1660 ν(C=O), 1591 ν(C=C), 1528 ν(C—N), 1312 Ar C—H in- plane-ring bending, 1258 Ar—C—H out-of-plane ring bending.

^{1}H NMR δ: 4.9 (s, 1H, N—H), 7.4 (t, 1H, Hc), 7.6 (d, 1H, Hd), 7.8 (4H, s, 2He and 2Hf), 7.9 (s, 1H, Hg), 8.0 (dd, 1H, Hb), 8.2 (d, 1H, Ha).

Same product is obtained when a mixture of benzoxazine and formamide in alcohol are refluxed for 30 min[7].

(ii) *Preparation of 2-alkyl/aryl 3-N-amino imino methyl quinazoline-4-one*: ixture of benzoxazine (0.01 mol), guanidine carbonate (0.02 mol) and 30 mL lycol were refluxed in a RB flask for 3 h. It was then diluted with cold dried and further crystallised from ethanol, *e.g.*, IIIb.

IR: ν_{max} (cm^{-1}): 3700–3500 ν(=N—H), 3450 ν(N—H), 3250–3100 (Ar—C—H stretching) broad, 1690 ν(C=O) weak, 1620 ν(C=C), 850 (N—H wagging), 630 N—H out-of-plane bending.

^{1}H NMR δ: 4.4 (s, 1H, NH), 4.9 (s, 2H, NH_2), 7.1 (s, 1H, Hg), 7.5 (m, 4H, 2He, 2Hf), 8.0 (s, 2H, Hb, Hc), 8.2 (d, 1H, Ha), 8.8 (d, 1H, Hd), 12 (s, 1H, —O···H—).

(iii) *Preparation of* 1,4-*di*-(2-*alkyl/aryl* 3-*amino-quinazoline-4-one*) 1,4-*dimethyl piperazine*: A mixture of piperazine (0.01 mol), formaldelyde (0.03 mol), 2-alkyl/aryl 3-aminoquinazoline-4-one and 30 mL ethanol with traces of conc. HCl were taken in a RB flask and refluxed for 1 h. Excess of ethanol was removed to get a solid. It was filtered and crystallised from ethanol, *e.g.*, VIb.

(iv) *Preparation of N-phenyl-*N^1-(2-*substituted*-4-*oxoquinazoline*-3-*yl*) *thiourea*: Phenyl isothiocyanate[9] (0.01 mol) and quinazoline-4-one (0.01 mol) were dissolved in dioxane (10 mL). The mixture was refluxed on water bath for 2 h. On trituration with petroleum ether, a white compound separated out which was crystallised from ethanol, *e.g.*, VIIa.

^{1}H NMR δ: 2.7 (s, 3H, CH_3), 7.2–7.3 (m, 5H, Ar—H), 7.4–7.7 (m, 4H, Hb, Hc, Hd and NH—Ar), 8.2 (d, 1H, Ha), 8.7 (s broad, N—NH).

(v) A mixture of benzoxazine and urea in alkaline ethanol was refluxed for 30 min. The mixture was diluted with cold water. The solid separated was filtered, washed and crystallised from rectified spirit to get V.

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