CHAPTER THREE

SCOPE, EXPERIMENTAL WORK AND GENERAL REMARKS

CHAPTER III

A: Scope of the Present Work

B: Experimental Work and General Remarks

Part I

Synthesis of 6-chloro-4(hydrazido)-3,4-dihydro-2H-1,4-benzoxazin-3-one.

Part II

i) Synthesis of 6-chloro-4(nicotinoyl hydrazido)-3,4-dihydro-2H-1,4-benzoxazin-3-one.

ii) Synthesis of 6-chloro-4(5'-phenyl-1',3',4' oxadiazolyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one.

(A) Scope of Present Work

Due to commendable pharmaceutical importance, the work on the synthesis of some derivatives of 1,4-benzoxazin-3-one has been undertaken. The present compound which we intended to synthesize is 4-substituted hydrazide derivative of 1,4-benzoxazin-3-one. The oxadizole and nicotinoyl hydrazido derivatives of 1,4-benzoxazin-3-one are also synthesised, which are expected to show high biological activities.

The novel route of synthesis of 1,4-benzoxazin-3-one is adopted which gives better yield of the products.

(B) Experimental Work and General Remarks

The experimental work was divided into two parts. Part-I consists of synthesis of 6-chloro-4(hydrazido)-3,4-dihydro-2H-1,4-benzoxazin-3-one from 2,4-dichloro phenoxy acetic acid (Scheme-I).

Part-II includes synthesis of two derivatives of 6-chloro-4-substituted-3,4-dihydro-2H-1,4-benzoxazin-3-one with oxadiazole and nicotinate moieties

(Scheme-II).

Yield percentage, physical constants (m.p./b.p.), elemental analysis (required and found) and spectral characteristics of the derivatives have been reported.

General Remarks

i) m.p./b.p. were determined by open-capillary method and are uncorrected.

ii) N.M.R. spectra were recorded on "Perkin-Elmer Varian-90" using T.M.S. as an internal reference, using CCl_4, $CHCl_3$ or $CDCl_3$, CH_3COCH_3 solvents. The chemical shifts (δ-values) are reported in ppm.

iii) I.R. spectrum was recorded on "Beckman-20" instrument in KBr pellet. The values are reported in Cm^{-1}.

iv) The purity of the compounds were checked by T.L.C. using Silica-gel as adsorbent.

v) UV-spectrum was recorded on Beckman DK.1 spectrophotometer in 95% ethanol.

Part-I

Synthesis of 6-chloro-4(hydrazido)-3,4-dihydro-2H-1,4-benzoxazin-3-one

The synthesis is reported in four steps:

Step I : Synthesis of 2-4-dichloro phenoxy-acetamide.

Step II : Synthesis of 6-chloro-3,4-dihydro-2H-1,4-benzoxazin-3-one.

Step III : Synthesis of 6-chloro-4(carbethoxy)-3,4-dihydro-2H-1,4-benzoxazin-3-one.

Step IV : Synthesis of 6-chloro-4(hydrazido)-3-4-dihydro-2H-1,4-benzoxazin-3-one.

I: Synthesis of 2,4-dichloro phenoxy-acetamide

This compound was prepared from 2,4-dichloro phenoxy acetic acid by a method given by Vogel*

A mixture of 10 gm (0.045 mole) of the finely powdered 2,4-dichloro phenoxy acetic acid and 50 ml of redistilled thionyl chloride was taken in a 500 ml clean and dry distilling flask, fitted with a vertical condenser and a guard-tube. The mixture was refluxed for 30 minutes. The excess of thionyl chloride was distilled off under vacuum to obtain 2,4-dichloro phenoxy-acetyl chloride. The acid chloride was carefully treated with 20 ml of concentrated ammonia solution (sp. gr. 0.88). The excess of ammonia was removed by heating to dryness. The white residue obtained was recrystallized from dilute alcohol.

Yield: 8.0 gm .... (80.40 %).

m.p.: 188°

%	C	H	N
Found	43.61	3.17	6.35
Required	43.63	3.18	6.36

For $C_8H_7O_2NCl_2$

(Mol. wt. = 220)

*A.I. Vogel, "Practical Organic Chemistry including qualitative analysis, 361 (1971).

II: Synthesis of 6-chloro-3,4-dihydro-2H-1,4-benzoxazin-3-one

A mixture of 9.0 gm (0.041 mole) of 2,4-dichlorophenoxy-acetamide (prepared in 1st step) and 1.5 ml of triethylamine in 30 ml of dry methanol was taken in a 500 ml clean and dry round-bottom flask, fitted with a condenser and a guard-tube. The mixture was refluxed at 110° on an oil-bath for about 5 hours, cooled and the solvent was removed under reduced pressure. The residue obtained was extracted with an ether and concentrated. The solid obtained was recrystallized from boiling ethanol.

Yield: 6.0 gm .... (80.00%)

m.p.: 138°

%	C	H	N
Found	52.25	3.22	7.56
Required	52.31	3.26	7.63

For $C_8H_6O_2NCl$

(Mol. wt. 183.5)

III: Synthesis of 6-chloro-4(carbethoxy)-3,4-dihydro-2H-1,4-benzoxazin-3-one

A mixture of 3.5 gm (0.019 mole) of 6-chloro-3,4-dihydro-2H-1,4-benzoxazin-3-one (prepared in 2nd step), 9.0 ml of chloroethyl formate and 1.5 ml of triethylamine in 10 ml of dry methanol was taken in a 500 ml clean and dry round-bottom flask, fitted with a condenser and a guard-tube. The mixture was refluxed at 90° on an oil-bath for 10 hrs. The mixture was cooled and neutralized by dilute hydrochloric acid (Tested with Congo red paper). Then extracted with an ether. The etheral solution on evaporation on a water-bath gave a heavy liquid which was purified by distillation.

Yield: 3.0 gm .... (60.61%).

b.p.: 294°

%	C	H	N
Found	51.65	3.85	5.45
Required	51.66	3.91	5.48

For $C_{11}H_{10}O_4NCl$

(Mol. wt. = 255.5)

IV Synthesis of 6-chloro-4(hydrazido)-3,4-dihydro-2H-1,4-benzoxazin-3-one

General Method*

The hydrazides were prepared by refluxing equimolecular mixture of corresponding methyl ester of an acid and hydrazine hydrate (80%), on water-bath till the disappearance of separation of layers took place. On cooling white fine needle-shaped crystals were separated which were recrystallized from slightly warmed alcohol.

A mixture of 2.5 gm (0.009 mole) of 6-chloro-4(carbethoxy)-3,4-dihydro-2H-1,4-benzoxazin-3-one (prepared in 3rd step) and 2 ml of hydrazine hydrate (80%) in 10 ml of dry ethanol was taken in a 250 ml round bottom flask fitted with water condenser and heated it on a water-bath at 80^{o} for about 10-15 minutes.

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*Smith P.A.S., "Organic Reactions", Vol. III, Ed. Roger Adam, John Wiley and Sons, Inc., New York, London, Sydney, p. 367 (1946).

On cooling white needle-shaped crystals were separated which were recrystallized from alcohol.

Yield: 1.8 gm .... (76.27%)

m.p.: 153°

%	C	H	N
Found	44.65	3.30	17.37
Required	44.72	3.31	17.40

For $C_9H_8O_3N_3Cl$

(Mol. wt. = 241.5)

Part-II

General

Substituted diacylated hydrazines can be used as starting materials for the synthesis of a wide variety of heterocyclic compounds containing nitrogen atoms.*

(i) Synthesis of 6-chloro-4(nicotinoyl hydrazido) -3,4-dihydro-2H-1,4-benzoxazin-3-one

A mixture of 6-chloro-4(hydrazido)-3,4-dihydro-2H-1,4-benzoxazin-3-one 0.1 gm (0.0004 mole) (prepared in 4th step Part I) and methyl nicotinate 0.5 gm in 10 ml of acetone was taken in a clean and dry round-bottom flask fitted with a condenser and a guard-tube. The mixture was refluxed on a water bath for about 5 hours in presence of 0.1 ml of H_2SO_4. The mixture was cooled and solvent removed under pressure. The residue obtained was recrystallized from ethanol.

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*R. Stolle, J. Pract. Chem., 73, 277 (1906).

Yield: 0.110 gm .... (76.92%)

m.p. = 195°

%	C	H	N
Found	51.92	3.16	16.14
Required	51.95	3.17	16.16

For $C_{15}H_{11}O_4N_4Cl$

(Mol. wt. = 346.5)

(ii) Synthesis of 6-chloro-4(5'phenyl,1',3',4'-oxadiazolyl)-3,4-dihydro-2H-1,4-benzoxazin-3-one

A mixture of 6-chloro-4(hydrazido)-3,4-dihydro-2H-1,4-benzoxazin-3-one 0.5 gm (0.002 mole) (prepared in 4th step Part I) and 0.5 gm of benzoyl chloride in 2 ml of pyridine was stirred for about 10 minutes. A white solid separated out on cooling in ice was extracted with an ether and concentrated to get viscous mass, which on further treatment with 0.5 ml of concentrated H_2SO_4 gave white solid. On further extraction in xylene and removal of a solvent under reduced pressure gave a white residue, which was recrystallized from xylene.

Yield: 0.400 gm .... (59.0%)

m.p.: 106°

%	C	H	N
Found	58.60	3.03	12.81
Required	58.63	3.05	12.82

For $C_{16}H_{10}O_3N_3Cl$

(Mol. wt. = 327.5)