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AN INVESTIGATION LEADING TO THE SYNTHESIS, CHARACTERIZATION AND MECHANISTIC DETAILS OF 2-[(6-METHYL-2-ARYL-3, 4-DIPHENYL-2H-BENZO[E][1,2]THIAZIN-5-YL)METHYL]ISOINDOLIN-1,3-DIOXO-1,1-DIOXIDES

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***Abstract*— A mixture consisting of phthalimide and formaldehyde contained in water was heated to give 2-(hydroxymethyl) isoindolin-1,3-dione (N-methylol phthalimide) (I), which on reaction with p-toluenesulphonic acid in presence of conc. sulphuric acid furnished 3-[(1,3-dioxoisoindolin-2-yl)methyl]-4-methyl benzenesulphonic acid (II). Reaction of (II) with benzoin in the presence of conc. sulphuric acid yielded 2-[(6-methyl-3,4-diphenyl benzo[c][1,2] oxathiin-5-yl) methyl] isoindolin-1,3-dioxo-1,1-dioxide (III) which on reaction with a primary amine in pyridine gave the target compounds i.e. 2-[(6-methyl-2-aryl-3,4-diphenyl-2H-benzo[e][1,2] thiazin-5-yl) methyl] isoindolin-1,3-dioxo-1,1-dioxides (IV a-d) in the yields varying from 50 to 65%.**

***Index Terms*— Antihyperglycemic, Anti-convulsant, Anti-epileptic, Benzothiazine, N-methylol phthal- imide.**

I. INTRODUCTION

Benzothiazines have been reported to exhibit a wide range of pharmacological properties including antifungal, immunostimulating, anti-aldoso-reductase, anti-rheumatic, anti-allergic, vasorelaxant, anti-arrhythmic, anti-hypertensive, neuroprotective and cytotoxic activities1. Some 1,2-benzothiazines also show marked activity against Bacillus subtilis2. These valid observations prompted the author to undertake the synthesis of 2-[(6-methyl-2-aryl-3,4-diphenyl-2H-benzo[e][1,2]thiazin-5-yl)methyl]iso indolin-1,3-dioxo-1,1-dioxides.

II. EXPERIMENTAL DETAILS

The synthesis of benzothiazine derivatives involved the following synthetic steps-

1) 2-(Hydroxymethyl)-isoindolin-1,3-dione.
2) 3-[(1,3-Dioxoisoindolin-2-yl)methyl]-4-methylbenzene sulphonic acid.
3) 2-[(6-Methyl-3,4-diphenylbenzo[c][1,2] oxathiin-5-yl)methyl] isoindolin-1,3-dioxo-1,1-dioxide.
4) 2-[(6-Methyl-2-aryl-3,4-diphenyl-2H-benzo [e][1,2]thiazin-5-yl) methyl]-isoindolin-1,3-dioxo-1,1-dioxides.

2-(Hydroxymethyl)-isoindolin-1,3-dione(I)

A mixture of properly powdered phthalimide (isoindole-1,3-dione) **(0.0348 mole), 40%** formaldehyde solution **(2.60 ml)** and water **(17.50 ml)** was heated until a clear solution resulted. This operation required only five minutes after the boiling was attained. The product was removed by filtration, washed with ice water and air-dried. The yield of 2-hydroxy methyl-isoindolin-1,3-dione **(I)** was 5.94 gm **(96%)** and melted at **141^{0}C[3].** The white product was sufficiently pure for the further reaction. Recrystallization from ethanol did not improve the melting point. For a pure sample the following procedure was employed[4]. A solution obtained by warming 4.25 gm of 2-hydroxy-methyl-isoindole-1,3-dione in 15ml of pure pyridine was filtered and left to crystallize. The pyridine complex crystallized in long lustrous needles which were collected after cooling in ice-bath. On drying in vacuum over concentrated sulphuric acid, the crystals lost their lustre and came to constant weight after 24-hours. The dried product melted at **148-149^{0}C** and on recrystallization from acetone furnished pure 2-hydroxy-methyl-isoindolin-1,3-dione, **m.p. 149.5^0 C, yield, 75%.**

3-[(1,3-Dioxoisoindolin-2-yl)-methyl]-4-methylbenzene sulphonic acid (II)

A slightly modified Tscherniac procedure was followed for the synthesis of the titled compound. Thus, a mixture of 2-(hydroxymethyl)isoindolin-1,3-dione **(I)** and 4-methylbenzene sulphonic acid **(both taken 0.04 mole)** was dissolved in a solution of H_2SO_4 : CH_3COOH **(9:1) (50 ml)** by stirring vigorously with caution. While dissolving, the contents were occasionally cooled and subsequently stirred for one hour mechanically. The acidic solution of the contents was heated at **100^0C** for two hours. The hot solution was allowed to attain the room temperature and left under refrigeration overnight. Pouring the solution in ice-cold water with stirring resulted in the precipitation of a white solid which was allowed to settle down. It was filtered off and washed with cold water and dried under vacuum. Recrystallization from rectified sprit afforded a white crystalline mass which melted at **122-123^0C,** yield, **75%.**

IR (KBr) (ν max^{-1}): 1785.4, 1705.2 (imide C=O).

^{1}H NMR (DMSO-d_6) (δ ppm): 7.70-7.75(m,7H,ArH), 3.95(s, 2 H, N-CH_2), 2.25(s, 3H, ArCH_3).

Preparation of polyphosphoric acid (PPA)

Phosphorous pentoxide **(20g)** was dissolved in o-phosphoric acid (12 ml) by heating the mixture at 90^0c for 30 minutes at 90^0c. The clear syrup mixture was used for each experiment.

$$P_2O_5 + H_3PO_4 \xrightarrow{90^0C} \text{PPA (Thick syrup)}$$

2-[(6-Methyl-3,4-diphenylbenzo[c][1,2] oxathiin-5-yl)methyl]isoindolin-1,3-dioxo-1,1-dioxide (III)

3-[(1,3-Dioxoisoindolin-2-yl)-methyl]-4- methylbenzene sulphonic acid **(XVI)(0.02 mole)** and 2-hydroxy-1,2-diphenyl-ethanone (benzoin**) (0.02 mole)** were placed in freshly prepared polyphosphoric acid **(PPA)** and heated at **100^0C** for four hours . Subsequently, the resultant viscous liquid after cooling at room temperature, was left under refrigeration for twelve hours. It was poured into ice cold water **(100 ml.)** with stirring not in one installment but in several installments. The gelatinous precipitate was allowed to settle down and filtered off. It was washed with sodium bicarbonate solution **(10%)** in order to remove any unreacted sulphonic acid. Final washing was done with cold water and the crude compound thus obtained was dried at **100^0C** and recrystallization from ethanol afforded a brown crystalline mass which was found analytically pure. It melted at **180^0C-181^0C,** yield **66%.**

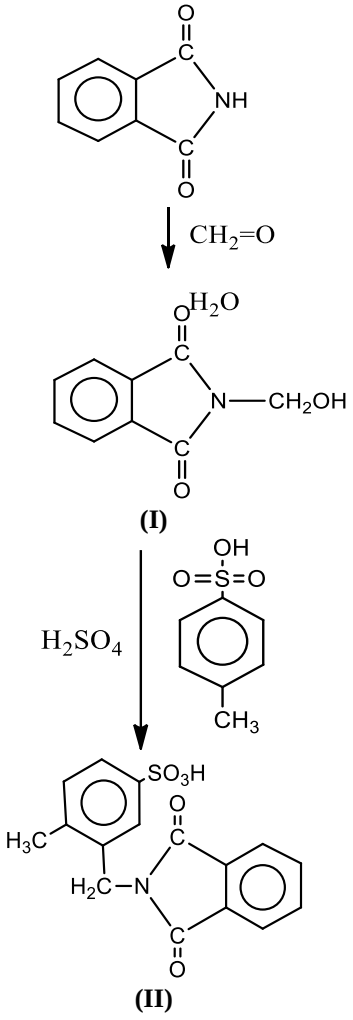
Anal. for $C_{30}H_{21}N_5O_2$; N, Calcd. 2.26, Found 2.55.

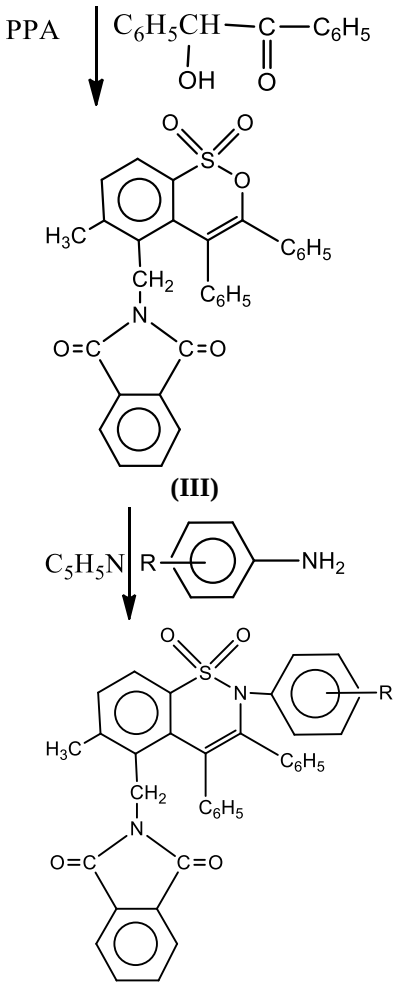
IR (KBr) (ν cm^{-1}): 1705.2 (tert. Amide C=O), 1374.5 (SO_2, symmetric), 1364.1 (SO_2 asymmetric).

^{1}H NMR (DMSO-d_6) (δ ppm) : 6.70-7.95 (m,15H, ArH), 2.20(s, 3H,ArCH_3), 4.30 (s, 2H, N-CH_2).

2-[(6-Methyl-2-aryl-3,4-diphenyl-2H-benzo[e][1,2]thiazin-5-yl)methyl]isoindolin-1,3-dioxo-1,1-dioxides (IV).

A mixture consisting of 2-[(6-methyl-3,4-diphenyl benzo[c][1,2]oxathiin-5-yl)methyl]-isoindolin-1,3-dioxo-1,1-dioxide **(0.01 mole)** and an aromatic primary amine **(0.01 mole)** was heated under reflux for six hours under anhydrous conditions of the reaction in dry pyridine **(50 ml).** The resultant solution was cooled at room temperature. After attaining the room temperature, the solution was allowed to cool under refrigeration overnight. Subsequently, it was poured into ice-cold water containing concentrated hydrochloric acid **(10 ml.)** Precipitation occurred which was allowed to be completed in about an hour. The solid mass was filtered off and washed with cold water till it was free from adhered pyridine i.e. there was no smell of pyridine. The crude compound thus obtained, was dried *in vacuo* and recrystallized from diluted ethanol.

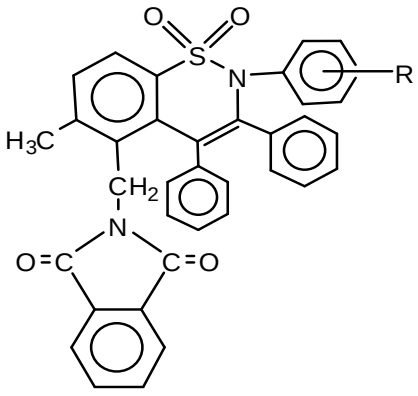




SCHEME

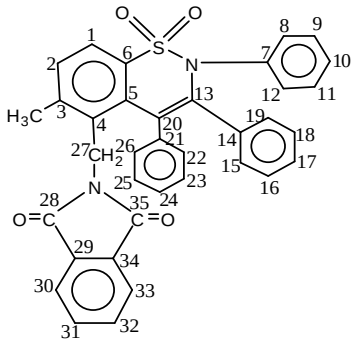
III. CHARACTERIZATION DATA

Characterization data of 2-[(6-Methyl-2-aryl-3,4-diphenyl-2H-benzo[e][1,2]thiazin-5-yl)methyl]-isoindolin-1,3-dioxo-1,1-dioxides**(IV a-d)**



Compd. No	R	m.p. (°C)	yield (%)	Colour	Molecular formula	Molecular weight	Analysis Nitrogen %	
							calculated	found
IV a.	H	150	60	brown	$C_{36}H_{26}N_2SO_4$	582	4.81	4.55
IV b.	4-OCH3	170-171	65	violet	$C_{37}H_{28}N_2SO_5$	612	4.57	4.52
IV C.	4-CH3	170	65	brown	$C_{37}H_{28}N_2SO_4$	596	4.69	4.88
IV d.	2-COOH	130	50	yellow	$C_{37}H_{26}N_2SO_6$	6.26	4.47	4.26

Characterization data of 2-[(6-methyl-2-phenyl-3,4- diphenyl-2H-benzo[e][1,2]thiazin-5-yl)methyl]-isoindolin1,3-dione(IV a)



IR(KBr) (ν cm^{-1}) :

1785.0, 1710.2 (inside coupled C=O vibrations) 1365.2 (SO2, asymmetric little affected) 1174.4 (SO2, symmetric by configuration) 2940.1 (C-H str. in CH3), 1365.2 (C-H def.) 3028.4 (=C-H str. in aromatics).

^{1}H NMR (DMSO-d$_6$) (δ ppm) : 6.65-7.90 (m, 21H,ArH), 4.25(s, 2H- N-CH2), 2.23(s, 3H, ArCH3).

^{13}C NMR (DMSO-d$_6$) (δ ppm) : 20.46 (C-36), 45.12 (C-27), 111.25, 112.12, 114.60, 115.27, 116.40, 117.58, 119.25, 123.60, 125.28, 127.31, 128.25, 129.60, 130.44, 131.50, 133.46, 134.57, 136.48, 139.27, 140.79, 141.25 (C-1 to C-6; C-7 to C-12, C-14 to C-19, C-21 to C-26, C-29 to C-34), 168.68 (C-28, C-35).

Important mass spectral peaks of 2-[(6-methyl2-phenyl-3,4-diphenyl-2H-benzo [e][1,2]thiazin-5-yl)methyl]-isoindolin-1,3-dione (IVa)

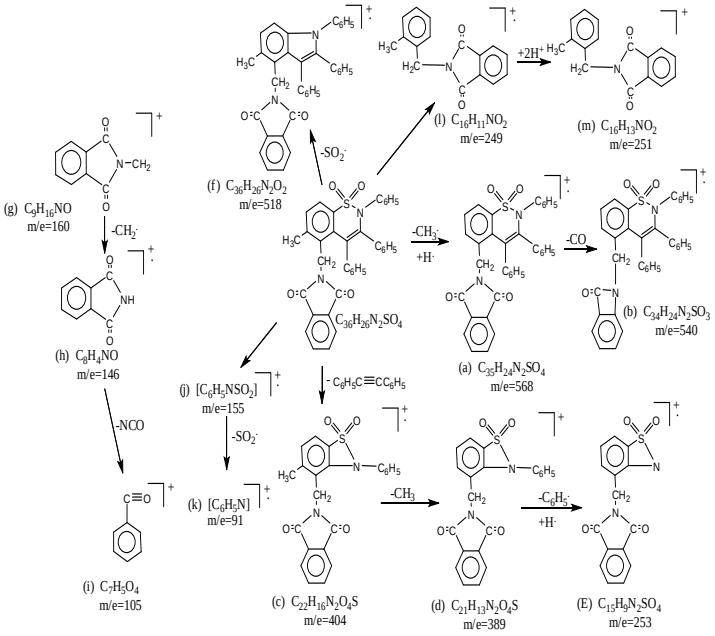
Fragment no.	Molecular formula	m/e
(a)	$C_{35}H_{24}N_2SO_4$	568
(b)	$C_{34}H_{24}N_2SO_3$	540
(c)	$C_{22}H_{16}N_2SO_4$	404
(d)	$C_{21}H_{13}N_2SO_4$	389
(e)	$C_{15}H_9N_2SO_4$	253
(f)	$C_{36}H_{26}N_2O_2$	518
(g)	$C_9H_6NO_2$	160
***(h)**	$C_8H_6NO_2$	146
(i)	C_7H_5O	105
(j)	$C_6H_5NSO_2$	155
(k)	C_6H_5N	91
(l)	$C_{16}H_{11}NO_2$	249
(m)	$C_{16}H_{13}NO_2$	251

M^+ was not observed

*** base peak**

Mass spectral pattern of2-[(6-methyl-2-phenyl -3,4-diphenyl-2H-benzo[e][1,2]thiazin-5-yl)methyl]-isoindolin-1,3-dione

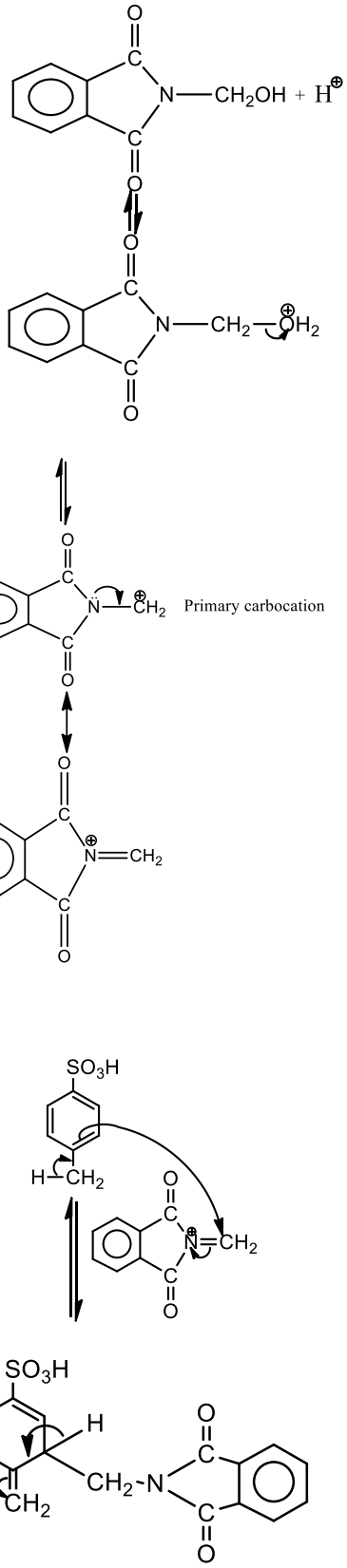
(IV a)



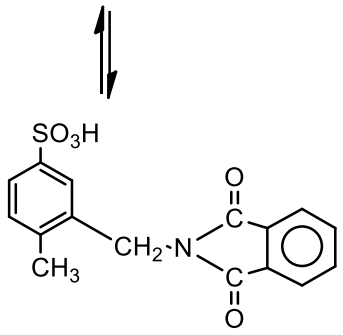
IV. MECHANISTIC DETAILS

Reaction of p-toluene sulphonic acid with N-(hydroxymethyl)-phthalimide both taken in equimolecular equivalents gives a C-imido-methylated product. The imidomethylation takes place at 2-position where electron density is highest as suggested here mechanistically.

(a)

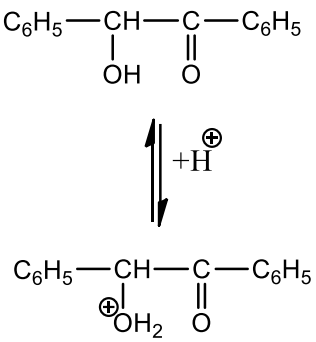


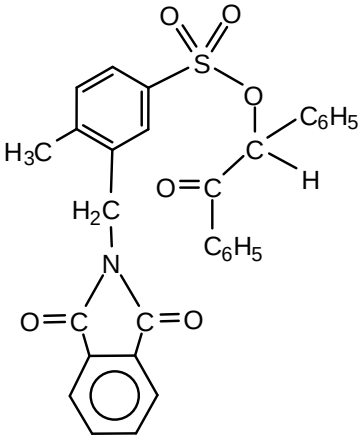
(b)

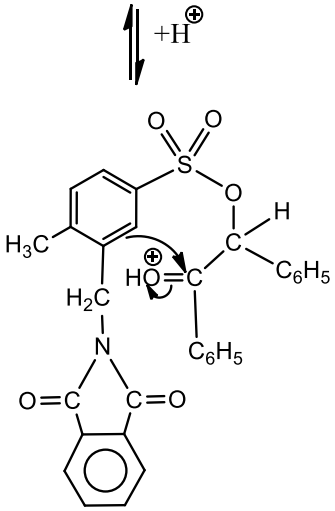


Reaction of **(II)** with benzoin gives a cyclized product most easily in the presence of polyphosphoric acid **(PPA).** This cyclisation may take place in the following manner:

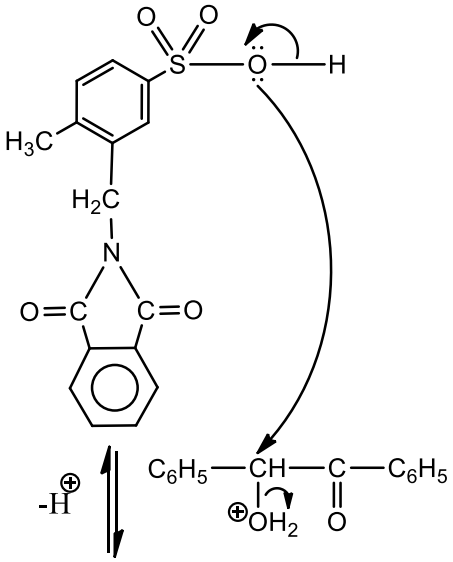
(a)

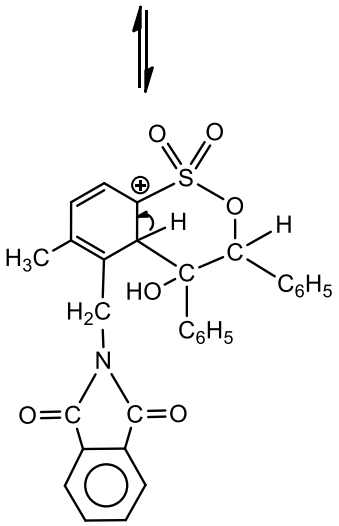


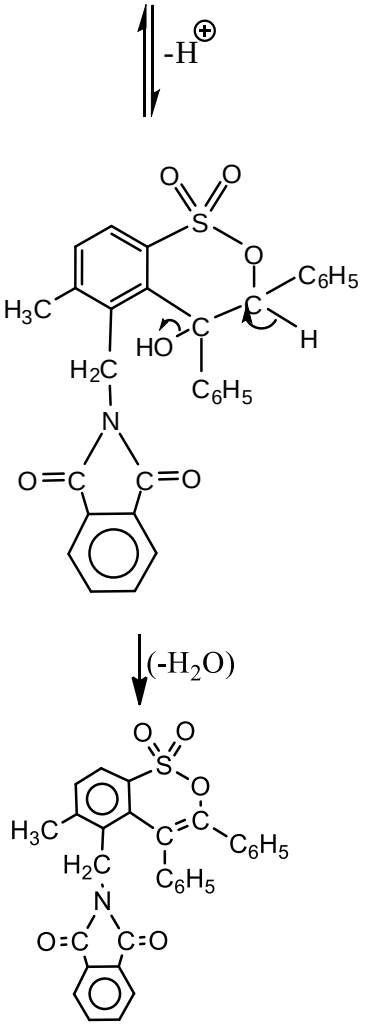


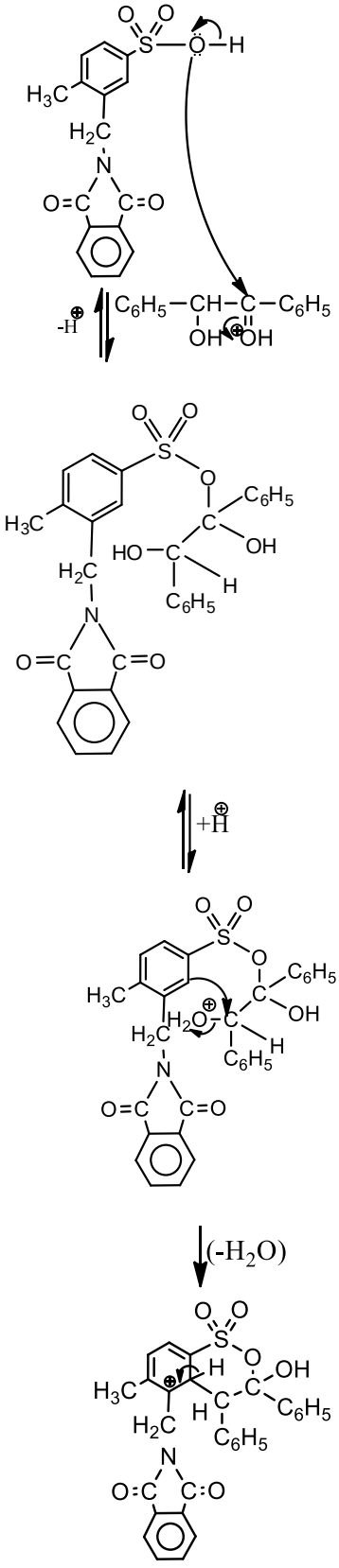


(b)



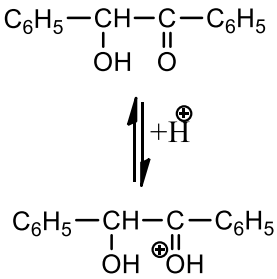




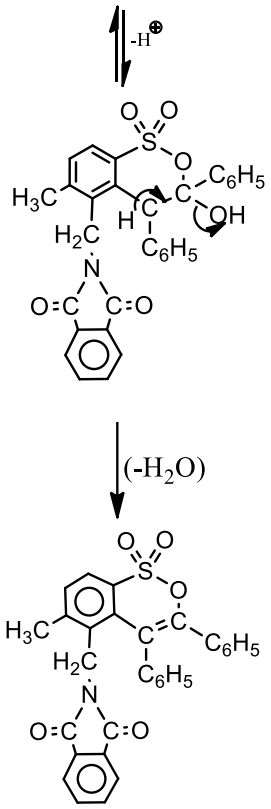


A second possibility is shown here:

(a)

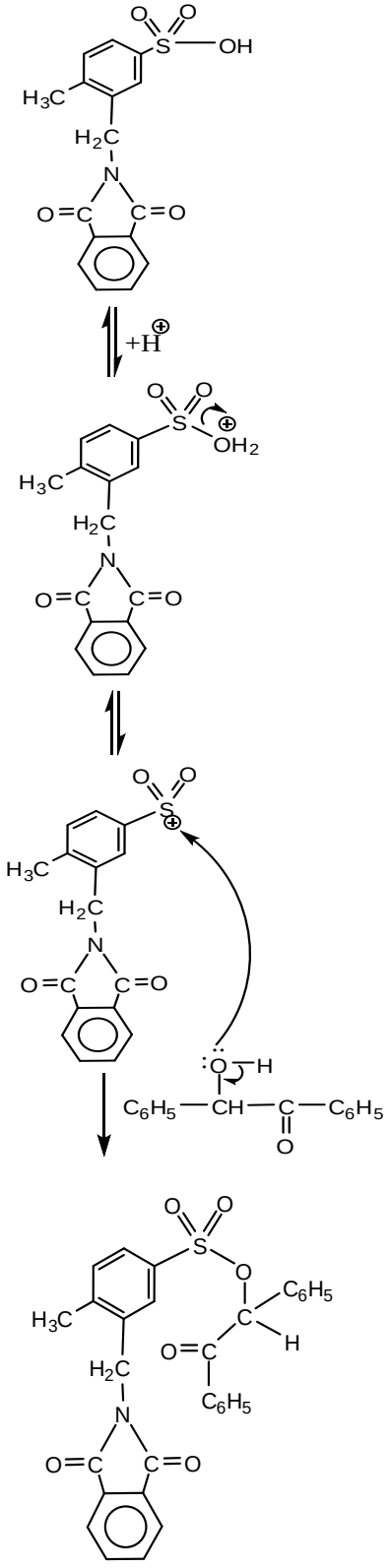


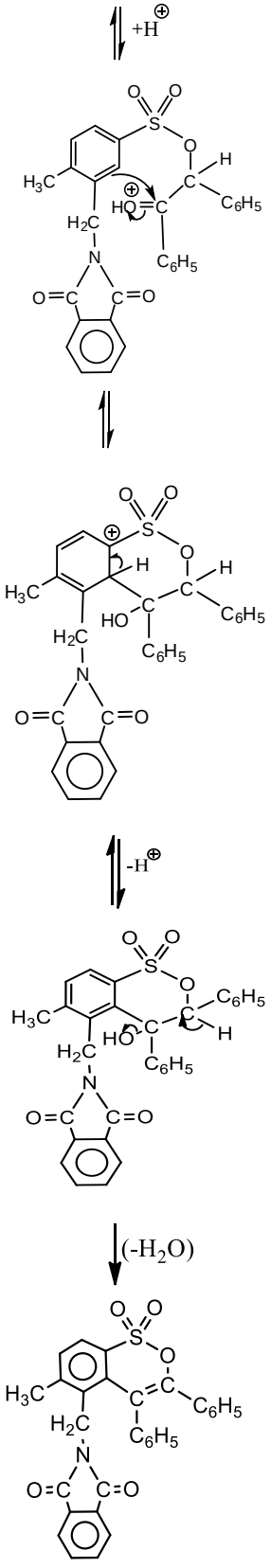
(b)



(III)

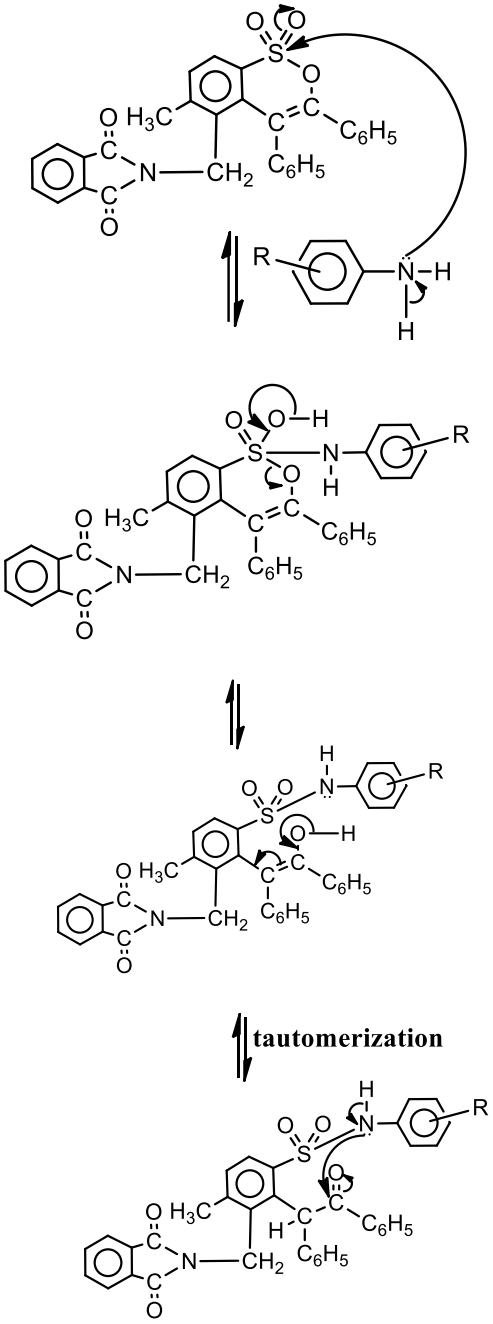
The third possibility is the attack by the alcoholic oxygen atom on the sulphonyl sulphur atom as suggested here mechanistically.

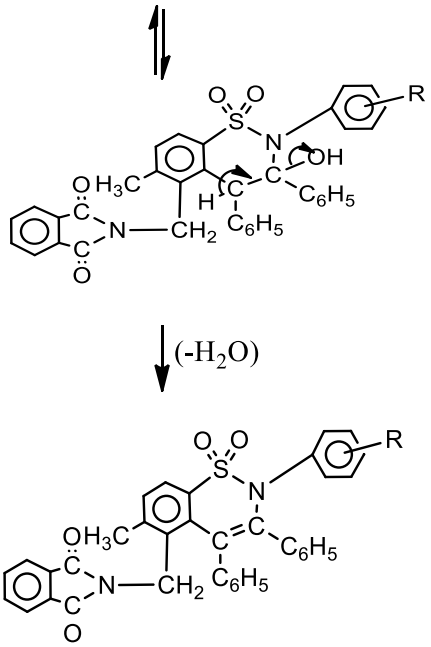




(III)

Conversion of **(III)** into **(IV)** involves the nucleophilic attack by the amine nitrogen on the sulphonyl sulphur atom as suggested here mechanistically.





(IV)

V. CONCLUSION

Besides antihypergyycemic activity benzothiazine derivatives act as orally-active anti-epileptic drug candidate molecules with broad anticonvulsant effect[5]. Author performed four steps linear synthesis of 2-[(6-Methyl-2-aryl-3,4-diphenyl-2H-benzo[e][1,2]thiazin-5-yl)methyl]-isoindolin-1,3-dioxo-1,1-dioxides and achieved moderate yields varying from 50 to 65 percent. It is observed that substitution of R at 2-C tends to lower the yield eg., with COOH at 2-C the yield is only 50 percent due to steric hindrance. However, with H, OCH_3, CH_3 at 4-C the yield is 60, 65, 65 percent respectively. Therefore, in order to enhance the yield, trial should be made to use reagents having substitution at 4-C with less bulky groups.

VI. ACKNOWLEDGEMENT

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