Synthesis of Some Derivatives of 4(1*H*)Quinazolinones

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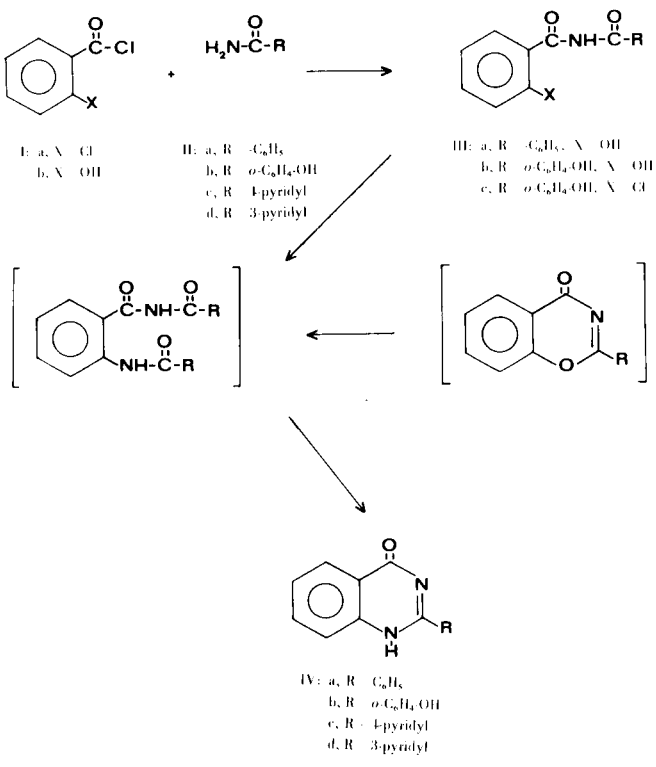
Several plants contain alkaloids with 4-quinazolinone nuclei and many have antimalarial, antiinflammatory, antibacterial and diuretic activities as well as CNS sedative properties comparable to the most potent barbiturates (1).

An improved method of synthesis of 4-quinazolinones is reported and shown in Scheme I.

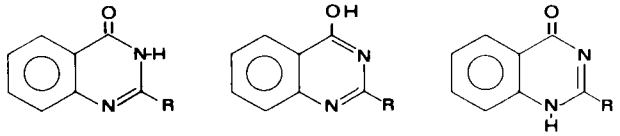
SCHEME I



It is known that amides of type III (X = OH) undergo cyclization to benzoxazines if heated over 150° in the presence of gaseous hydrogen chloride as the condensing agent (2). However, benzoxazines are not obtained under our reaction conditions.

The structures of the products were assigned based upon their chemical properties as well as their uv, ir and nmr spectra. The uv spectra showed maxima at about 225, 260 and 300 nm. These compounds may exist in three tautomeric forms with form α predominating (3).

SCHEME II



A carbonyl band at about 1620 cm^{-1} was observed in the ir spectra and was common to all of the quinazolinones. This shift to higher wave lengths together with the presence of a maximum at 225 nm in the uv spectra is typical of α,β-unsaturated carbonyl compounds. Moreover, a slight inflection at about 3400 cm^{-1} due to NH stretching was observed. The nmr spectra were consistent with the proposed structures.

We have observed a remarkable stability toward both alkaline and acid hydrolysis in these compounds and the structures were confirmed by the synthesis of the quinazolinones by another route (4) and by comparison of the ir spectra and mixed melting points.

EXPERIMENTAL

All melting points were taken in a Buchi-Tottoli capillary apparatus and are uncorrected. Ir spectra were determined on a Perkin-Elmer Mod. 157 infrared spectrometer as nujol mulls. The uv spectra were determined on a Beckmann DB ultraviolet spectrometer in 95% ethanol. The nmr spectra were taken using a Jeol, C-60 H, 60 MHz instrument using TMS as internal standard. The purity of the compounds was confirmed by tlc on silica gel Merck platten 0.25 mm, using the following solvent system: benzene-ethyl acetate (3:7).

The bis-benzamides were prepared as described below for IIIa and their physical constants and analytical data are recorded in Table I.

N-(2-Hydroxybenzoyl)benzamide (IIIa).

2-Hydroxybenzoyl chloride (3.13 g., 0.02 mole) and benzamide (2.42 g., 0.02 mole) were heated under reflux during which foaming occurred and hydrogen chloride was evolved. After 10 minutes the reaction was complete. The cooled mixture was extracted with boiling ethanol to give a white product m.p. 213°.

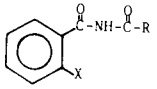
The quinazolinones are shown in Table II.

2-Phenyl-4(1*H*)quinazolinone (IVa).

(i) A mixture of *o*-hydroxybenzoyl chloride (Ib) (3.13 g., 0.02

TABLE I

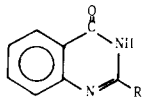
N-Substituted Benzamides



Compound III	X	R	Recryst. solvent	Yield, %	M.p. °C	Formula	Analyses Calcd. (Found) C	H	N	Cl
a	-OH	$-C_6H_5$	EtOH	85	213	$C_{14}H_{11}NO_3$	69.7 (69.85)	4.59 (4.62)	5.80 (5.87)	
b	-OH	o-C_6H_4-OH	EtOH	90	222	$C_{14}H_{11}NO_4$	65.36 (65.48)	4.31 (4.45)	5.45 (5.33)	
c	-Cl	o-C_6H_4-OH	EtOH	75	166	$C_{14}H_{10}ClNO_3$	60.98 (61.05)	3.63 (3.72)	5.08 (5.12)	12.88 (13.05)

TABLE II

2-Substituted 4(1*H*)Quinazolinones



Compound IV	R	Recryst. solvent	Yield, %	M.p. °C	Formula	Analyses Calcd. (Found) C	H	N
a	$-C_6H_5$	dioxane	40	267	$C_{14}H_{10}N_2O$	75.65 (75.30)	4.54 (4.35)	12.61 (13.05)
b	o-C_6H_4-OH	dioxane	70	327	$C_{14}H_{10}N_2O_2$	70.59 (70.31)	4.23 (4.30)	11.76 (11.73)
c	4-pyridyl	ethanol	30	308	$C_{13}H_9N_3O$	69.94 (69.67)	4.06 (3.92)	18.83 (18.70)
d	3-pyridyl	methanol	25	273	$C_{13}H_9N_3O$	69.94 (69.70)	4.06 (3.84)	18.83 (18.90)

mole) and benzamide (IIa) (4.84 g., 0.04 mole) was heated under reflux for two hours. The mixture became dark brown. It was cooled and extracted with boiling ethanol. The insoluble yellow residue melted at 267° when crystallized from dioxane; ir (nujol mull): 3380 cm^{-1} (NH), 1618 cm^{-1} (C=O), 1580 cm^{-1} (NH); nmr (deuteriochloroform): 6.98-7.7 δ (5H, m, $-C_6H_5$); 8.1-8.8 δ (3H, m, C_6-H, C_7-H, C_8-H); 8.78 δ (1H, s, C_5-H); 13.12 δ (1H, s, NH exchanged with deuterium oxide).

(ii) A mixture of *N*-(*o*-hydroxybenzoyl)benzamide (IIIa) (4.82 g., 0.02 mole) and benzamide (IIa) (2.42 g., 0.02 mole) was heated as described above. The yellow reaction mixture was extracted with boiling ethanol and the residue crystallized from dioxane melted at 267°.

(iii) A mixture of *o*-chlorobenzoyl chloride (Ia) (3.5 g., 0.02 mole) and benzamide (IIa) (4.84 g., 0.04 mole) was heated under reflux for two hours. The reaction mixture was extracted with boiling ethanol and the yellow residue, after crystallization from dioxane, melted at 267°.

2-(*o*-Hydroxyphenyl)-4(1*H*)quinazolinone (IVb).

(i) A mixture of *o*-hydroxybenzoyl chloride (Ib) (3.13 g., 0.02 mole) and *o*-hydroxybenzamide (IIb) (5.48 g., 0.04 mole) was heated as previously described for two hours. The reaction product which was insoluble in almost all organic solvents was crystallized from dioxane as yellow crystals which melted at 325-327°; ir (nujol mull): 3450 cm^{-1} (NH stretch), 1620 cm^{-1} (C=O), 1595 cm^{-1} (NH bend); nmr: (DMSO) 6.82-7.22 δ (4H, m, $-C_6H_4$); 7.4-8.28 δ (3H, m, C_6-H, C_7-H, C_8-H); 8.38 δ (1H, s, C_5-H); 12.7 δ (deuteriochloroform) (1H, s, NH exchanged with deuterium oxide); OH undetectable due to its acidity.

(ii) A mixture of *N*-(*o*-hydroxybenzoyl)-*o*-hydroxybenzamide (IIIb) (5.14 g., 0.02 mole) and *o*-hydroxybenzamide (IIb) (2.74 g., 0.02 mole) was heated under reflux as described above. The yellow reaction residue after crystallization from dioxane melted at 325-327°.

(iii) A mixture of *N*-(*o*-chlorobenzoyl)-*o*-hydroxybenzamide (IIIc) (5.51 g., 0.02 mole) and *o*-hydroxybenzamide (IIb) (2.74 g., 0.02 mole) was heated under reflux and the reaction residue was crystallized from dioxane giving yellow crystals which melted at 325-327°.

(iv) A mixture of *o*-chlorobenzoyl chloride (Ia) (3.5 g., 0.04 mole) and *o*-hydroxybenzamide (IIb) (5.48 g., 0.04 mole) was heated for two hours as described above. After extraction with boiling ethanol the yellow residue was crystallized from dioxane and melted at 325-327°.

2-(4-Pyridyl)-4(1*H*)quinazolinone (IVc).

(i) A mixture of *o*-hydroxybenzoyl chloride (Ib) (3.13 g., 0.02 mole) and isonicotinamide (IIc) (4.88 g., 0.04 mole) was heated under reflux for two hours. Extraction of the brown reaction mixture with boiling ethanol gave a yellow product which melted at 308° (ethanol); ir (nujol mull): 3400 cm^{-1} (NH stretch), 1619 cm^{-1} (C=O), 1592 cm^{-1} (NH bend); nmr (deuteriochloroform): 6.78-7.48 δ (4H, m, C_5H_4N); 8.18-9.0 δ (3H, m, C_6-H, C_7-H, C_8-H); 8.55 δ (1H, s, C_5-H); 12.48 δ (1H, s, NH exchanged with deuterium oxide).

(ii) A mixture of *o*-chlorobenzoyl chloride (Ia) (3.5 g., 0.02 mole) and isonicotinamide (IIc) (4.88 g., 0.04 mole) was heated under reflux as described above. A yellow product (ethanol) m.p. 308° was obtained.

2-(3-Pyridyl)-4(1*H*)quinazolinone (IVd).

(i) After heating for two hours a reaction mixture of *o*-hydroxybenzoyl chloride (Ib) (3.13 g., 0.02 mole) and nicotinamide (IId) (4.88 g., 0.04 mole) yellow crystals from methanol (m.p. 273°) were obtained; ir (nujol mull): 3390 cm^{-1} (NH stretch), 1620 cm^{-1} (C=O), 1580 cm^{-1} (NH bend); nmr (deuteriochloroform): 6.8-7.5 δ (4H, m, C_5H_4N); 8.2-9.0 δ (3H, m, C_6-H, C_7-H, C_8-H); 8.5 δ (1H, s, C_5-H); 12.5 δ (1H, s, NH exchanged with deuterium oxide).

(ii) A mixture of *o*-chlorobenzoyl chloride (Ia) (3.5 g., 0.02 mole) and nicotinamide (IId) (4.88 g., 0.04 mole) was heated under reflux as previously described. A yellow product (m.p. 273°) (methanol) was obtained.

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