SYNTHESIS OF SOME NITROGEN HETEROCYCLIC COMPOUNDS OF EXPECTED BIOLOGICAL ACTIVITY

A THESIS IN PARTIAL FULFILMENT OF THE REQUIREMENTS OF
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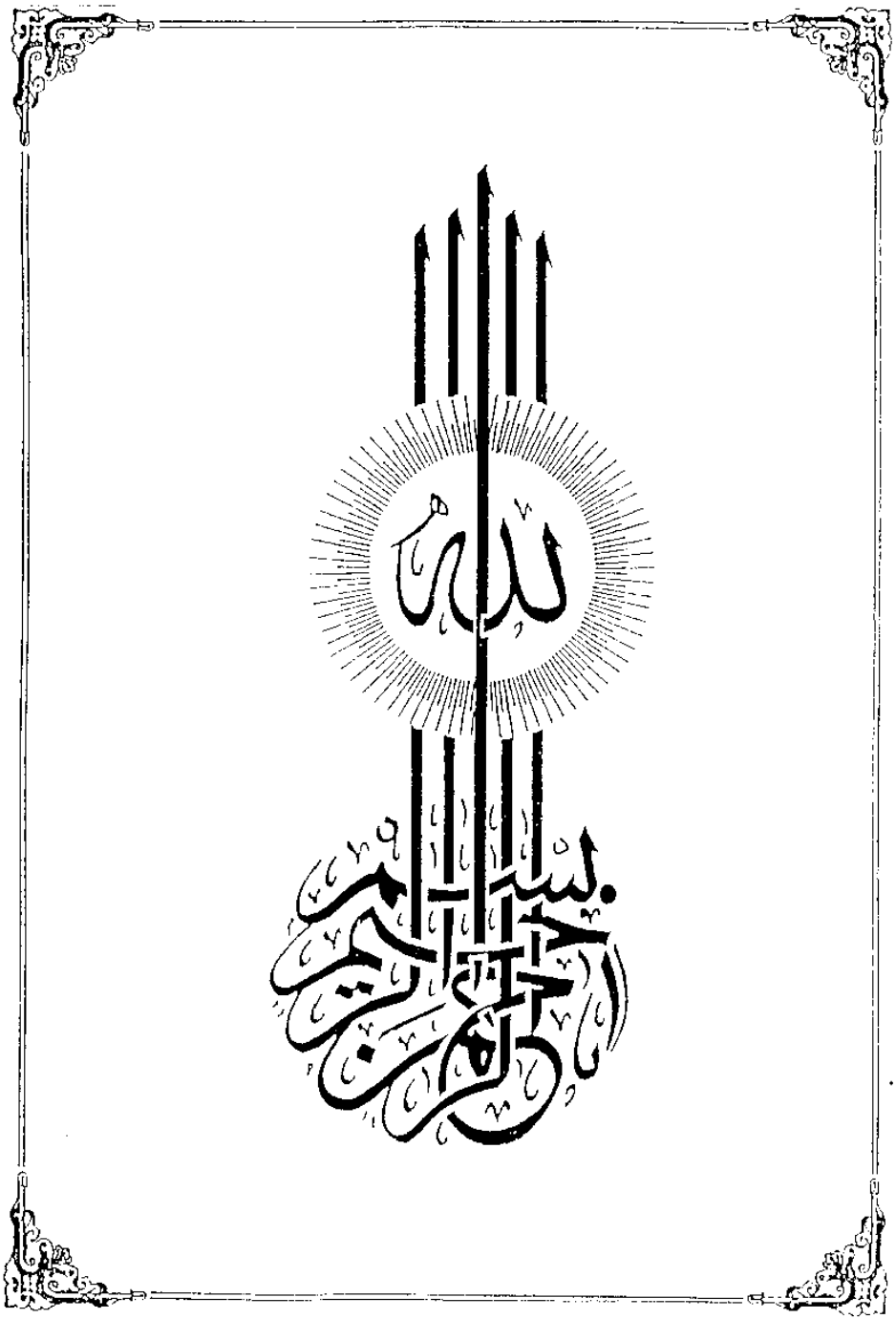

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SUMMARY

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PART I

Some Reactions with 2-Substituted 4(H)-3,1-benzoxazin-4-one

Bis-2,2-[3,1-benzoxazine-4-one]phenylene(-m) (**1**) has been recently prepared as a starting material for polymers syntheses.

In this study, some other reactions have been carried out with the benzoxazin-4-one derivative **1** with the aim of synthesis of some derivatives to test their biological activity.

Bis-2,2-[3,1-benzoxazin-4-one]phenylene(-m) (**1**) has been obtained in good yield by the reaction of anthranilic acid with isophthaloyl chloride in pyridine as solvent and as catalyst. The anilide produced was cyclized using acetic anhydride.

The benzoxazin-4-one under investigation **1** was subjected to aminolysis with primary amines, as well as, secondary amines providing the expected isophthalamides (**2a-g**). Reaction of **1** with carbon nucleophiles such as ethyl acetoacetate, diethyl malonate and /or ethyl cyanoacetate, gave bis-N,N'[2,2-benzoylacetic]isophthalamide (**3**).

The Hydrazide **2d**, produced from treatment of **1** with hydrazine hydrate was subjected to varieties of chemical

reactions, such as :

(i) under the influence of acetyl chloride **2d** gave the corresponding acetylated derivative **2h** beside slight amount of its cyclized quinazolinone derivative **9b**.

(ii) Catalytic condensation of **2d** with p-anisaldehyde gave the expected schiff's base **2i**, beside a small amount of the corresponding quinazolinone derivative **9c**.

(iii) When the hydrazide **2d** was reacted with carbon disulphide, N,N'-bis-[2,2-(1',3',4'-oxadiazo-2'-thion-5'-yl)phenyl]isophthalamide (**4**) was obtained in a satisfactory yield.

(iv) Treatment of the hydrazide **2d** with KSCN in hydrochloric acid gave the corresponding thiosemicarbazide **5**, while fusion of the hydrazide **2d** with ammonium thiocyanate yielded. N,N'-bis-[2,2-(1',3',4'-triazol-2'-thion-5'yl) phenyl]isophthalamide (**6**).

The synthesis of the pyrazoles **7** and **8** was achieved. by the condensation of the hydrazide **2d** with the electrophilic reagents; acetylacetone and/or ethyl acetoacetate respectively.

PART II

Synthesis and Reactions of Bis(quinazolin-4-one-2-yl) Phenylene (-m) and Its 3-N-Substituted Derivatives (9)a-e

Bis[3-Aminoquinazolin-4-one-2-yl]phenylene(-m) (**9**)**a** was prepared either by conducting hydrazinolysis of **1** in

refluxed n-butanol or refluxing the hydrazide **2d** with n-butanol. The suggested structure for **9a** was supported by its acetylation to the 3-N-acetyl derivative **9b** and its base catalytic condensation with p-anisaldehyde to the corresponding schiff's base **9c** Bis[quinazolin-4-one-2-yl]phenylene(-m) **(9)d** was obtained in a good yield, via ammonolysis of **1** by its fusion with ammonium acetate. The structure of **9d** was established by its conversion to the 3-N-acetyl quinazoline derivative **9e** with acetyl chloride.

Moreover, the quinazolin-4-one derivative **9d** was converted to the corresponding 4-thione derivative **11** (PART III), and to the corresponding 4-chloro-derivative **10** (PART IV).

PART III

Synthesis and Reactions of Bis[4-thionoquin-azolin-2-yl]phenylene(-m)(11)

The hitherto unknown Bis[4-thionoquinazolin-2-yl]phenylene(-m) **(11)** has been prepared via four different methods:

(i) Refluxing the quinazoline-4-one **9d** with phosphorous pentasulphide in xylene.

(ii) Refluxing **9d** with Lawesson's reagent.

(iii) Reaction of **9d** with N, N'-dimethylcarbamoyl chloride and DABCO (1,4-Diazobicyclo[2,2,2]octane) at room temperat-

ure followed by hydrolysis.

(iv) Treatment of the 4-chloroquinazoline derivative **10** with thiourea.

The structure of **11** was based on analytical as well as spectral data. Furthermore, **11** can be alkylated or acylated into the corresponding 4-S-substituted derivatives (**13a-d**). The 4-thionoquinazoline **11** was found to respond to desulphurization on treatment with either p-chloroaniline to give the corresponding 4-(p-chlorophenylimine) **14**, or by benzoyl hydrazine to give the corresponding hydrazone which undergoes simultaneous cyclization to give the triazoloquinazoline derivative **15a**.

PART IV

Synthsis and Reactions of Bis-[4-chloroquinazolin-2-yl]phenylene(-m)

Bis-[4-chloroquinazolin-2-yl]phenylene(-m) (**10**) has been prepared by the action of a mixture of phosphorous pentachloride and phosphorous oxychloride on the bis [quinazolin-4-one-2-yl] phenylene(-m) (**9**)**d**.

As mentioned before **10** has been converted into the corresponding 4-thionoquinazoline derivative **11**. The structure suggested for **10** was confirmed by a series of chemical reactions. The 4-chloroquinazoline derivative **10** reacts with acidic sodium azide to produce the tetrazolo-

quinazoline derivative **16** , and with semicarbazide to give the amino triazoloquinazoline derivative **17** . Also **10** undergoes nucleophilic reaction with hydrazine hydrate to afford 4-hydrazinoquinazoline derivative **18** whose structure was confirmed by some chemical evidence (PART V).

PART V

Synthesis and Reactions of Bis[4-hydrazinoquinazolin-2-yl]phenylene(-m)

Bis[4-hydrazinoquinazolin-2-yl]phenylene(-m) **(18)** has ben prepared as mentioned before in part IV. The structure proposed for **18** was confirmed by micro-analysis, as well as, spectroscopic analyses. Moreover, some chemical evidence support the assigned structure:

(i) Treatment of **18** with nitrous acid gave the tetrazolo-qunizaoline derivative **16** .

(ii) When **18** was subjected to react with glacial acetic acid, the triazoloquinazoline derivative **19** was obtained.

(iii) Carbon disulphide was found to react with **18** to give the triazoloquinazoline-thione derivative **20** .

(iv) Condensation of **18** with aromatic aldehyde produced the schiff's base **21** which underwent cyclization under the influence of Br_2/Acetic acid to give the triazoloquinazoline derivatives **(15 a and b)** which was previously isolated from

the reaction of the 4-thionoquinazoline derivative **11** with benzoyl hydrazine (part III).

The structures of all represented compounds were confirmed by correct elemental analyses, IR, mass and ^1H-NMR spectral data.

PART VI

Biological Activity

Twenty two compounds were tested against both Gram-positive, Gram-negative and yeast. Among them, four only exhibited antimicrobial activity (Table 7).

PART VII

γ-Irradiation of Some Produced Compounds

Four compounds (2c,2i,9d and 21b) were irradiated by Gamma-rays and the ultraviolet measurements for these four compounds before and after irradiation were discussed. From these results, it was observed that all absorption bands for each of the different irradiated compounds showed the highest absorptivity values at a particular irradiation integral dose.

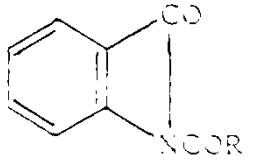
Moreover, it was found that the quinazolin-4-one derivative **9d** required the highest irradiation integral dose to undergo decomposition.

INTRODUCTION

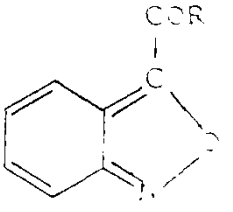
SYNTHESIS AND REACTIONS OF SOME NEW HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN

General Introduction of 3,1-(4H)-benzoxazinones

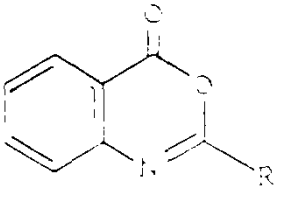
4-Keto-3,1,4-benzoxazines comprise a relatively large group of substances which have come to be known as acyl-anthranils. This name was given to the compounds when it was believed that they were represented by structures (A) or (B). However, the preponderance of evidence now favours a 3,1,4-benzoxazone structure (I).



(A)



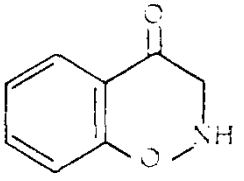
(B)



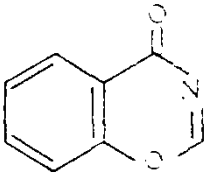
(I)

Nomenclature of benzoxazinone compounds

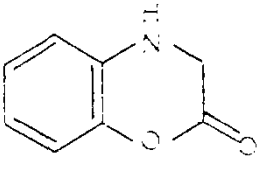
Benzoxazinones are of six possible isomeric types as shown in the following :



1,2-Benzoxazin-4-one



1,3-Benzoxazin-4-one



1,4-Benzoxazin-2-one