Some Reactions of Pyrazolinyl Benzoxazones and Quinazolones

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Summary: 2-(3-Aryl-2-pyrazoline-5-yl)-4H-benzoxazin-4-ones I react easily with amines in ethanol or glacial acetic acid to furnish the corresponding anilide or quinazolone derivatives. Acetylation, benzoylation and nitrosation of led to the formation of N-acetyl, N-benzoyl and N-nitroso derivatives. Other transformations of I were also investigated.

Some pyrazolines have many demonstrated medicinal applications as anaesthetics [1], anthelmentics [2] and inflammation reducing agents [3].

We have investigated the reaction of 2-(3-aryl-2-pyrazoline-5-yl)-4H-benzoxazin-4-ones (Ia and b) with primary amines in boiling ethanol to furnish the corresponding anilide derivatives IIa-l via opening of the benzoxazine ring.

Alternatively, when the reaction takes place in boiling glacial acetic acid [4], the corresponding acetyl quinazolone derivatives Ic-l were generated. Compounds Ic,e.g and j were obtained via ring closure of IIa, d,g and j, followed by acetylation of the intermediates.

Acetylation and/or benzoylation of Ia and b using acetyl and/or benzoyl chloride, gave rise to the N-acetyl and/or N-benzoyl derivatives Im-p. Compounds IIm and n can also be obtained via acetylation of Ia and b using acetic acid/sodium acetate mixture.

Nitrosation of Ia and b using sodium nitrite and concentrated HCl led to the formation of the N-nitroso derivatives Iq and r.

It is known that cyanoethylation of pyrazolines is not unusual [5]. When Ia and b were treated with secondary amines such as morpholine or piperidine in the presence of formaldehyde under Mannich conditions, the corresponding Mannich bases Is-u were obtained.

Bromination of Ia and b using a solution of bromine in chloroform gave rise to the 4-bromo derivative IIIa and b [6], respectively.

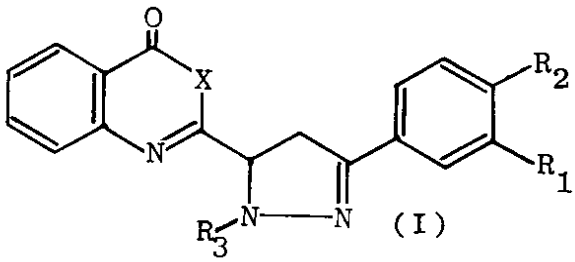
Compounds Ia and b could also be converted to the corresponding benzothiazine thiones IVa and b by treatment with P_2S_5 in dry xylene [7].

Experimental

The infrared absorption spectra were determined with a Unicam SP 1200 Spectrophotometer using the KBr Wafer technique and the values are listed with other physical data in Table 1. The NMR spectra were obtained by using a Varian A - 90 Spectrophotometer and are given in Table 2. All melting points are not corrected.

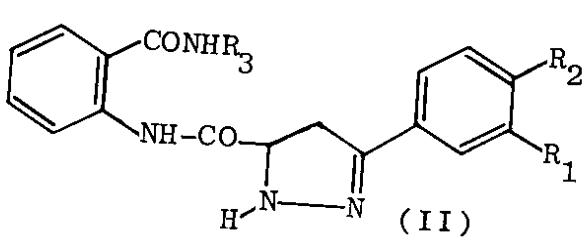
Reaction of Ia and b with amines. Formation of IIa-l and IIc-l

Compound IIa or Ib (0.01 mole), a primary amine (methylamine, ethylamine, butylamine, p-toluidine, p-ani-



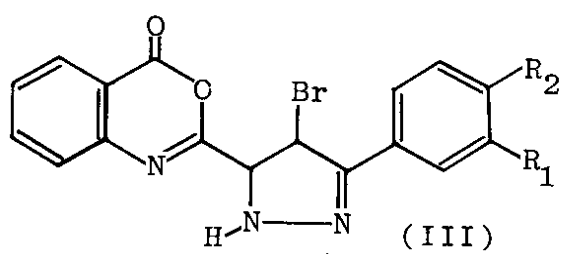
(I)

	R_1	R_2	R_3	X
a,	CH_3	Cl	H	O
b,	Br	H	H	O
c,	CH_3	Cl	$COCH_3$	NCH_3
d,	CH_3	Cl	$COCH_3$	NC_4H_9(n)
e,	Br	H	$COCH_3$	NCH_3
f,	Br	H	$COCH_3$	NC_6H_4(n)
g,	CH_3	Cl	$COCH_3$	$NC_6H_4CH_3$(p)
h,	CH_3	Cl	$COCH_3$	$NC_6H_4OCH_3$(p)
i,	CH_3	Cl	$COCH_3$	$NCH_2C_6H_5$
j,	Br	H	$COCH_3$	$NC_6H_4CH_3$(p)
k,	Br	H	$COCH_3$	$NC_6H_4OCH_3$(p)
l,	Br	H	$COCH_3$	$NCH_2C_6H_5$
m,	CH_3	Cl	$COCH_3$	O
n,	Br	H	$COCH_3$	O
o,	CH_3	Cl	COC_6H_5	O
p,	Br	H	COC_6H_5	O
q,	CH_3	Cl	NO	O
r,	Br	H	NO	O
s,	CH_3	Cl	$CH_2NC_4H_8O$	
t,	Br	H	$CH_2NC_4H_8O$	
u,	CH_3	Cl	$CH_2NC_5H_{10}O$	



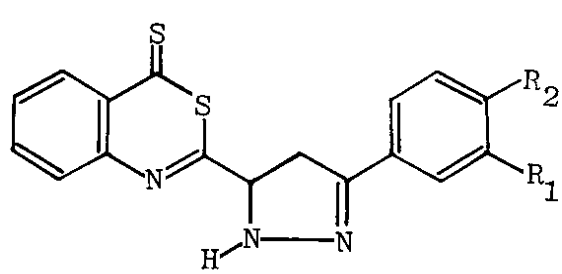
(II)

	R_1	R_2	R_3
a,	CH_3	Cl	CH_3
b,	CH_3	Cl	C_2H_5
c,	CH_3	Cl	C_4H_9(n)
d,	Br	H	CH_3
e,	Br	H	C_2H_5
f,	Br	H	C_4H_9(n)
g,	CH_3	Cl	$C_6H_4CH_3$(p)
h,	CH_3	Cl	$C_6H_4OCH_3$(p)
i,	CH_3	Cl	$CH_2C_6H_5$
j,	Br	H	$C_6H_4CH_3$(p)
k,	Br	H	$C_6H_4OCH_3$(p)
l,	Br	H	$CH_2C_6H_5$



(III)

	R_1	R_2
a,	CH_3	Cl
b,	Br	H



(IV)

	R_2	R_2
a,	CH_3	Cl
b,	Br	H

Table-1: The physical properties and infrared of new compounds

Comp.	M.P. °C	Colour	Solvent* (Yield)	Formula (M.Wt.)	Analysis % Found	Analysis % Required	Group frequencies (KBr, cm^{-1})		
II_a	245	colourless	E	$C_{19}H_{19}O_2N_4Cl$	C	61.21	61.53	νCH_2	ν NH	$\nu C=O$
			(60)		H	5.08	5.12	2980.1920	3340	1695
				(370.5)	N	14.86	15.11	$\nu C=N$	$\nu C=C$	
								1630	1590	
II_b	255	yellow	E	$C_{20}H_{21}O_2N_4Cl$	C	62.44	62.41	νCH_2	ν NH	ν C=O
			(75)		H	5.11	5.46	2980	3440	1680
				(384.5)	N	14.62	15.56	ν C=N	ν C=C	
							1620	1580		
II_c	235	colourless	E	$C_{22}H_{25}O_2N_4Cl$	C	63.78	64.00	νCH_2	ν NH	$\nu C=O$
			(70)		H	5.66	6.06	2960	3440.3350	1720.1680
				(412.5)	N	13.48	13.57	$\nu C=N$	$\nu C=C$	
								1620	1580	
II_d	223	colourless	E	$C_{18}H_{17}O_2N_4Br$	C	53.52	53.86	νCH_2	ν NH	$\nu C=O$
			(70)		H	0.13	4.23	2920	3430.3300	1680
				(401)	N	13.61	1396	$\nu C=N$	$\nu C=C$	
								1620	1590	
II_e	280	colourless	B	$C_{19}H_{19}O_2N_4Br$	C	54.75	54.93	νCH_2	ν NH	ν C=O
			(65)		H	4.56	4.57	2930	3440	1660
				(415)	N	13.17	13.49	$\nu C=N$	$\nu C=C$	
								1620	1600	
II_f	270	colourless	E	$C_{21}H_{23}O_2N_4Br$	C	56.48	56.88	ν CH	νNH	$\nu C=O$
			(63)		H	5.14	5.19	2980,2930	3300	1680
				(443)	N	12.66	12.64	ν C=N	ν C=C	
								1630	1590	

Table-1: cont.

II_g	212	colourless	E	$C_{22}H_{23}O_2N_4Cl$	C	67.16	67.18	νCH_2	ν NH	$\nu C=O$
			(55)		H	5.22	5.15	2920	3420	1680
				(446.5)	N	12.43	12.54	$\nu C=N$	$\nu C=C$	
								1640	1585	
II_h	192	colourless	E	$C_{25}H_{23}O_3N_4Cl$	C	64.68	64.86	νCH_2	ν NH	ν C=O
			(80)		H	4.62	4.97	2970,2920	3440.3340	1720.1690
				(462.5)	N	12.00	12.10	$\nu C=N$	$\nu C=C$	
								1620	1580	
II_i	215	colourless	E	$C_{25}H_{24}O_2N_4Cl$	C	67.13	67.18	νCH_2	ν NH	ν C=O
			(70)		H	5.01	5.15	2940	3420	1690
				(446.5)	N	12.32	12.54	$\nu C=N$	$\nu C=C$	
								1650	1590	
II_j	243	colourless	T	$C_{24}H_{21}O_2N_4Br$	C	59.87	60.37	νCH_2	ν NH	ν C=O
			(72)		H	3.41	4.40	2940.2920	3450.3300	1690
				(477)	N	11.68	11.74	$\nu C=N$	$\nu C=C$	
								1630	1595	
II_k	242	colourless	E	$C_{24}H_{21}O_3N_4Br$	C	58.12	58.41	νCH_2	ν NH	ν C=O
			(63)		H	4.32	4.25	2940	3480	1710.1680
				(493)	N	11.16	11.35	$\nu C=N$	$\nu C=C$	
								1640	1580	
II_l	214	pale yellow	E	$C_{24}H_{21}O_2N_4Br$	C	60.25	60.37	νCH_2	ν NH	ν C=O
			(57)		H	4.18	4.40	2860	3460	1690
				(477)	N	11.78	11.74	$\nu C=N$	$\nu C=C$	
								1635	1600	
I_c	258	colourless	A	$C_{21}H_{19}O_2N_4Cl$	C	63.68	63.87	ν C=O	$\nu C=O$	νCH_2
			(80)		H	4.72	4.81	1660.1700	1620	2980,2920
				(394.5)	N	14.12	14.19	$\nu C=C$		
								1580		

Table-1: cont.

I_d	250	colourless	E (75)	$C_{24}H_{25}O_2N_4Cl$ (436.5)	C H N	65.82 5.64 12.56	65.97 5.72 12.82	νC=O 1680,1700 νC=C 1580	ν C=O 1620	ν CH 2930
I_e	237	colourless	B/E (85)	$C_{20}H_{17}O_2N_4Br$ (425)	C H N	56.22 3.84 13.00	56.47 4.00 13.17	νC=O 1670,1720 νC=C 1600	ν C=O 1640	ν CH_2 2860
I_f	243	colourless	B/E (60)	$C_{23}H_{23}O_2N_4Br$ (467)	C H N	59.12 4.48 11.90	59.10 4.92 11.99	νC=O 1680,1720 νC=C 1600	ν C=N 1630	ν CH_2 2980
I_g	230	colourless	A (50)	$C_{27}H_{23}O_2N_4Cl$ (470.5)	C H N	68.63 4.51 11.82	68.86 4.88 11.90	νC=O 1680,1695 νC=O 1590	ν C=N 1620	νCH_2 2920,2960
I_h	245	colourless	A (52)	$C_{27}H_{23}O_3N_4Cl$ (486.5)	C H N q	66.32 4.28 11.81	66.59 4.72 11.51	νC=O 1680,1720 νC=C 1590	ν C=N 1620	ν CH_2 2910
I_i	250	colourless	A (55)	$C_{27}H_{23}O_2N_4Cl$ (407.5)	C H N	68.44 4.52 11.67	68.86 4.88 11.90	νC=O 1685,1690 νC=C 1595	ν C=N 1630	ν CH_2 2920
I_j	130	colourless	A (65)	$C_{26}H_{21}O_2N_4Br$ (501)	C H N	62.18 4.05 11.21	62.27 4.19 11.17	νC=O 1660,1690 νC=C 1590	ν C=N 1620	ν CH_2 2930

Table-1: cont.

I_k	213	colourless	A (70)	$C_{26}H_{21}O_3N_4Br$ (517)	C	60.18	60.34	νC=O 1660.1710	νC=N 1630	ν CH_2 2960
					H	3.97	4.06			
					N	10.63	10.83	νC=C 1590		
I_l	232	colourless	A (68)	$C_{26}H_{21}O_2N_4Br$ (501)	C	62.16	62.27	νC=O 1680,1720	νC=N 1640	νCH_2 2940
					H	4.16	4.19			
					N	11.22	11.17	νC=C 1605		
I_m	248	colourless	A (58)	$C_{20}H_{16}O_3N_3Cl$ (381.5)	C	62.72	62.90	νC=O 1680,1690	νC=N 1635	ν CH_2 2980
					H	4.18	4.19			
					N	11.46	11.00	νC=C 1595		
I_n	241	colourless	A (60)	$C_{19}H_{14}O_3N_3Br$ (412)	C	55.22	55.33			
					H	3.81	3.39			
					N	10.38	10.19			
I_o	260	colourless	B (73)	$C_{25}H_{18}O_3N_3Cl$ (443.5)	C	67.60	67.64	νC=O 1710,1670	ν C=N 1640	ν CH_2 2920
					H	4.10	4.05			
					N	9.28	9.47	νC=C 1590		
I_p	260	yellow	B (76)	$C_{24}H_{16}O_3N_3Br$ (474)	C	60.40	60.75			
					H	3.58	3.37			
					N	8.72	8.86			
I_q	250	yellow	E (45)	$C_{18}H_{13}O_3N_4Cl$ (368.5)	C	58.18	58.61	νC=O 1700	ν C=N 1635	ν CH_2 2980
					H	3.55	3.52			
					N	14.98	15.19	νC=C 1600		
I_r	204	colourless	E (60)	$C_{17}H_{11}O_3N_4Br$ (399)	C	50.86	51.12			
					H	2.46	2.75			
					N	14.12	14.03			

Table-1: cont.

I_s	235	colourless	E (55)	$C_{23}H_{23}O_3N_4Cl$ (438.5)	C	62.76	62.94	νC=O	ν C=N	νCH_2
					H	5.05	5.24	1690,1670	1655	2870
					N	12.61	12.77	νC=C 1590		
I_t	300	colourless	E (60)	$C_{22}H_{21}O_3N_4Br$ (469)	C	56.12	56.28	νC=O	ν C=N	ν CH_2
					H	4.23	4.47	1690	1640	2950
					N	11.75	11.94	νC=C 1600		
I_u	249	colourless	E (60)	$C_{24}H_{25}O_2N_4Cl$ (436.5)	C	65.81	65.97	νC=O	ν C=O	ν CH_2
					H	5.70	5.72	1670	1640	2960
					N	12.54	12.82	νC=C 1580		
III_a	218	colourless	B (60)	$C_{18}H_{13}O_2N_3BrCl$ (418.5)	C	51.56	51.61	νC=O	νC=N	νC=C
					H	3.13	3.10	1720	1630	1600
					N	10.21	10.03	νNH		
					Br	18.85	19.11	3440		
III_b	240	colourless	T (72)	$C_{17}H_{12}O_2N_3Br_2$ (450)	C	45.13	45.33			
					H	2.26	2.66			
					N	9.00	9.33			
					Br	35.41	35.55			
IV_a	250	yellow	N (64)	$C_{18}H_{14}N_3S\ Cl$ (371.5)	C	57.66	58.14	νC=S	ν C=N	νCH_2
					H	3.38	3.76	1320	1630	2920
					N	13.06	13.22	νC=C	ν NH	
					S	16.87	17.22	1600	3440,3460	
IV_b	158	yellow	E (71)	$C_{17}H_{12}N_3S_2Br$ (402)	C	50.71	50.74			
					H	2.76	2.98			
					N	10.13	10.44			
					S	15.80	15.92			

Table-1: cont.

I_k	213	colourless	A	$C_{26}H_{21}O_3N_4Br$	C	60.18	60.34	νC=O	ν C=N	νCH_2
			(70)		H	3.97	4.06	1660.1710	1630	2960
				(517)	N	10.63	10.83	νC=C		
								1590		
I_l	232	colourless	A	$C_{26}H_{21}O_2N_4Br$	C	62.16	62.27	νC=O	ν C=N	νCH_2
			(68)		H	4.16	4.19	1680,1720	1640	2940
				(501)	N	11.22	11.17	νC=C		
								1605		
I_m	248	colourless	A	$C_{20}H_{16}O_3N_3Cl$	C	62.72	62.90	νC=O	ν C=N	ν CH_2
			(58)		H	4.18	4.19	1680,1690	1635	2980
				(381.5)	N	11.46	11.00	νC=C		
								1595		
I_n	241	colourless	A	$C_{19}H_{14}O_3N_3Br$	C	55.22	55.33			
			(60)		H	3.81	3.39			
					N	10.38	10.19			
I_o	260	Colorless	B	$C_{25}H_{18}O_3N_3Cl$	C	67.60	67.64	νC=O	ν C=N	νCH_2
			(73)		H	4.10	4.05	1710,1670	1640	2920
				(443.5)	N	9.28	9.47	νC=C		
								1590		
I_p	260	yellow	B	$C_{24}H_{16}O_3N_3Br$	C	60.40	60.75			
			(76)		H	3.58	3.37			
				(474)	N	8.72	8.86			
I_q	250	yellow	E	$C_{18}H_{13}O_3N_4Cl$	C	58.18	58.61	νC=O	ν C=N	νCH_2
			(45)		H	3.55	3.52	1700	1635	2980
				(368.5)	N	14.98	15.19	νC=C		
								1600		
I_r	204	colourless	E	$C_{17}H_{11}O_3N_4Br$	C	50.86	51.12			
			(60)	(399)	H	2.46	2.75			
						14.12	14.03			

A = Acetic acid B = Benzene E-Ethanol P-Pet.ether (b.p. 100-120) T - Toluene

Table-2: The N.M.R. Spectra of some new compounds

Compound	Solvent	δ Values	Group
Ic	$(CD_3)_2CO$	7.10 - 7.5	7 aromatic hydrogens.
		6.90	1 H of - CH - in pyrazoline ring
		2.90	3 H of - N - CH_3
		2.60	3 H of - CO - CH_3
		2.45	2 H of - CH_2 - in pyrazoline ring.
		2.30	3 H of - CH_3 in phenyl group.
In	DMSO	7.00 - 7.70	8 aromatic hydrogen
		6.75	1 H of - CH - in pyrazolin ring
		2.65	3 H of - CO - CH_3
		2.45	2 H of - CH_2 - in pyraoline ring
Is	$(CD_3)_2CO$	7.25 - 7.80	7 aromatic hydrogens
		6.60	1 H of - CH - in pyrazoline ring
		3.20 , 2.70	8 H of 4 - CH_2 - in morpholine
		2.45	2 H of - N - CH_2 -
		2.40	3 H of - CH_3 in phenyl group.
IId	DMSO	7.25 - 7.70	8 aromatic hydrogens
		6.75	1 H of - CH - in pyrazoline ring
		3.45	1 H of - NH - in pyrazoline ring
		3.40	2 H of 2 - CO - NH -
		2.75	3 H of - NH - CH_3
		2.50	1 H of - NH - in pyrazoline ring
IIIa	$CDCl_3$	7.60-7.95	7 aromatic hydrogen
		7.15	1 H of - CH - Br
		6.90	1 H of - CH - in pyrazoline ring
		2.35	3 H of - CH_3 in phenyl group
IV_b	DMSO	6.90 - 7.55	8 aromatic hydrogens
		6.80	1 H of - CH - in pyrazoline ring
		3.30	1 H of - NH - in pyrazoline ring
		2.55	2 H of - CH_2 - in pyrazoline ring.

sidine or benzylamine) (0.01 mole), and ethanol or acetic acid 20 ml, were refluxed for 4 hours. The solid product obtained after evaporation of most of the solvent was recrystallized to give the corresponding anilide derivatives IIa-l or the quinazolone derivatives Ic-l respectively.

Ring closure of IIa, d,g and j. Formation of Ic,e,f and j

A solution of 5 g of IIa, d,g or j, in 10 ml of glacial acetic acid and 10 ml acetic anhydride was refluxed for 4 hours. The reaction mixture was poured into water and left overnight. The solid product formed was recrystallized to give Ic,e,f and j respectively.

Acetylation or benzoylation of Ia and b. Formation of Im-p

A solution of Ia and b (0.01 mole) in 20 ml acetyl or benzoyl chloride was refluxed for 2 hours on a water bath. The reaction mixture was poured into ice, and the solid product obtained was washed several times with boiling

water and recrystallized to give the N-acetyl or N-benzoyl derivative Im-p.

Alternative preparation of Im

A mixture of Ia (0.01 mole), sodium acetate and 15 ml of glacial acetic acid was refluxed for 4 hours: then the reaction mixture was cooled and poured into ice. The solid product separated was filtered, washed with water several times, dried and then recrystallized from acetic acid to give Im.

Nitrosation of Ia and b. Formation of Iq and r

A solution of Ia and b (0.01 mole) in hydrochloric acid 10 ml was heated with a solution of sodium nitrite (0.03 mole) in water 3 ml. The reaction mixture was heated on a water bath for one hour, the solution was then poured into ice and the solid separated was recrystallized from ethanol to give the corresponding N-nitroso derivative Iq and r respectively.

Reaction of Ia and b with secondary amines. Formation of Is-u

A mixture of Ia and b (0.01 mole), formaldehyde (0.02 mole) and amine namely, morpholine or piperidine (0.012 mole) in 20% HCl was dissolved in 30 ml ethanol. The reaction mixture was heated under reflux on a steam bath for 6 hours and left to stand overnight, diluted the solution with water, dilute NaOH was added till the solution become alkaline, extracted with ether, then acidified with acetic acid, diluted with water, and the precipitated solid was filtered off, dried and recrystallized to give the corresponding Mannich base Is-u.

Bromination of Ia and b. Formation of IIIa and b

A solution of Ia and b (0.01 mole) in $CHCl_3$ (20 ml) was treated with a solution of bromine (0.03 mole) in $CHCl_3$ (20 ml). The solid product obtained after evaportion of $CHCl_3$ was recrystallized to give IIIa and b respectively.

Reaction of Ia and b with P_2S_5. Formation of IVa and b

A mixture of Ia and b (0.01 mole), P_2S_5 (0.02 mole) and dry xylene (20 ml) was refluxed for 8 hours. The solid product obtained after hot filteration and cooling of the filtrerate was recrystallized to give the thione derivatives IVa and b respectively.

References

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