SYNTHESIS OF 6-(1,2-DIHYDRO-1-OXO-PHTHALAZIN-4-YL)-2H-1,4-BENZOXAZIN-3-(4H)-0NES.

K.S.Chowdary. A.Prashant, S.Srinivas Rao, & V.S.H.Krishnan*
Dr.Krishnan's Laboratories, Plot.No:99, Prashant Nagar, Kukatpally,
Hyderabad-500 072, INDIA.E-mail . Krishnan @ nomus.net.in

Abstract: A series of new 6-(1,2-dihydro-1-oxo-phthalazin-4-yl)-2H-1,4-benzoxazin-3-(4H)ones were prepared by Friedel-Crafts reaction of 2H-1,4-benzoxazin-3-(4H)-ones with phthalicanhydride & cyclizing the o-substituted ketobenzoicacid with hydrazine hydrate to yield the title compound.

Introduction : The diuretic & muscle relaxtant activities of triazolobenzoxazines & triazolo benzothiazines have been reported earlier [1,2]. Later publications [3-5] have brought out significant anthelmintic, antinflammatory & cardiotonic activities of benzoxazine & benzothiazine ring systems. Similarly phthalazines too are endowed with very broad spectrum of pharmacological activities viz antihypertensive [6,7], bronchodialator etc. Hence we wanted to synthesise compounds containing both these rings in order to study their pharmacological activity.

Results & Discussion :

2H-1,4-Benzoxazin-3-(4H)-one was prepared according to the reported procedure [9].Friedel-Crafts reaction of benzoxazinone with phthalic anhydride was studied indichloromethane (40°) & dichloroethane (83°). The reaction is faster in the latter solvent,whereas in the former, product can be directly obtained as it is less soluble in the solvent 2H-1,4-Benzoxazin(see experimental). The formation of 6-(2-carboxybenzoyl)-2H-1,4-benzoxazin-3-(4H)-one 3a was confirmed by chemical test (evolution of carbondioxide with saturated solution of sodiumbicarbonate) spectral data (table-1),

and satisfactory elementalanalysis. The Friedel-Crafts reaction of N-methyl benzoxazinone yielded the expected product 3b but other N-substituted derivatives like N-benzyl, N-ethoxycarbonyl methyl,N-(2-cyano ethyl) derivatives yielded complex mixtures. 6-(2-Carboxybenzoyl)-2H-1,4-benzoxazin-3-(4)-one 3a on treatment with hydrazine hydrate in alcohol under reflux conditions yielded the title compound 4a. The formation of 4a was confirmed from IR spectra the carbonyl streching vibrations for 4a appear at 1713 cm^{-1} and 1667 cm^{-1} (sharp), whereas for 3a the vibrations appear at 1700 cm^{-1}(broad) and 1646 cm^{-1} . The ^1H NMR spectral data (table-1) and elemental analysis confirmed this. 4b was similarly prepared from 3b. Alkylation of 4a and 4b were studied in acetonitrile & DMF. The reactions proceeded smoothly in DMF giving the products in pure form. Alkylation of 4a yielded 5a-5c and 4b yielded 5d-5f. (refer experimental). The yields, mp's & other physical data are given in table-1 . (Reaction are depicted in scheme-1).

Apparatus & methods :

The melting points are uncorrected. The infrared spectra were recorded in KBr wafer & ^1H NMR spectra were recorded in DMSO-d_6 /$CDCl_3$. Elemental analysis were also determined.

Experimental:

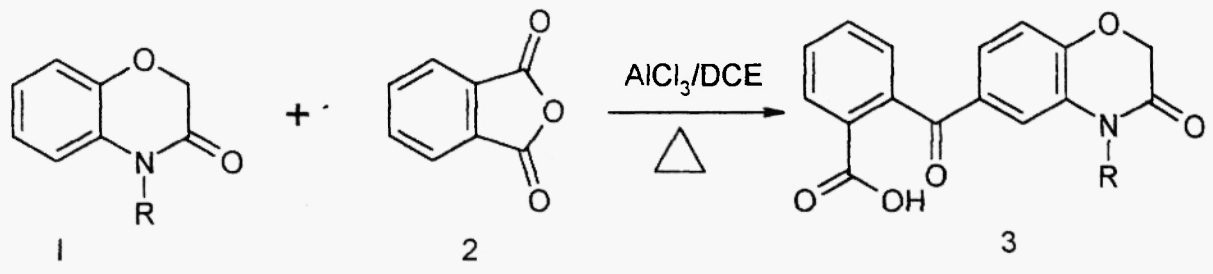
6-(2-Carboxybenzoyl)-2H-1,4-benzoxazin-3-(4H)-one : In a 250 ml three-necked RB flask, fitted with a stirrer, a double surface condenser, carrying a calcium chloride guard tube & a stopper, 2H-1,4- benzoxazin-3-(4H)-one (2.98g,0.002m), phthalic anhydride (3.26g, 0.022m) & dichloromethane (50ml) were taken. Anhydrous aluminum chloride (10.7g, 0.08m) was added in two to three instalments at room temperature. After the additions, the reactions mixture was stirred at reflux for about 4 hrs, the reaction mixture was cooled to room temperature, poured into 100ml ice-water containing concentrated hydrochloric acid, stirred for 30 minutes & filtered. The solid was washed with water to neutral pH, dichloromethane (3x10ml) & dried to give pure 3a,

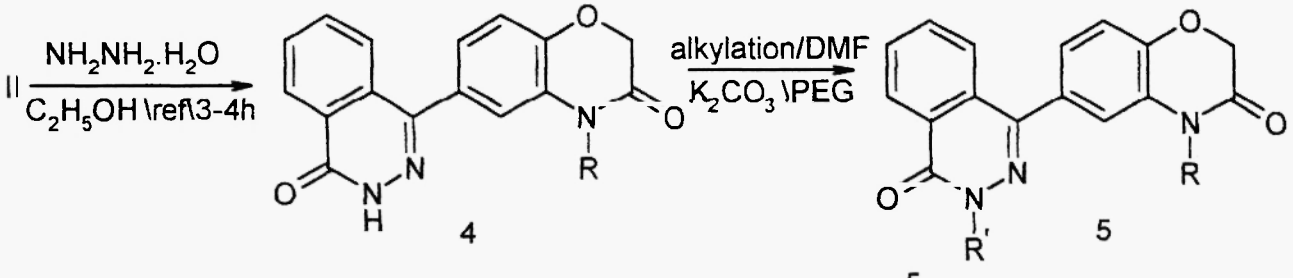
5gm in about 85% yield. When dichloroethane was used as solvent, the reaction was complete in 2 hrs (TLC). On work up, the organic layer was separated, washed with water (to neutral pH) & concentrated. The residue on stirring with dichloromethane yielded pure 3a in 85% yield. 3b was prepared in dichloroethane in 80% yield. Refer Table-I for spectral data.

6-(1,2-dihydro-1-oxo-phthalazin-4-yl)-2H-1,4-benzoxazine-3-(4H)-one.: A mixture of 3a or 3b (0.02m), hydrazine hydrate(0.03m, 98%) & ethyl alcohol (50 ml) was stirred under reflux for 3-4 hrs. When the reaction was cooled, solid crystallised out & the solid was filtered, washed with ethyl alcohol (2x10ml) & dried to give pure 4a or 4b in about 80% yield. Refer Table-I for spectral data.

4-Ethoxycarbonylmethyl-6-(1,2-dihydro-1-oxo-2-ethoxy carbonyl methyl-pthalazin-4-yl)-2H-1,4-benzoxazine-3-(4H)-one : A mixture of 6-(1,2-dihydro-1-oxo-phthalazin-4-yl)-2H-1,4-benzoxazin-3-(4H)-one (2.93g,0.01m), anhydrous potassium carbonate (5.52g,0.04m) & dimethylformamide (20ml) was taken in a 100 ml three-necked RB flask, fitted with a stirrer, condenser carrying a calcium chloride guard tube & a pressure-adjustable addition funnel. Ethyl bromoacetate (5.01g, 0.03m) was dissolved in dimethylformamide(5ml) & added dropwise from the addition funnel at room temperature. After the addition, the reaction mixture was slowly heated to 90° for about 3-4 hrs. On completion (TLC followed) the reaction mixture was cooled to room temperature, added into water (100ml) & stirred for 30 minutes. The precipitated solid was filtered, washed with water & dried to give pure 5c. Details regarding yield, & physical data for all the compolunds [5a-5l] are given in table. Similarly methylation was done with dimethylsulfate, benzylation with benzylchloride & cynomethylation with acrylonitrile.

SCHEME - 1





1,3,4

	a	b
R=	H	CH_3

5

R	R'
a) CH_3	CH_3
b)-CH_2Ph	-CH_2Ph
c)-$CH_2COOC_2H_5$	-$CH_2COOC_2H_5$
d)CH_3	-CH_2CH_2CN
e)CH_3	-CH_2Ph
f)CH_3	-$CH_2COOC_2H_5$

Table-I

Cpd No	M.P (°c) yield (%)	Molecular Formulae	%(N) calcd Found	I.R.(cm^{-1})	^{1}HNMR(DMSO-d_6) δ
3a	252-254 85	$C_{16}H_{17}NO_5$	4.71 4.72	3268(NH), 1700, 1685, 1647(CO)	4.6(s,2H,OCH_2), 6.9(d,J=9Hz, 1H, C_8 H)7.2 (d/d, J=9Hz/3Hz,1H, ArH), 7.35 (d/d,J=9Hz/3Hz 1H Ar H), 7.45 (d, J=3Hz, 1H,(5H), 7.5-7.7(m, Ar H), 8.05 (d/d, J=9Hz/3Hz, C_7H) & 10.7(s,1H,NH).
3b	192-194 80	$C_{17}H_{13}NO_5$	4.50 4.52	3508(OH), 1690,1665, 1650(CO).	---
4a	>280 80	$C_{16}H_{11}N_3O_3$	14.33 14.30	3230(NH), 1713, 1667(CO).	4.3(s,2H,OCH_2),7.0-7.2(m,3H,benzoxazineArH), 7.7-7.9(m,3H,C_5H-C_7HphthalazineArH),8.5(m,1H, C_8H,phthalazineArH),10.7(s,1H,NH,benzoxazinone), 12.4(s,1H,NH,phthalazinone).
4b	>280 80	$C_{17}H_{13}N_3O_3$	13.68 13.69	3292(NH), 1672, 1653(CO)	3.3(s,3H,NCH_3),4.65(s,2H,OCH_2),7.0-7.3(m,3H, benzoxazineAr-H),7.7-7.9(m,3H,C_5H-C_7Hphthalazine ArH),8.4(m,1H,C_8HphthalazineArH),12.7(s,1H, NH,phthalazine).
5a	230-232 72	$C_{18}H_{15}N_3O_3$	13.08 13.10	1683, 1654(CO)	3.4(s,3H,NCH_3,benzoxazine),3.9(s,3H,NCH_3,phthalazine),4.8(s,3H,OCH_2),7.15-7.35(m,3H,benzoxazineArH),7.75-7.9(m,3H,C_5H-C_7HpthalazineArH), 8.45(m,1H,C_8HphthalazineArH).
5b	204-206 68	$C_{30}H_{23}N_3O_3$	8.88 8.86	1689, 1655(CO)	4.9(s,2H,NCH_2benzoxazine),5.2(s,2H,OCH_2),5.4(s, 2H,NCH_2phthalazine),7.2-7.5(m,10H,ArH),7.6-8.0 (m,3H,ArH),8.4(m,1H,C_8Hphthalazine).
5c	150-154 75	$C_{24}H_{23}N_3O_7$	9.03 9.00	1739,1701, 1655(CO)	1.2-1.5(m,6H,2XCH_3),4.15-4.40(m,4H,2XCH_2),4.65 (s,2H,NCH_2benzoxazine),4.75(s,2H,OCH_2),4.95(s,2H, NCH_2phthalazine),6.95(d,J=3Hz,1H,C_5Hbenzoxazine-ArH),7.15-7.3(m,2H,C_7H&C_8Hbenzoxazine,ArH),7.65 -7.9(m,3H,C_5H-C_7HphthalazineArH),8.55(m,1H,C_8H phthalazineArH).
5d	235 80	$C_{20}H_{16}N_4O_3$	15.56 15.58	2248(CN), 1683, 1653(CO)	---
5e	237 78	$C_{24}H_{19}N_3O_3$	10.58 10.57	1678, 1647(CO)	3.45(s,3H,NCH_3),4.75(s,2H,OCH_2),5.5(s,2H,NCH_2-C_6H_5),7.15-7.45(m,6H,ArH),7.55(d,2H,benzoxazine-ArH),7.85-7.95(m,3H,C_5H-C_7H,phthalazineArH), 8.6(m,1H,C_8HphthalazineArH).
5f	218 75	$C_{21}H_{19}N_3O_3$	11.63 11.64	1754, 1683 1652(CO)	1.3(t,3H,CH_3),3.35(s,3H,NCH_3),4.25(q,OCH_2ester), 4.65(s,2H,OCH_2benzoxazine),4.95(s,2H,NCH_2CO), 7.05-7.30(m,3H,benzoxazineArH),7.8-8.0(m,1H,C_5H-C_7HphthalazineArH),8.45(m,1H,C_8HphthalazineArH).

References :

1. D.R. Shridhar, M.Jogibhukta, V.S.H. Krishnan, P.P.Joshi, M.U.R.Naidu, G.S.Thapar, A.Krishnamoorthy & G.P.Thomas. Indian J. chem., 23B,1279 (1984).
2. .C.V.Reddy sastry, G.K.A.S.S.Narayan, V.S.H.Krishnan, K.Vemana,D.R.Shridhar, P.P.Singh & A.Y. Junnarkar. Indian .J. chem., 30B,953 (1991).
3. D.R.Shridhar, K.Srinivasa Rao, A.N.Singh, K.Rastogi, S.S.Gandhi, V.S.H.Krishnan, M.Jogibhukta,C.D.Lovekar,H.N.Tripathi&G.S.T.Sai.Indian.J.chem,24B,1263 (1985)
4. D.R.Sridhar, C.V.Reddy Sastry, O.P.Bansal, P.Pulla Rao, P.P.Singh, R.M.Tripathi, C.Seshagiri Rao, A.Y.Junnarkar & G.P.Thomas. Indian.J.chem., 22B,1236 (1983).
5. C.V.Reddy Sastry, K.Srinivasa Rao, V.S.H.Krishnan, K.Rastogi, M.L.Jain, R.K.Verma,R.M.Tripathi, C.Seshagiri Rao & R.Kausal. Indian.J.Chem., 28B,882 (1989)
6. Von J. Druey & B.H.Rinigier., Helv. Chimica Acta 34,195 (1951).
7. Von J. Druey & B. H.Ringer., Helv . Chimica Acta 34,204 (1951)
8. Drug News and Perspectives 7(1), 38 (1994).
9. D.R.Sridhar, M.Jogibhukta & V.S.H.Krishnan, Org.prep. Proc. Int., 14(3), 195 (1982)

Received on July 12, 2000