Possible Antifertility Compounds - Part III : Synthesis of 2-Hippuryl-3-Aryl-Quinazolinones

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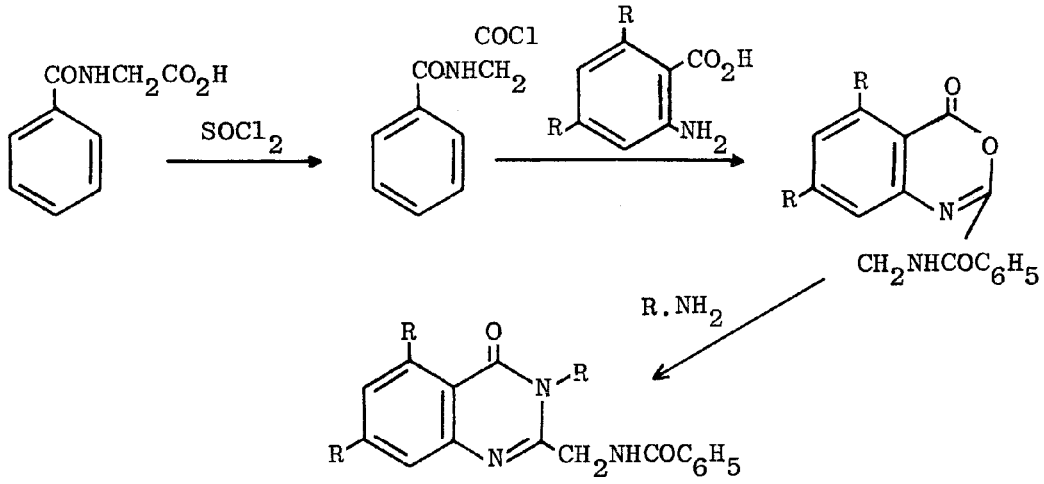
Summary: A number of 2-Hippyryl-3-aryl-quinazolinones were synthesised by the condensation of 2-Hippyryl-3, 1(4H)-benzoxainone and various aromatic amines. No significant antifertility activity in male rats was observed with any of them.

Quinazolinonos are known to have a variety of pharmacological properties[1]. More recently, Saksena & Nadkarni[2] observed that the oral dose of 2-(p-anisyl)-3-isopropyl-3, 4-dihydro quinazolinone inhibited pregnancy in rats. 2-Methyl-3-o-tolyl-quinazolinone has been found to interfere with blastocysts development in pregnant rats and rabbits[3] and increased offspring mortality in pregnant rabbits.[4]

However, inhibition of spermatogenesis has been observed by the oral administration of 2,3-dihydro-2-(1-naphthyl)-4 (1H)-quinazolinone without loss of libido[5,6]. The reports prompted us to synthesis a new series of quinazolinones (Scheme-1).

The melting points were taken in open capillaries and are uncorrected. The I.R. spectra were recorded



(R, R=See Table I and II)

Scheme I

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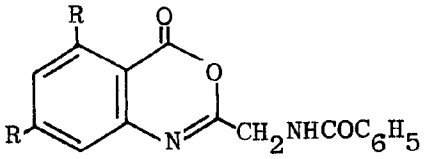
in KBr phase.

2-Hippuryl-3-1(4H)-bensoxazinon- A solutionof anthranitic acid (0.01M) in pyridine (30 ml.) was added to Hippuryl chloride (002M), prepared from equimolar quantities of hippuric acid and thionylchloride. The solution was shaken for 10 minutes and allowed it to stand at room temperature for 30 minutes with occassional shaking. Cold water was added to it and the Solid that separated was filtered, washed with water and recrystallised from alcohol.

IR - 3300 cm^{-1}, 3050 cm^{-1}, 2900 cm^{-1}, 1750 cm-1, 1670 cm^{-1}, 1620 cm-1, 1540 cm^{-1} etc.

The compounds thus synthesised are listed in Table 1. *2-Hippuryl-3-aryl quinazolinones-* Equimolar

Table I. 2-Hippuryl-3, 1-(4H)-benzoxazinones

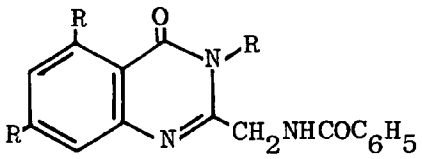


Sl. No	R	m.p. (°C)	Molecular formula	Anal % N. Calcd/Found	
1.	H	160	$C_{16}H_{12}N_2O_3$	10.00	9.8
2.	Br	190	$C_{16}H_{10}N_2O_3Br_2$	6.3	6.5

amounts of benzoxazinone and different aromatic amines were suspended in 15 ml of pyridine. The reaction mixture was reflexed on a sand bath for 4 hours. The solution was poured into ice cold water containing HCl. The crude product thus separated was recrystallised from benzene and petroleum ether (40°-60°) (Table-II).

The I.R. spectrograph of 2-Hippuryl-3(p-methoxyphenyl)-quinazolin-4-(3H)-one showed peaks at 3300 cm^{-1}, 3050 cm^{-1}, 2900 cm^{-1}, 1690 cm^{-1}, 1670 cm^{-1}. 1620 cm^{-1}, 1540 cm^{-1} etc.

Table II. 2- Hippuryl-3-aryl-quinazolinones



Sl. No.	R'	m.p. (°C)	mo. formula*
		R = H	
1.	p OCH_3 - C_6H_4 -	150	$C_{23}H_{19}N_3O_3$
2.	o - OCH_3 - C_6H_4 -	165	$C_{23}H_{19}N_3O_3$
3.	p . Cl. C_6H_4 -	170	$C_{22}H_{16}N_3O_2Cl$
4.	- C_6H_5	190	$C_{22}H_{17}N_3O_2$
5.	p. $OC_2H_5C_6H_4$ -	115	$C_{24}H_{21}N_3O_3$
6.	o. $OC_2H_5.C_6H_4$ -	190	$C_{24}H_{21}N_3O_3$
7.	$C_6H_5.CH_2$ -	185	$C_{23}H_{19}N_3O_2$
8.	m. $CH_3.C_6H_4$ -	172	$C_{23}H_{19}N_3O_2$
9.	o. $CH_3.C_6H_4$ -	80	$C_{23}H_{19}N_3O_2$
10.	p. $CH_3.C_6H_4$ -	87	$C_{23}H_{19}N_3O_2$
11.	m. $NO_2.C_6H_4$ -	72	$C_{22}H_{16}N_4O_4$
12.	- C_6H_{11}	97	$C_{22}H_{23}N_3O_2$
13.	o. $OH.C_6H_4$ -	148	$C_{21}H_{17}N_3O_3$
14.	m. Cl - C_6H_4 -	80	$C_{22}H_{16}N_3O_2Cl$
		R = Br	
15.	m. Cl. C_6H_4 -	182	$C_{22}H_{14}N_3O_2Cl\,Br_2$
16.	o. $CH_3.C_6H_4$ -	120	$C_{23}H_{17}N_3O_2Br_2$
17.	p. Cl. C_6H_4 -	90	$C_{22}H_{14}N_3O_2Cl.Br_2$
18.	- C_6H_5	100	$C_{22}H_{15}N_3O_2Br_2$
19.	m. $CH_3.C_6H_4$ -	160	$C_{23}H_{17}N_3O_2Br_2$
20.	m. $NO_2.C_6H_4$ -	122	$C_{22}H_{14}N_4O_2Br_2$
21.	p. $OC_2H_5.C_6H_4$ -	185	$C_{24}H_{19}N_3O_3Br_2$
22.	o. $OC_2H_5.C_6H_4$ -	68	$C_{24}H_{19}N_3O_3Br_2$
23.	p. $CH_3.C_6H_4$ -	250	$C_{23}H_{17}N_3O_2Br_2$
24.	p. $OCH_3.C_6H_4$ -	240	$C_{23}H_{15}N_3O_3Br_2$
25.	o. $OCH_3.C_6H_4$ -	172	$C_{23}H_{15}N_3O_3Br_2$

*Elemental analysis for nitrogen corresponded well with the theory.

The absence of peak at 1750 cm^{-1} in the final compound and the presence of an additional peak at 1690 cm^{-1} confirmed the formation of the quinazolonyl ring from benzoxazinone during the final step of reaction.

Biological Activity

Anti implantation screening- Four compounds, 2-Hippuryl-3(o-methoxy phenyl)-quinazolinone, 2-Hippuryl-3(benzyl)-quinazolinone, 2-Hippuryl-3-(m-chlorophenyl)- 5,7-dibromo-quinazolinone were tested for anti-implantation activity in rats. The test compounds had no significant anti-implantation activity at the oral dosage of 20 mg/kg/day, all the test animals became pregnant.

2-Hippuryl-3(o-ethoxyphenyl) - 5,7-dibromo-quinazolinone was tested in rats for postcoital activity. The drug dissolved in propylene glycol was administered orally at 10 mg/kg/day for 4 days, did not show any postcoital activity and all animals tested became pregnant.

Male anti-fertility screening - 2 Hippuryl-3-(p-tolyl)-quinazolinone was screened for antispermatogenesis activity in male rats. The test compound, dissolved in propylene glycol, was given orally at 100 mg/kg/day once daily for 5 days. No significant effect on wieghts of saminal vesicle, prostate and testes were observed. Histology showed testes with normal spermatogenesis, however, 3 out of 5 males had cellular debris in the epididymis.

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