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Preparation of 3-(2-amino-thiazol-4-yl)-chromen-2-one and its derivatives.

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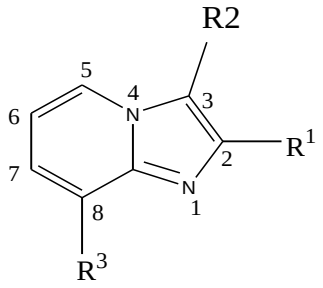
ABSTRACT
Thiourea product (5) is treted with the corresponding α-halo carbonyl compounds (Phenyl bromide, Phanacolone bromide and chloroacetone), Obtained.. a)Syntesis of 3-(6- Phenylimadazo[2.1-b] thiazol-3-yl)-chromen-2one.b) Synthesis of 3-(6-Tert-butyl imadazo[2,1-b] thiazol-3-yl- chromen-2 one AND c) Synthesis of 3-(6-Methyl imadazo[2,1-b] thiazol-3-yl- chromen-2 one.

KEYWORDS:
Thiazoles,imadazoles,Thiourea,chromens, Phenyl bromide, Phenacolone bromide and chloroacetone

I. INTRODUCTION:

Bradykinin(BK) is an endogenous Nona peptide produced by tissue and plasmakallikreins from kininogens in the course of inflammatory responses. It displays potent and diverse biological activities, such as relaxation of venular smooth muscle,contraction of smooth muscle of airway,plasmaextravasation,stimulation of sensory neurons,alteration of ion secretion of epithelial cells and release of nitric oxide,prostaglandins,leukotrienes,and cytokines. On the basis of these strong proinflammatoryproperties,BK is believed to play important roles in a variety of inflammatory diseases including asthma,rhinitis,pancreatities,sepsis,rheumatoidarthritis,brain edema and angioneuroticedema.BK has at least two sub types of specific G protein coupled cell surface receptors designated as B1 and B2 , Both of which have been identified by molecular cloning and pharmacological means. B2 receptors are expressed constitutively in many tissues and are thought mediate most of the biological actions of BK.



A number of peptide B2 antagonists have been synthesized, and the representative ‘’second-generation’’ antagonists, icatibant and broadycor are in clinical trials.Although they have very strong affinity for B2 receptors and longer duration of acton in vivo than the ‘’ first-generation’’ peptide antagonists their therapeutic use is still limited becapse of their poor oral bio bioavailability.recently some non-peptideB2 antagonists have been reported, but they are much less potent than peptide antagonists and unsatisfactory with regard to selectivity and (or)oral bioavailability.

II. OBJECTVES AND RESULTS OF PRESENT WORK

The Chemistry of heterocyclic compounds of Thiazoles and imadazoles is challinging, at the same time important field for study. Each year witnesses the growing inclusion of many thousands of heterocyclic compounds,inlitrtature,both on account of their intrinsic chemical interest and on the basis of therapeutic biological and Industrial potential. The routes adopted for the synthesis of these new entrants to this large family very from time honored methods and variations of old thems to entirely Novel procedures

It is thus observed that a variety of heterocycles containing oxygen,Sulphur and Nitrogen have revealed important biological action.Many of this heterocycles in the earlier years have laid firm foundation for the development of

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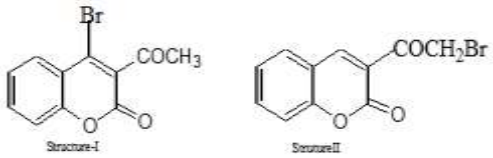
medicinal chemistry. The earlier concept the structure activity relationship, chemical and biological forms of active molecules and other consideration such as the lead from the natural products were the strengthening guidelines of a medicinal chemistry, In the development of new molecules during last two decades (or) so, mush emphasis on the biological feed back particularly mechanism or mode of action of the drugs, metabolism and excretion have taken a great prominence and development of new molecules.

A number of benzoxazins were found to exhibit wide range of pharmalogical Activities like coronary vasodilatorytranquilizing,bactericidal, sedative, diuretic,CNS depressant blood pressure depressant and non hypnotic activities. Hence they were claimed as potential biological active compounds. Even though large number of benzoxazins were synthesized and screened for variety of pharmological activities none of them appears to have been tested for their anti-inflammatory activity. hence it is felt the title compounds,if tested for anti inflammatory activity may show good result during routine analgesic and anti inflammatory screening the title compounds,showed some activity in anti-inflammatory tests, so a programme of structural modification in the N-propinoicbenzoxazin was under taken in the present investigation.

When 3-acetocoumarin is treated with bromine, there is obtained a monobromo derivative to which structure I has been assigned. Such a derivative would be a useful intermediate in synthesis of compounds related to morphine. But the evidence for structure 1,formation of an unstable addition compound during the bromination,and formation of salicylic acid when the bromo compound is fused with alkali, does not exclude structure II.a study of the behaviour of the substance toward thio urea now indicates that structure II is correct.



Of the compounds corresponding to structures I and II, only the latter could yield a diazole with thiourea, and ,and degradation shows that a thiazole,III,is formed with this reagent.

When the thiourea product is treted with the corresponding α-halo carbonyl compounds (Phenyl bromide, Phanacolone bromide and chloroacetone), Obtained…

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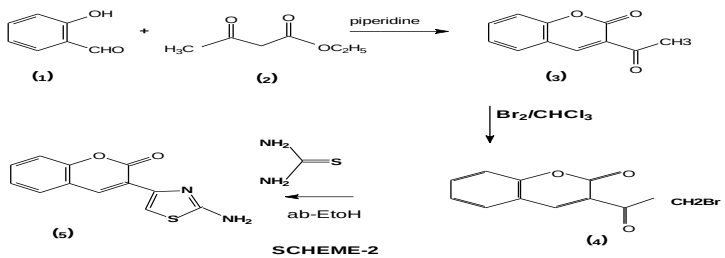
a)Syntesis of 3-(6- Phenylimadazo[2.1-b] thiazol-3-yl)-chromen-2one.

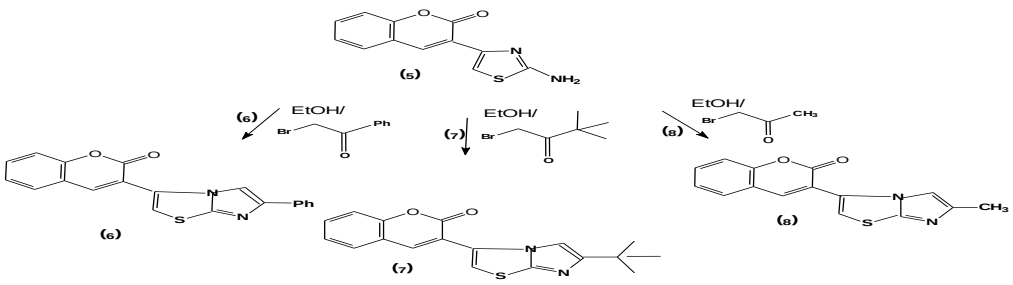
b) Synthesis of 3-(6-Tert-butyl imadazo[2,1-b] thiazol-3-yl- chromen-2 one AND

c) Synthesis of 3-(6-Methyl imadazo[2,1-b] thiazol-3-yl- chromen-2 one.

SCHEME-1



SCHEME-2



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III. EXPERIMENTAL

Preparation of 3-acetyl chromen-2-one (3):

Salicylaldehyde (12.2g, 0.10mole), ethyl aceto acetate (13.0g, 0.10 mole) were added together in a clean conical flask, followed by the addition of 1.0g of piperidine and allowed to stay for 15-20 minutes , light yellow coloured solid was formed gradually, formed solid was filtered and washed with ethanol .Crude product was recrystallised by ethanol to get the 3-acetyl chromen-2-one as pale yellow crystals m.p. 119-122 °,^{1}H-NMR(CDCl3) : δ 2.65(s, 3H,), 7.5(m,4H), 8.45(s, H).

MS: m/z : (188+.,60.8 %) , (173,100%), (145,10.20%), (118,10.5%), (101,11.0%), (89,30.9%), (63,28.0%), (43,58.5%).

IR (KBr) :λmax1723 (O-C=O), 1686(C=O).

Preparation of 3-(2-bromo-acetyl)-chromen-2-one (4):

3-acetyl chromen-2-one (1.88g , 0.01 mole) was added to 30ml chloroform in a clean two necked RB-flask to it (2.55g) bromine (0.01mole, 3 % excess) dissolved in 30 ml chloroform was added slowly using a droping funnel with refluxion under 70°C temp for 3 hrs. Reaction mixture was then allowed to concentrate, crude 3-(2-bromo-acetyl)-chromen-2-one, is recrystallised with ethanol.

m.p 163-165°. H1-NMR(CDCl3) : δ 4.7(s,2H) , 7.5(m, 4H), 8.71(s, H).

MS-m/z : (266+.,1.1%), (187,74%), (173,100%), (115,100%), (115,6%), (101,13.1%), (89,50%), (63,35%), (39,14%).

IR-(KBr) :λmax 1733(O-C=O), 1686 (C=O).

Preparation of 3-(2-amino-thiazol-4-yl)-chromen-2-one (5):

When a suspension of 2.7g. of II in 15 ml. of hot alcohol was treated with 1.6g. ofThioUrea,a smooth exothermic reaction took place,giving a clear solution that soon deposited crystals. The deposit was removed,washed with alcohol,and then boiled with water containing sodium acetate.This furnished 2.2 g. of bright yellow needles, m.p 220-225^{o} C; crystallization from 200ml of alcohol gave a pure product,m.p 225-227^{0} C.^{1}H-NMR(CDCl3) : δ 3.1(s- 2H) , 7.65(m, 4H) , 8.85(s,1H),MS-m/z :(244+.,100.0%), (211,12.85%), (174,14.57%), (145,13.57%), (102,14.85%),IR-(KBr) : λmax 1721(O-C=O), 1628 (C=O).

Typical procedure

A) Syntesis of 3-(6- Phenylimadazo[2.1-b] thiazol-3-yl)-chromen-2oneS(6):

A mixture of 3-(2-amino thiazol-4-yl)-chromen-2-one (5, 0.1 g, m moles) and 2-bromoacetophenone (0.15g, m moles) in absolute ethanol (20mL) was reflxed for 24h. After cooling the reaction mixture was concentrated in vacume and the residue was dissolved in water (100mL) neutralized with saturated sodium carbonate and extracted with Ethyl acetate(3 times) the EtoAclayer was dried over Na2So4 and evaporated in vacuo.The residue was purified by column chromatography using EtOAc:Hexane(90:10) as elunt,obtained as pale yellow solid,m.p :222-225 0C,1H-NMR (DMSO-D_6) : δ 7.01-7.98 (m,11 H, Ar-H), 8.42(s,1H,Coumarin-H_3).

B) Synthesis of 3-(6-Tert-butyl imadazo[2,1-b] thiazol-3-yl- chromen-2 one(7):

A mixture of 3-(2-amino thiazol-4-yl)-chromen-2-one (5,0.1 g,…..m moles) and 1-bromo Pinacolone (0.15g,…..m moles) in absolute ethanol(20 ml) was reflxed for 24h. After cooling the reaction mixture was concentrated in vacume and the residue was dissolved in water(100ml) neutralized with saturated sodium carbonate and extracted with Ethyl acetate(3 times) the EtoAclayer was dried over Na2So4 and evaporated in vacuo.The residue was purified by column chromatography using EtOAc:Hexane(90:10) as elunt,obtained as pale yellow solid,m.p : 196-198 0 C, Yield-20%, ^{1}H-NMR(DMSO-D_6) : δ 1.22 (s,9H,t-butyl), 7.45-7.95 (m, 6H,Ar-H), 8.40(s,1H, Coumarin-H)

C) Synthesis of 3-(6-Methyl imadazo[2,1-b] thiazol-3-yl- chromen-2 one (8):

A mixture of 3-(2-amino thiazol-4-yl)-chromen-2-one (5,0.1 g,…..m moles) and 2- chloro acetone (0.15g,…..m moles) in absolute ethanol(20 ml) was reflxed for 24h. After cooling the reaction mixture was concentrated in vacume and the residue was dissolved in water(100ml) neutralized with saturated sodium carbonate and extracted with Ethyl acetate(3 times) the EtoAclayer was dried over Na2So4 and evaporated in vacuo.The residue was purified by column chromatography using EtOAc:Hexane(90:10) as elunt,obtained as pale yellow solid, Yield-18% Melting point-182-1850C, ^{1}H-NMR(DMSO-D_6) : δ 2.20 (D,3h,-CH3), 7.20-7.75 (M,6h,Ar-H), 8.65 (s,1H, Coumarin-H).

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