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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NEW *N*-SUBSTITUTED BENZYLIDENE-6,8-SUBSTITUTED-2-ETHYL-QUINAZOLIN-4-OXY-ACETIC ACID HYDRAZIDES

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INTRODUCTION

4(3H) Quinazoline-4-ones, have been reported to possess various biological activities[1-3] and exist as 4-ol-[II] tautomers in the presence of anhydrous potassium carbonate and dry acetone[4]. Although compounds synthesised from tautomeric form have not been reported so far to be biologically active, it was considered of interest to synthesise such compounds as having both the tautomeric 6,8-substituted-2-ethyl-quinazolin-4-oxy-acetic acid moiety as well as $-N=C<$ group, the presence of which in the compounds, as is well known[5,6], makes them highly biologically active. In this communication, the synthesis and the antibacterial and antifungal evaluation of the title compounds are described.

Reaction of propionic anhydride with 3,5-substituted anthranilic acids yielded 6,8-substituted-2-ethyl benzoxazin-4-ones [I] which were reacted with formamide to yield 6,8-substituted-2-ethyl-quinazolin-4-one [II]. The latter in the presence of anhyd. K_2CO_3, dry acetone and chloroethyl-acetate, yielded 6,8-substituted-2-ethyl-quinazolin-4-oxy-ethyl-acetate [III], which on reaction with hydrazine hydrate in alcohol gave the corresponding hydrazide [IV]. *N*-benzylidene-derivatives from IV were obtained on condensation with different aromatic aldehydes and substituted acetophenones. The structure of the compounds was established on the basis of their elemental analysis and spectral data.

EXPERIMENTAL

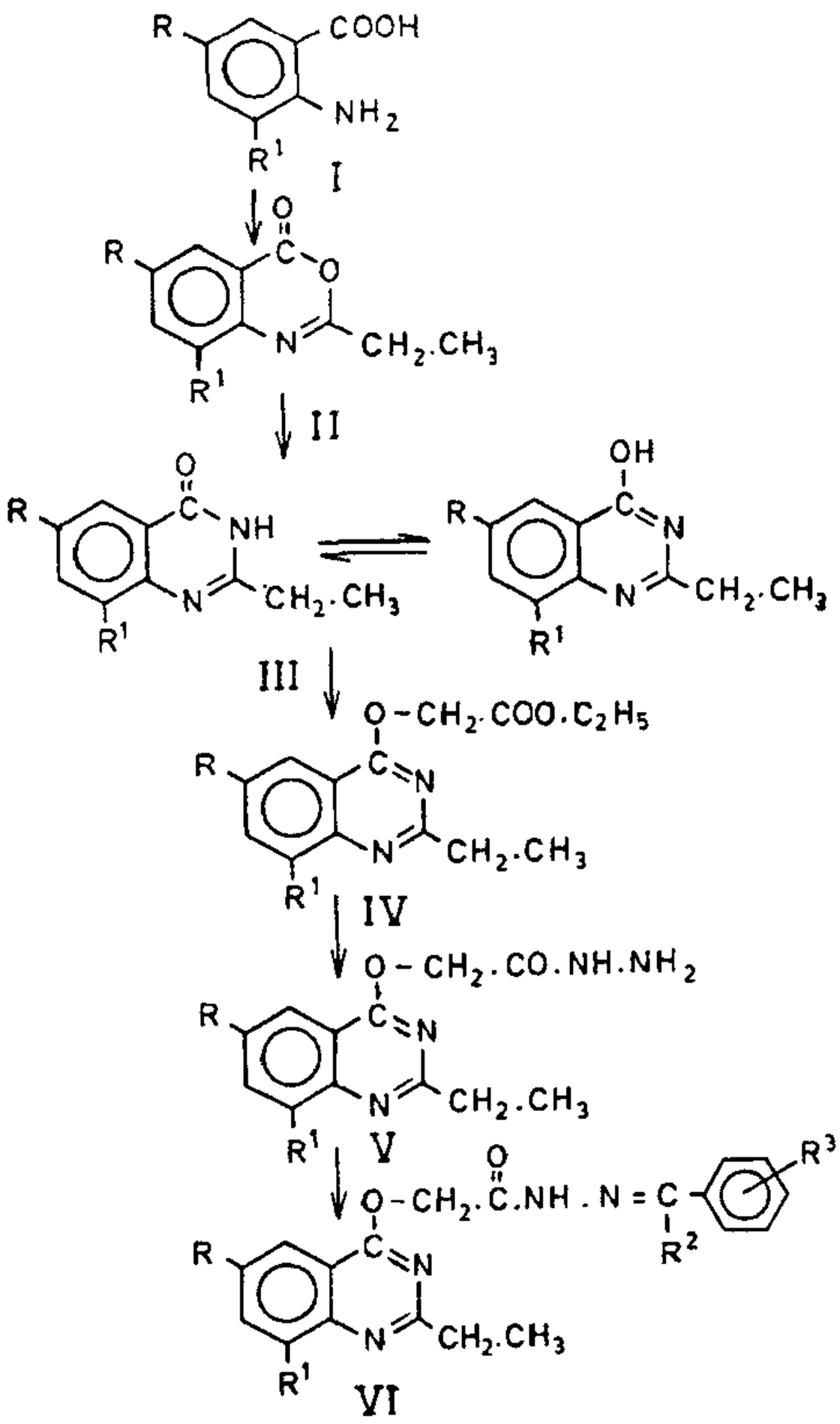
The melting points were determined using sulphuric acid bath in open capillary tubes and are uncorrected. IR spectra in KBr were recorded on a Perkin Elmer spectrophotometer (υ max in cm^{-1}) and PMR spectra in DMSO d_6 on a Varian A–90D instrument using TMS as internal standard (chemical shift in δ ppm). The purity of each compound was checked on TLC.

6,8-Substituted-2-ethyl-benzoxazin-4-ones [I]

A mixture of substituted anthranilic acid (0.1 mol) and propionic anhydride (0.2 mol) was refluxed for 4 hr. The reaction mixture was poured into ice cold water and the solid that separated was recrystallised from hot water and methanol. Yield 85–90% IA (R = R = H) mp 120°, IB (R = Br, R' = H) mp 180°, IC (R' = R = Br) mp 125°. Their IR spectra showed bands around 2950 cm^{-1}, 1660 cm^{-1} characteristic of (–C–H) and (–C–) groups respectively.

6,8–Substituted-2-ethyl-quinazolin-4-ones [II]

The compound I (0.1 mol) and formamide (0.15 mol) were heated at 170° for 4 hr. On cooling with ice, a solid, separated which was recrystallised from hot water. Yield 70–75%. Following compounds were thus prepared:- IIA (R = R' = H) mp 212°, IIB (R = Br, R' = H) mp 180°, IIC (R = R' = Br) mp 270° I.R. spectra showed bands around 3300, 2900 and 1670 cm^{-1} characteristic of (NH), (CH) and (CO) groups respectivley.



6,8-Substituted-2-ethyl-quinazolin-4-oxy-ethylacetate [III]

A mixture of II (0.1 mol) anhydrous potassium carbonate (0.2 mol) and ethyl chloroacetate (0.1 mol) was refluxed in dry acetone for about 24 hr. The excess acetone was distilled and the contents cooled and poured in ice water. The solid thus obtained was filtered and recrystallised from methanol (yield 60–65%). Following compounds were prepared:- IIIA (R = R′ = H) mp 184°, IIB (R = Br, R′ = H) mp 110°, IIIC (R = R′ = Br) mp 130°. I.R. spectra showed bands around 2950, 1680 and 1600 cm^{-1} characteristic of ester (-C-H), (-CO, > C = N-) groups respectively. The complete absence of the band for (NH) indicated the formation of oxy compound.

6,8-Substituted-2-ethyl-quinazolin-4-oxy-acetic acid hydrazides [IV]

The compound III (0.1 mol) and hydrazine hydrate (99.5%, 0.15 mol) were refluxed in absolute alcohol (150 ml) on a steam bath for 14–16 hr. The excess solvent was distilled under vacuum and the crude hydrazide obtained on cooling was filtered recrystallised from acetone to give IV in 50–60% yield. The following compounds were thus prepared:- IVA (R = R′ = H) mp 254° IVB (R = Br, R′ = H) mp 228° IV (R = R′ = Br) mp above 270° I.R. spectra (cm^{-1}) showed bands around 3400, 1900, 1690 (broad) characteristic of (-N-H), (C-H), (-CO) groups respectively.

N-Substituted-benzylidine-6,8-substituted-2-ethyl-quinazolin-4-oxy-acetic hydrazides [V]

Equimolar amounts of IV and an appropriate aromatic aldehyde or acetophenone were refluxed in methanol in presence of 2–3 drops of glacial acetic acid for 4 hr. The solid which separated on cooling, was filtered and recrystallised from a suitable solvent. The compounds, thus synthesised are listed in table I yield 70–75%.

IR Spectra (cm^{-1})

Va 3400 (-NH)-, 2960 (-C-H-), 1680 (-C(=O)-NH-), 1600 (-C=N-) Vh 3400 (-NH-)-, 2900–3000 (-C-H), 1680 (-C(=O)-NH), 1610 (-C=N-). Vt 3200 (OH), 3400 (NH), 3000 (CH), 1680 (-C(=O)-NH), 1600 (-C=N-).

PMR (δ)

Va 8.25 (s, 1H, -C-NH), 8.85 (s, 1H, -N=CH-), 7.6–7.4 (hump, 8H, Ar-H), 4.88 (s, 2H, $-OCH_2-C-$), 4.55 (s, 3H, OCH_3), 1.2 (m, 3H, $-CH_3$ of $-C_2H_5$), 2.9 (m, 2H, $-CH_2-$ of $-C_2H_5$).

Antibacterial activity

All the compounds (V) were screened for their inhibitory action against *B. subtilis, S. typhi* and *S. aureus* following the method of Varma and Nobles[7]. Only one compound[Vc] showed significant inhibition against *S. aureus* (zone size 16 mm) while other compounds were completely inactive.

Antifungal activity

Compound (V) was screened for its antifungal activity against *Helminthosporium* sp., *A. niger* and *Fusarium moniliforme* by following the agar plate diffusion method[8]. The compounds inhibited fungus growth 50%, 35%, 25% respectively at conc. 1:1000 and 30%, 17%, 10% at conc. 1:10000 respectively.

The authors are grateful to Professor V. S. Misra, for facilities as well as to the Director, Central Drug Research Institute, Lucknow for the microanalysis and spectral data.

TABLE 1

N-Substituted-benzylidene-6,8-substituted-2-ethyl-quinazolinyl-4-oxy-acetic acid hydrazides

Compound*	R	R^1	R^2	R^3	mp °C
Va	H	H	H	4-OCH_3	234
Vb	H	H	H	4-$N(CH_3)_2$	263
Vc	H	H	H	4-NO_2	225
Vd	H	H	H	3-OCH_3,4-OH	275
Ve	H	H	H	3-NO_2,4-OCH_3	200
Vf	H	H	CH_3	2-OH,4-OH	215
Vg	Br	H	H	4-OCH_3	235
Vh	Br	H	H	4-$N(CH_3)_2$	245
Vi	Br	H	H	4-NO_2	244
Vj	Br	H	H	3-OCH_3,4-OH	265
Vk	Br	H	H	3-NO_2,4-OCH_3	260
Vl	Br	H	H	3-Cl	242
Vm	Br	H	CH	2-OH,4-OH	above 270
Vn	Br	Br	H	4-OCH_3	255
Vo	Br	Br	H	4-$N(CH_3)_2$	250
Vp	Br	Br	H	4-NO_2	above 270
Vq	Br	Br	H	3-OCH_3,4-OH	275
Vr	Br	Br	H	3-NO_2,4-OCH_3	270
Vs	Br	Br	H	3-Cl	253
Vt	Br	Br	CH_3	2-OH,4-OH	265

* All compounds gave satisfactory N analysis.

18 June 1982; Revised 21 August 1982

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