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SYNTHESIS AND CHARACTERIZATION OF 2-CARBAMAZEPINYL–4- QUINAZOLONE AND 6, 8-DIBROMO-2-CARBAMAZEPINYL-4-QUINAZOLONE

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ABSTRACT

A simple, efficient and general method has been developed for the synthesis of 2-hetero substituted -4-quinazolones by using Niementowski reaction. The synthetic reaction involves thermal condensation and cyclisation of a drug amide with anthranilic acid and 6, 8–dibromo anthranilic acid at elevated temperatures to yield the hetero-moieties namely carbamazepinyl –4–quinazolone and 6, 8-dibromo-2-carbamazepinyl-4-quinazolone. The structures of the compounds were characterized by IR, NMR, MS and elemental analysis. The compounds were evaluated for antimicrobial activity.

Key words : Quinazolinone, Carbamazepine, 6, 8–Dibromo anthranilic acid

INTRODUCTION

According to recent data, quinazolinone nucleus has attracted the attention of medicinal chemists due to its wide range of pharmacological properties. The present work deals with the synthesis of quinazolone derivative with carbamazepine moiety. The preparation of 2-carbamazepinyl-4-quinazolone (NC) and 6, 8-dibromo-2-carbamazepinyl-4-quinazolone (NCB) is based on Niementowski reaction by modification of reaction conditions[1]. The structures were established by IR, ^{1}H NMR, MS and elemental analysis.

EXPERIMENTAL

Synthesis of 2-carbamazepinyl-4-quinazolone (NC) and 6, 8- dibromo-2-carbamazepinyl -4-quinazolone (NCB):

Reaction mixture consisting of equimolar quantities of anthranilic acid and carbamazepine in pulverized condition was transferred to a porcelain dish. The porcelain

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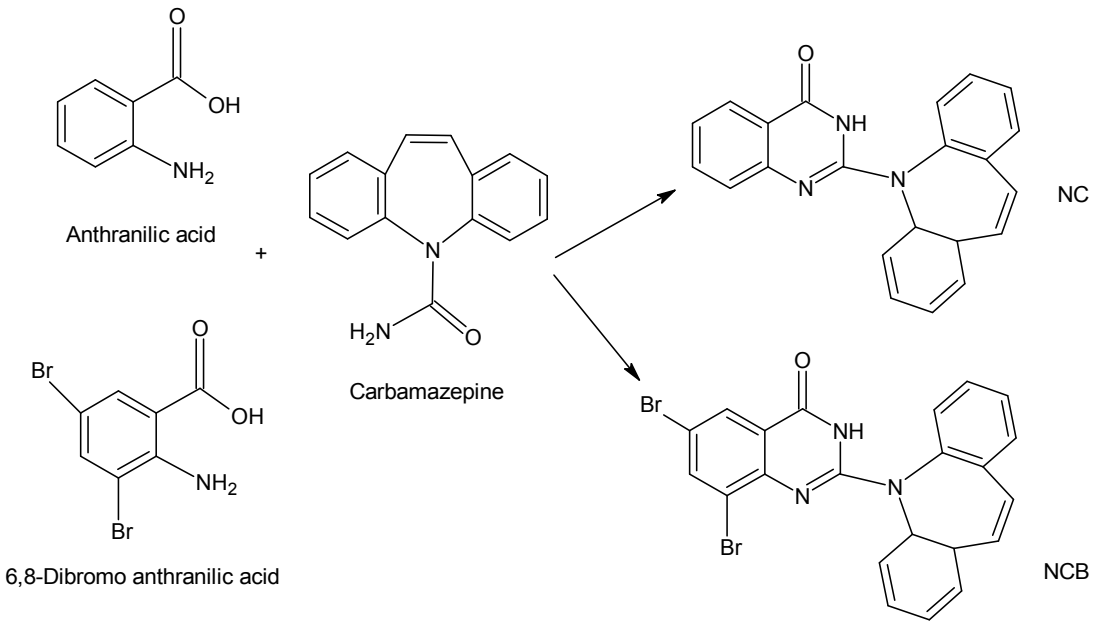
dish, with a funnel inverted over, it was placed on wire gauze and heated over a bunsen flame. The contents were heated carefully to avoid charring until the evolution of white and yellow fumes ceased. A shiny fluffy, crystalline powder was found to deposit on the periphery of the porcelain dish and also inside the funnel. The above procedure was used for the preparation of 6, 8-dibromo-2-carbamazepinyl-4-quinazolone(NCB) also using 3, 5-dibromo-anthranilic acid instead of anthranilic acid, which was prepared in the laboratory by bromination of anthranilic acid[2].

The synthetic route is shown in scheme –



Scheme

Materials and methods

All the chemicals used were procured from reputed firms.

The melting points of the compounds were determined by capillary tube method and are presented (uncorrected). IR spectra were recorded using KBr pellets in the range of 4000-500 cm^{-1} on a FTIR spectrometer Shimadzu model. ^1H NMR Spectra (400 MHz) was recorded in $CDCl_3$ in Jeol GSX liquid state NMR spectrometer with reference to internal standard TMS. Mass spectra were recorded on Q -TOF MICRO spectrometer using electron ionization technique. The percentage compositions of the elements present were

analyzed using Perkin–Elmer C, H, N, O elemental analyzer, Model No. 2400.

Purification

The compounds were purified by column chromatography using chloroform as eluent. The fractions, which gave a single spot without any impurity were combined. Then solvent was allowed to evaporate and the pure product was obtained. The purity was checked by TLC on precoated silica gel G plates using chloroform and methanol (95 : 5) as mobile phase. The spots were detected using UV chamber/iodine vapors in a tightly closed chamber. Presence of a single principal spot and no secondary spot confirmed the purity of the compounds.

Analytical data

2-Carbamazepinyl – 4–quinazolone (NC)

Yellow, shiny and fluffy crystalline compound, Melting Point : 165–169^{o}C, Yield : 60%, Molecular formula C_{22} H_{15} N_3O, Molecular weight : 337.

IR $\nu_{KBr}^{cm^{-1}}$: 1558.4 (s) C = N, 1646.1 (s) C = O of amide and 3360.7 (s) NH of amide.

^{1}H NMR $\delta_{CDCl_3}^{ppm}$: 1.7 (s, NH), 7-7.2 (m, 5H, 8H), 6.8–6.9 (m, 1'H-4'H, 6'H -9'H), 6.5 (d, 10'H, 11'H), 6.3 (s, 6H, 7H).

MS m/z : 337 $(M)^+$ ion peak.

Elemental analysis: Carbon : Hydrogen : Nitrogen, Found (%) : 76.70 : 4.80 : 13.12, Calculated values (%) : 78.33 : 4.45 : 12.46

6, 8 - Dibromo -2- carbamazepinyl - 4- quinazolone (NCB)

Yellow and fluffy crystalline compound, Melting Point : 102 –105^{o}C, Yield : 60%, Molecular formula : $C_{22}H_{13}N_3OBr_2$, Molecular weight : 495

IR $\nu_{KBr}^{cm^{-1}}$: 1606.63 (s) C = N, 1685.62 (s) C = O of amide, 3360.87 (s) NH of amide.

^{1}H NMR $\delta^{ppm}_{CDCl_3}$:1.8 (s NH), 6.3 (s, 1'H– 4'H, 6'H- 9'H), 6.49 (d, 10'H, 11'H), 7.05 (m 7H) and 6.85 (m 5H).

MS m/z : 494 $(M)^+$ ion with isotope peak.

Elemental analysis : Carbon : Hydrogen : Nitrogen Found (%) : 54.50 : 3.02 : 8.90, Calculated values (%) : 53.30 : 2.60 : 8.50.

RESULTS AND DISCUSSION

The method of fusion by heating on a direct flame provided the high temperature required; thereby, reducing the reaction time and it also decreases the chance of undesired side reactions and impurities. This method of heating was found effective as compared to heating in an oil bath for 6 hours or refluxing the mixture in a water bath for 1.5 hours using sulphuric acid as a dehydrating agent. As the number of reaction steps is minimal, using proper chemical development technology, a high overall yield of high purity could be obtained[3]. Bands were observed in the IR spectra of synthesized compounds at 1650-1550, 1700-1600 and 3400-3300 cm^{-1} due to C = N str, C = O str and NH str vibrations, respectively. The ^{1}H NMR spectral data of all the synthesized compounds were in conformity with the structure assigned[4]. In mass spectra of compounds, the molecular ion (M^+) with isotopic peaks appeared with different intensities, which confirmed the molecular weights of the examined compounds. The assigned structure was further supported by elemental analysis. The compounds NC and NCB were found to exhibit antibacterial activity against *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhi, Salmonella paratyphi A, Salmonella paratyphi B, Staphylococcus aureus, Coagulase negative staphylococci* at 400 µg/mL. It was also observed that the compounds have inhibitory effect on pathogenic fungi *Aspergillus niger, Microsporum gypseum, Rhizopus spp. and Aspergillus fumigatus* at a concentration of 166 µg/mL.

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