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2-Aryl-4(3*H*)quinazolinones

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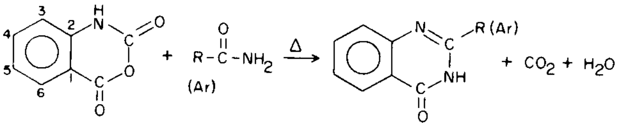
Reaction of isatoic anhydride with benzamides is shown to produce 2-aryl-4(3*H*)quinazolinones. The quinazolinones carrying a 2-(*o*-hydroxyphenyl) group are obtained in high yields.

2-Alkyl-4(3*H*)quinazolinones are conveniently prepared by the Niementowski reaction, a condensation between anthranilic acid and alkanamides (1). Although benzamides do not undergo this reaction, thiobenzamide does react (2). An attractive extension of the Niementowski synthesis involves reacting arenecarboxamides with isatoic anhydride (I) in place of anthranilic acid as a source of the anthraniloyl group. v. Meyer and Bellmann (3) found that the use of acetamide in this reaction yields amorphous products, and later it was reported (4) that the course of the reaction employing benzamides does not parallel the Niementowski reaction.



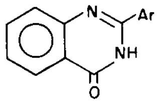
I II

Contrary to these findings, Ziegler, Steiger and Kappe (5) recently demonstrated the formation of several 2-alkyl-, 2-aralkyl- and 2-aryl-4(3*H*)quinazolinones (II) in low yields ($\sim$10%) from isatoic anhydride (I) and the corresponding carboxamides. Their observations agree with those made in the course of this work (6). We have found that the reaction of isatoic anhydride (I) with benzamides carrying substituents other than an *o*-hydroxy group, operating at elevated temperatures in a melt or in the presence of suitable solvents, leads directly to the formation of 2-aryl-4(3*H*)quinazolinones (II) in low yields. These quinazolinones (Table I) are known compounds (7). In addition, it was found that high yields of the corresponding 2-(*o*-hydroxyphenyl)-4(3*H*)quinazolinones are obtained when salicylamide or a substituted salicylamide is allowed to react with isatoic anhydride (I), or with 5-nitro- or 5-chloroisatoic anhydride. For instance, isatoic anhydride (I) and salicylamide at 140° give, in the absence of solvent, a 65% yield of 2-(*o*-hydroxyphenyl)-4(3*H*)quinazolinone (V). Information regarding these quinazolinones obtained in high yields is also given in Table I.

2-(*o*-Hydroxyphenyl)-4(3*H*)quinazolinone (V) was of interest in this laboratory as a useful intermediate in the synthesis of certain photostable 2-(*o*-hydroxyphenyl)-quinazolines substituted in the 4-position (8). Compound V was also described as a fluorescent agent and was claimed as novel (9). It was prepared by condensing anthranilamide (which normally is obtained from isatoic anhydride and ammonia) with salicyloyl chloride, followed by a base-catalyzed ring closure. It appears that 2-(*o*-hydroxyphenyl)-4(3*H*)quinazolinone (V) had been prepared by Kilroe-Smith and Stephen (7), although it was erroneously identified as 2-(*o*-hydroxyphenyl)-1,2,3,4-tetrahydro-4-oxoquinazoline (IV). Their route involved condensing anthranilamide with salicylaldehyde to give salicylidene anthranilamide (III), orange, m.p. 165° with decomposition, which, after being heated in the presence of refluxing 1*N* hydrochloric acid for 1/2 hour, allegedly isomerized to the tetrahydro compound IV (colorless, reported m.p. 300°). We find that the colorless compound so obtained and melting at 300° is identical to 2-(*o*-hydroxyphenyl)-4(3*H*)quinazolinone (V) prepared from isatoic anhydride

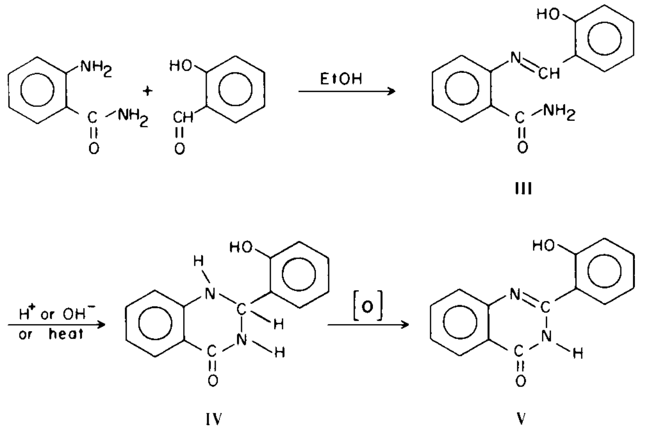
TABLE I

2-Aryl-4(3*H*)quinazolinones



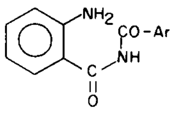
							Analysis					
								Calculated			Found	
Formula	Reaction Solvent	Temp	Crystallized from	Yield (%)	M.p. °C	Formula	C	H	N	C	H	N
2-(*o*-Hydroxyphenyl)- (a)	None	140°	AcOH	65	298	$C_{14}H_{10}N_2O_2$	70.57	4.23	11.76	70.57	4.46	11.97
2-Phenyl- (b)	DMF	150°	C_6H_6	15	235-236	$C_{14}H_{10}N_2O$	75.68	4.51	12.61	75.66	4.64	12.54
2-(*m*-Nitrophenyl)- (c)	$PhNO_2$	170°	AcOH	8	352-353	$C_{14}H_9N_3O_3$	62.92	3.40	15.73	62.98	3.67	15.69
2-(*p*-Nitrophenyl)- (d)	None	185°	AcOH	7	362-363	$C_{14}H_9N_3O_3$	62.92	3.40	15.73	63.13	3.60	15.70
2-(*p*-Chlorophenyl)- (e)	None	190°	AcOH	20	303-304	$C_{14}H_9ClN_2O$	65.50	3.53	10.92	65.72	3.66	10.90
2-(*p*-Tolyl)- (f)	None	190°	Acetone	15	240	$C_{15}H_{12}N_2O$	76.25	5.12	11.83	76.41	5.29	11.60
2-(*o*-Hydroxyphenyl)-6-nitro-	None	160°	DMF	71	399-400	$C_{14}H_9N_3O_4$	59.37	3.20	14.84	59.21	3.46	14.79
2-(5-Chloro-2-hydroxyphenyl)- (g)	DMF	145°	DMF	57	365-366	$C_{14}H_9ClN_2O_2$	61.66	3.33	10.27	61.36	3.39	10.26
2-(4-Chloro-2-nitrophenyl)-	p-Cymene	180°	C_2H_5OH	10	257-258	$C_{14}H_9ClN_3O_3$	55.73	2.67	13.93	55.70	3.03	13.95
6-Chloro-2-(*o*-hydroxyphenyl)-	DMF	145°	DMF	67	329-330	$C_{14}H_9ClN_2O_2$	61.66	3.33	10.27	61.52	3.34	10.61

(a) Ref. 9, m.p. 297-298°. (b) Ref. 7, m.p. 238°. (c) Ref. 7, m.p. 354°. (d) Ref. 7, m.p. 365°. (e) D. T. Zentmyer and E. C. Wagner, *J. Org. Chem.*, 14, 967 (1949), m.p. 306°. (f) Ref. 7, m.p. 241°. (g) Ref. 9, m.p. not reported.

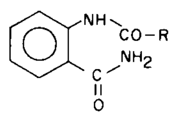


and salicylamide. Thus, the isomerization of III to IV under conditions employed by Kilroe-Smith and Stephen (7) was obviously accompanied by an oxidation or a disproportionation of IV to give the more stable compound V. We prepared the elusive tetrahydro compound (IV) readily by heating a suspension of the original condensation product (III) in refluxing ethanol under nitrogen for six hours. The compound IV is colorless and melts at 235-238° with decomposition to give V. The latter also forms from IV in the presence of refluxing 1*N* hydrochloric acid in the course of 1/2 hour under conditions used by Kilroe-Smith and Stephen (7) to convert III to V.

The reaction between isatoic anhydride and benzamides probably involves a nucleophilic attack of the benzamide on isatoic anhydride (I), which would explain the observation that electron-withdrawing substituents in the benzamide retard the condensation. This may be followed by loss of carbon dioxide to give an intermediate VI. In contrast, the accepted intermediate of the Niementowski reaction has structure VII, R = alkyl (4). Apparently, VI



VI



VII

and VII (R = alkyl) cyclize spontaneously, whereas VII (R = aryl) requires the presence of a base to give the corresponding quinazolinone (9). This would explain the failure of the Niementowski reaction when applied to benzamides. In agreement with the above, we find that, when isatoic anhydride (I) is allowed to react with anthranilamide, the nucleophilic attack is provided by the *o*-amino group and not the carbamoyl group of anthranilamide, giving VII (R = *o*-aminophenyl) which must be treated with 3% aqueous sodium hydroxide to form 2-(*o*-aminophenyl)-4(3*H*)quinazolinone.

EXPERIMENTAL

2-(*o*-Hydroxyphenyl)-4(3*H*)quinazolinone (V).

Isatoic anhydride, 163 g. (1.0 mole), and salicylamide, 137 g. (1.0 mole), were mixed intimately and the mixture was heated in an open, short-necked flask at 140° (oil-bath temperature) with occasional stirring until carbon dioxide evolution and precipitation of a solid product were complete (3 hours). The solid was crushed and extracted with boiling ethanol to give 154 g. (65% of theory) of the title compound, m.p. 296-298°. The material was crystallized from acetic acid to furnish an analytical sample, m.p. 298°. Lit., 300° (7) and 297-298° (9); uv spectrum (in acetonitrile): maxima at 331 (ϵ 14,460), 299 (ϵ 12,740) and 286 $m\mu$ (ϵ 12,950); shoulders at 340 and 322 $m\mu$; ir spectrum (in potassium bromide pellet): N-H and C=O stretching bands at 3,200 and 1,667 cm^{-1}, respectively, other strong peaks (in cm^{-1}) at 1,604, 1,330, 1,249, 825, 757 and 623.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.57; H, 4.23; N, 11.76; O, 13.43. Found: C, 70.57; H, 4.46; N, 11.97; O, 13.81.

2-(*o*-Hydroxyphenyl)-1,2,3,4-tetrahydro-4-oxoquinazoline (IV).

A mixture of 6.8 g. (0.05 mole) of anthranilamide and 6.1 g. (0.05 mole) of salicylaldehyde in 100 ml. of ethanol was heated at reflux under nitrogen for six hours. The original orange precipitate of salicylidene anthranilamide went into solution and a colorless compound separated. The mixture was filtered hot and the cake was washed with ethanol to give 5.89 g. of a vacuum-dried colorless solid (IV), m.p. 235-238°; ir spectrum (in potassium bromide pellet): N-H stretching bands at 3,412 (sharp) and 3,230 cm^{-1} (broad); C=O stretching band at 1,645 cm^{-1} (doublet); strong peaks at 1,611, 1,596, 1,576, 1,232 and 745 cm^{-1} (doublet); pmr spectrum (in deuterated dimethyl sulfoxide; chemical shifts downfield from TMSi): two protons (at 3.5 and 6.1 ppm) absent from the spectrum of 2-(*o*-hydroxyphenyl)-4(3*H*)quinazolinone; proton of the *o*-OH group at 9.82 ppm.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66; O, 13.32. Found: C, 70.07; H, 5.08; N, 11.73; O, 13.28.

2-(*o*-Aminophenyl)-4(3*H*)quinazolinone

A mixture of 4.1 g. of isatoic anhydride and 6.8 g. of anthranilamide in 50 ml. of dimethylformamide was heated at 70° for four hours and at 90° for four hours. The solvent was removed by distilling in vacuum and the residue was dissolved in 175 ml. of boiling water. The hot solution was filtered and a solid product was allowed to crystallize from the filtrate. It was recrystallized from ethanol and appeared to be *o*-(*o*-aminobenzamido)benzamide (ir). The intermediate was cyclized in a boiling 3% aqueous solution of sodium hydroxide to 2-(*o*-aminophenyl)-4(3*H*)quinazolinone which was isolated after acidification with a dilute solution of aqueous hydrochloric acid. The material was crystallized from ethanol (1.7 g.), m.p. 240-241°. Lit., m.p. 241° (10); ir spectrum (in potassium bromide pellet): N-H stretching bands at 3,450 and 3,360 cm^{-1} (primary amino group) and at 3,200 cm^{-1} (secondary amido group); C=O stretching band at 1,670 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.90; H, 4.83; N, 17.34.

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