Photostable *o*-Hydroxyphenylquinazolines

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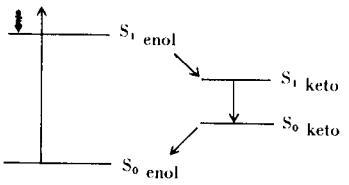
The correlation between intrinsic photostability (Φ_R^{-1}) and structure of several intramolecularly hydrogen-bonded heterocycles containing suitable *o*-hydroxyphenyl groups is briefly discussed in terms of the changes in resonance energy resulting in such compounds from a reversible keto-enol rearrangement in the lowest excited singlet state. The influence of intramolecular hydrogen bonding, resonance and steric effects on photostability in *o*-hydroxyphenylquinazolines as elucidated with the aid of spectroscopic methods is discussed in detail.

It appears that no systematic study of factors determining photostability of organic molecules has been conducted. Although various *o*-hydroxyphenyl containing 2*H*-benzotriazoles, imidazoles, thiazoles, triazines and pyrimidines were patented as UV light stabilizers, no correlation between structure and photostability has been attempted.

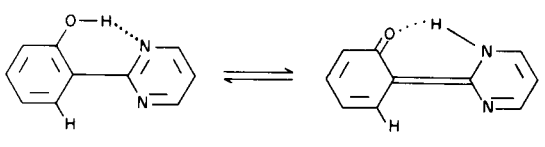
It has been well established that a significant increase in photostability resulted from attaching a hydroxy group in the *ortho* position of a benzophenone or *o*-hydroxyphenyl group in a suitable position of a nitrogen-containing heterocycle in order that a six-membered ring including an intramolecular hydrogen bond between H and O or N could form. The photostability of such compounds was related to reversible enolization (1,2) and to charge-transfer configuration of their excited states (3). Merrill and Bennett (4) showed that intramolecular hydrogen bonding provided a deactivation mechanism for excited states of *o*-amidophenyl-2*H*-benzotriazoles by increasing internal conversion (a radiationless mode of dissipating the photoexcitation energy in the form of heat within the singlet system) from excited singlet to ground state by a factor of one hundred. This was accompanied by lower quantum yields for fluorescence and intersystem crossing to triplet, although neither the triplet levels nor the rate constant of the intersystem crossing were affected.

Significant progress in understanding the mechanism of photodeactivation in intramolecularly hydrogen-bonded compounds was made in this laboratory by Otterstedt (5). He postulated that a charge-transfer in the lowest excited singlet state provided a driving force for a reversible formation of a lower-energy keto form (I ⇌ II) which had the effect of decreasing the energy gap separating its excited and ground states, as shown in the diagram below:



The postulate was substantiated by a direct observation at 77°K of a very weak, strongly red-shifted keto fluorescence characterized by very large Stoke shifts, up to 15,000 cm^{-1}, in intramolecularly hydrogen-bonded quinolines, pyrimidines, quinazolines, 2*H*-benzotriazoles and benzophenones. A decrease in the energy gap separating the excited and ground states of the keto form resulted in an exponential increase in the rate of internal conversion which became, by far, the fastest mode of de-excitation of photoexcited molecules. The probability of an intersystem crossing to the chemically reactive triplet was decreased. Photostability, defined as the inverse of the quantum yield of photochemical reaction, was proportional to the rate of internal conversion ($\Phi_R^{-1} \propto k_{i.c.}$).

Thus, correlation appeared possible for a number of *o*-hydroxyphenyl-substituted heterocycles of photostabilities with changes in resonance energy taking place when enol rearranged to ketone in the lowest excited singlet state. This was apparent following the syntheses (6) and determination of photostability (7) of certain model compounds, of which an *o*-hydroxyphenylpyrimidine showed a vastly superior photostability to that of a similarly structured *o*-hydroxyphenylpyridine. Additional measurements were made on simpler *o*-hydroxyphenylpyrimidines

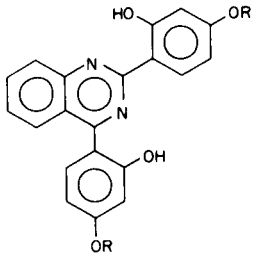
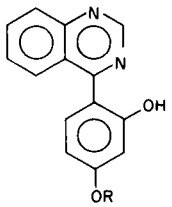
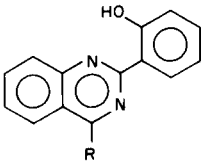


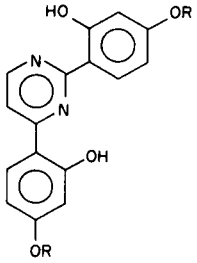
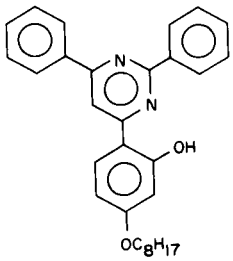
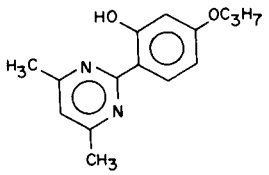
I II

(8) and on tris-(*o*-hydroxyphenyl)-*s*-triazine to establish an increasing order of photostability with a decreasing resonance stabilization of the heterocycle (pyridine > pyrimidine > triazine). Thus, a decrease in the resonance energy of the heterocycle facilitated the enol-ketone rearrangement in the lowest excited singlet state—a finding consistent with the proposed theory of photostability (5). It was not immediately apparent, however, what the influence of a benzene ring fused to the heterocycle would be on photostability, for in such a case, one would increase the total resonance energy of the system. This interesting problem was studied extensively in application to *o*-hydroxyphenylquinazolines. Comparison of the photostability data for analogous *o*-hydroxyphenylquinazolines and pyrimidines (Table I) showed that the benzene-ring fusion constituted a structural factor enhancing photostability. It thus appeared that the latter was not related to the total resonance energy of the heterocycle (which

TABLE I

Photostabilities of *o*-Hydroxyphenyl-substituted Quinazolines and Pyrimidines

	R	Matrix	$\Phi^{-1} \times 10^{-6}$
	H	PAN (a)	3.3
		Nylon	3.0
		CH_3CN	0.45
	n-C_3H_7	PAN (a)	0.41
		Nylon	11.0
		CH_3CN	0.79
		Hexane	0.52
	n-C_4H_9	Nylon	6.1
		CH_3CN	1.5
		Hexane	0.77
Tripropyl Derivative of the above		Nylon	10.0
		CH_3CN	8.2
		Hexane	2.7
	n-C_3H_7	PAN (a)	0.007
		Nylon	0.0036
		CH_3CN	0.065
		Hexane	0.21
	C_6H_5	PAN (a)	9.8
		Nylon	10.5
		CH_3CN	22.0
		Hexane	3.3
	CH_3	PAN (a)	5.6
		Nylon	7.1
		CH_3CN	6.2
		Hexane	4.2
	$N(CH_3)_2$	PAN (a)	0.088
		Nylon	0.33
		CH_3CN	0.83
		Hexane	0.80

	R	Matrix	$\Phi^{-1} \times 10^{-6}$
	H	PAN (a)	0.68
		Nylon	1.7
		CH_3CN	0.59
	n-C_3H_7	PAN (a)	1.1
		Nylon	2.7
		CH_3CN	1.7
		Hexane	0.39
		PAN (a)	0.075
		Nylon	0.022
		CH_3CN	0.099
		Hexane	0.86
		Nylon	1.0
		CH_3CN	0.15
		Hexane	0.14

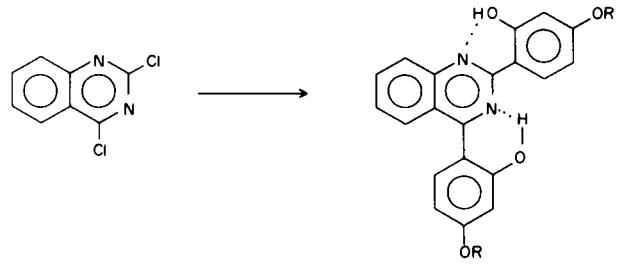
(a) Polyacrylonitrile

was larger for quinazoline than for pyrimidine), but depended on the relative loss in resonance energy of the heterocycle occurring when enol rearranged to ketone in the lowest excited singlet state. This was smaller for quinazoline than for pyrimidine, hence, the rearrangement, providing a mechanism for photostabilization, was facilitated in the case of quinazoline compounds. Similarly, an enhancement of photostability should be observed by substituting quinoline for pyridine, quinoxaline for pyrazine and 4,7-phenanthroline for 3,3′-bipyridyl.

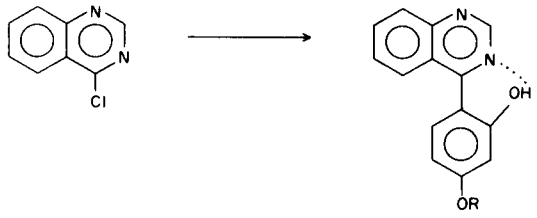
This paper discusses the syntheses and the structure-photostability relationships as revealed by a study of the intramolecular hydrogen-bonding, resonance and steric effects in various *o*-hydroxyphenylquinazolines.

Syntheses.

o-Hydroxyphenylquinazolines were prepared mostly by known methods (9). 2,4-Dichloroquinazoline or 4-chloroquinazoline was allowed to react with resorcinol in nitrobenzene in the presence of anhydrous aluminum chloride to give 2,4-bis(2,4-dihydroxyphenyl)quinazoline or 4-(2,4-dihydroxyphenyl)quinazoline, respectively:

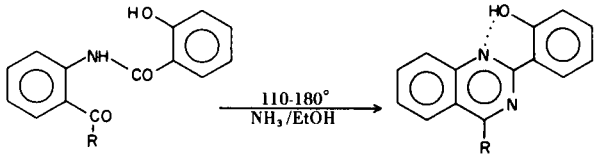


III a, R = H
b, R = *n*-propyl
c, R = *n*-butyl



IV a, R = H
b, R = *n*-propyl

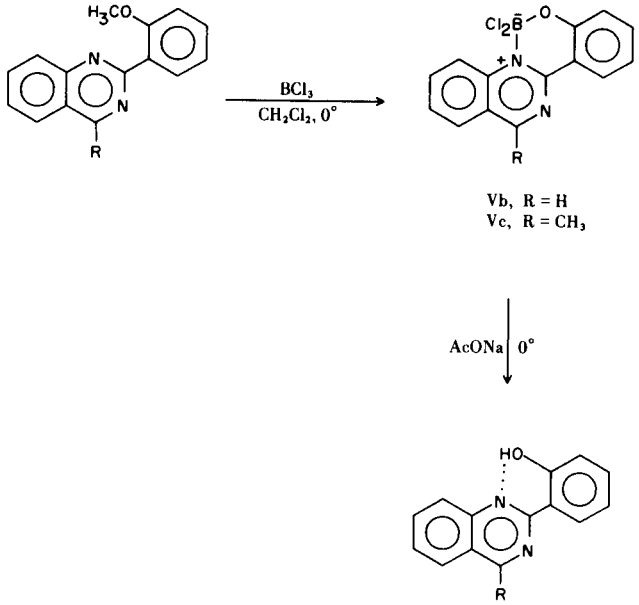
Several 2-(*o*-hydroxyphenyl)quinazolines, substituted in the 4-position of the quinazoline ring by carboxyl, hydrogen, methyl and phenyl, were prepared by condensing *o*-salicylaminobenzaldehyde, *o*-salicylaminobenzophenone, and other substrates of the general formula shown below, with ammonia under pressure (Bischler's synthesis):



V a, R = COOH
b, R = H
c, R = CH_3
d, R = C_6H_5

Compound Va was decarboxylated at an elevated temperature to give Vb.

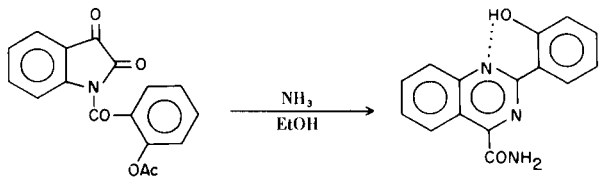
Analogous cyclizations provided *o*-methoxy derivatives of Vb and Vc. These underwent a novel demethylation by a chelation mechanism with gaseous boron trichloride under very mild conditions (0°C) to give products identical to Vb and Vc:



Vb, R = H
Vc, R = CH_3

Demethylation under more drastic conditions (refluxing concentrated hydrogen bromide or anhydrous aluminum chloride in boiling toluene) failed, probably due to a quinazoline-ring fission. Recent literature (10) described the use of boron trichloride to cleave methoxy groups *ortho* to a carbonyl group at room temperature. Boron tribromide was also found to be a powerful demethylating agent for aryl methyl ethers at, or below, room temperature (11).

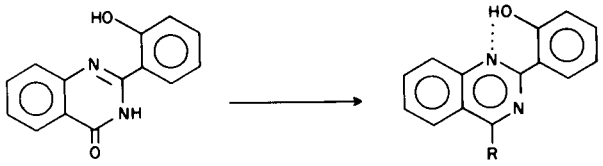
Another cyclization method with ammonia under pressure was adapted from Meyer (12) and involved *N*-(*o*-acetoxybenzoyl)isatin, which gave in one step 2-(*o*-hydroxyphenyl)quinazoline-4-carboxamide:



Ve

The carboxylic acid (Va, R = COOH), obtained as described above, was esterified with methanol and the methyl ester was treated with ammonia to give a carboxamide identical to Ve.

Additional 2-(*o*-hydroxyphenyl)quinazolines carrying such 4-substituents as amino, chloro, dimethylamino and methoxy were prepared from 2-(*o*-hydroxyphenyl)-4(3*H*)-quinazolinone (13). The compound underwent a direct amination with ammonia in analogy to 4-quinazolinone which was converted to 4-aminoquinazoline with ammonia in methanol at 200° (14). The product (Vf) was readily acetylated to give 2-(*o*-hydroxyphenyl)-4-acetamidoquinazoline. Chlorination of the quinazolinone was accomplished at room temperature with a phosgene-dimethylformamide mixture in *o*-dichlorobenzene as solvent and produced Vg in a high yield. Subsequent treatment of Vg with dimethylamine gave Vh. Finally, the 4-methoxy derivative (Vi) was obtained by treatment of 2-(*o*-hydroxyphenyl)-4(3*H*)-quinazolinone with diazomethane or methyl iodide.



Vf, R = NH_2
g, R = Cl
h, R = NMe_2
i, R = OCH_3

Spectra and Structure.

In view of a very large difference in photostability shown by quinazolines and, to a somewhat lesser degree, by pyrimidines having either 2- or 4-*o*-hydroxyphenyl group (see discussion below), a detailed examination of the intramolecular hydrogen bonding was in order. IR spectra provided a sufficient means of distinguishing between the inter- and intramolecular hydrogen bonding in 2,4-bis(2,4-dihydroxyphenyl)quinazoline (IIIa) and 4-(2,4-dihydroxyphenyl)quinazoline (IVa). The former compound (IIIa) showed distinct peaks at 2.95 and 3.03 μ in addition to a weak, diffuse band at 3.6-4.0 μ. The bands centered around 3 μ were due to a nonchelated O–H stretching vibration. The latter compound (IVa) displayed only an unusually broad and very weak band between 3.1 and 4.2 μ partly superimposed on C–H stretching bands. The higher frequency portion of this band was, undoubtedly, due to stretching of an intermolecularly bonded O–H group in the *para* position. In agreement with these IR data and as a consequence of IIIa and IVa possessing unchelated *p*-OH groups in the phenyl rings, the compounds were found to be soluble in 5% aqueous solution of sodium hydroxide. The lower frequency, very weak and diffuse band at 3.6-4.0 μ in the spectra of IIIa and IVa appeared to be due to intramolecularly hydrogen-bonded *ortho* OH groups. This was confirmed by examing IR spectra of their alkyl derivatives. IVa readily gave a monopropyl derivative (IVb, R = propyl) which was insoluble in 5% aqueous sodium hydroxide solution and whose spectrum showed the weak, diffuse band at 3.6-4.0 μ. It was more conveniently observed in a dilute carbon tetrachloride solution at 2,600-2,800 cm^{-1}. Thus, the *p*-OH group was propylated, whereas the *o*-OH group remained chelated to the 3-nitrogen. A more complex product mixture was obtained following the alkylations of 2,4-bis(2,4-dihydroxyphenyl)-quinazoline (IIIa). A large excess of diazomethane or an alkyl iodide gave a rather high yield of a trimethyl or a trialkyl derivative, respectively, but never a fully tetrasubstituted derivative. Stoichiometric quantities (two molar equivalents) of an alkyl iodide produced a mixture consisting mainly of a dialkyl and trialkyl derivative (both were insoluble in 5% aqueous sodium hydroxide solution). Their separation was achieved by chromatography on a silicic-acid column and fractional crystallization. In addition, a fraction soluble in 5% aqueous sodium hydroxide solution, which presumably contained a mixture of monoalkyl derivatives and the unchanged IIIa, was obtained, and thus, was not examined. Neither dialkyl nor trialkyl derivatives showed a peak around 3 μ, in accord with the lack of solubility in 5% aqueous sodium hydroxide solution. This indicated that the dialkylations involved two *p*-OH groups, the two *o*-OH groups being hydrogen-bonded to nitrogen atoms of the quinazoline. Apparently, a lower ground state energy was provided when the *o*-OH group in the 2-phenyl ring chelated to the N-1 atom and the *o*-OH group in the 4-phenyl ring chelated to the N-3 atom, although these two hydrogen bonds could not be of equal strength, as trialkylations of 2,4-bis(2,4-dihydroxyphenyl)quinazoline (IIIa) were possible. IR spectra, however, were neither suited for determination of the structure of trialkylated 2,4-bis(2,4-dihydroxyphenyl)-quinazolines nor useful in distinguishing between dialkylated and trialkylated derivatives of the parent compound. In each case, there was a very weak, diffuse band extending down to about 2,600 cm^{-1} and obscured partly by C–H stretching bands at 2,960-2,840 cm^{-1} (potassium bromide

pellet). In a dilute carbon tetrachloride solution, the band appeared at 2,600-2,800 cm^{-1} and was obscured by C–H stretching absorption above 2,800 cm^{-1}. The center of the band seemed to be located at or somewhat above 2,800 cm^{-1}, indicating a displacement to higher frequencies relative to an analogous band of 2-(*o*-hydroxyphenyl)quinoline which occurred at 2,720 cm^{-1} in dilute carbon tetrachloride. These bands were assigned to an O–H stretch of a strongly intramolecularly hydrogen-bonded OH group in agreement with Branch *et al.* (15) who found one in the spectrum of 2-phenacylpyridine at 2,600 cm^{-1} (dilute carbon tetrachloride solution). Analogous bands due to a strongly chelated OH group were also found in the spectra of compounds Va-i.

The most useful structural assignments and correlations with photostability were made on the basis of PMR spectra. These were recorded (Table II) mainly to determine whether chelation between OH and N-1 or N-3 produced different chemical shifts of the hydroxyl protons. The PMR spectra showed the presence of strongly deshielded hydroxyl protons considerably displaced from the usual phenolic region (16). Deshielding due to hydrogen bonding between OH and N was expected on the basis of the MO theory: the lone pair of nitrogen electrons occupies a π-antibonding orbital of the OH group, thereby weakening the O–H bond. Thus, the stronger the hydrogen bonding, the larger the downfield shift of the hydroxyl proton in the PMR spectrum. The most interesting finding was that the dialkyl derivatives of 2,4-bis(2,4-dihydroxyphenyl)quinazoline and -pyrimidine displayed two rather broad, but sufficiently well resolved, proton signals. Also significant was a rather large difference in the position of signals in the spectrum of 4-(2-hydroxy-4-propoxyphenyl)-quinazoline (at 12.78 ppm) and those in the spectra of many 2-(*o*-hydroxyphenyl)quinazolines substituted in the 4-position (at 13.47-14.62 ppm). These results provided convincing evidence for a weaker hydrogen bonding of the *o*-hydroxy group in the 4-phenyl ring to the N-3 atom than that of the *o*-hydroxy group in the 2-phenyl ring to the N-1 atom. The conclusion was especially compelling in view of the fact that the proton signal of 4-(2-hydroxy-4-propoxyphenyl)quinazoline at 12.78 ppm agreed closely with the higher field signal of dibutylated 2,4-bis(2,4-dihydroxyphenyl)quinazoline at 12.70 ppm. On the other hand, the lower field signal of the latter compound at 13.80 ppm agreed closely with those of several 2-(*o*-hydroxyphenyl)quinazolines substituted in the 4-position at 13.47-14.62 ppm. This made it possible to assign the higher field signal at 12.70 ppm and the lower field signal at 13.80 ppm in the spectrum of 2,4-bis(2-hydroxy-4-butoxyphenyl)quinazoline to the *o*-OH group in the 4-phenyl ring chelated to the N-3 atom and to the *o*-OH group in the 2-phenyl ring chelated to the N-1 atom, respectively. Thus, the PMR spectra, like the IR spectra,

TABLE II

PMR Signals of Chelated Hydroxyl Groups (a)

Compounds	Protons
4-(2-Hydroxy-4-propoxyphenyl)quinazoline	12.78
2,4-bis(2-Hydroxy-4-butoxyphenyl)quinazoline	13.80; 12.70
2,4-bis(2-Hydroxy-4-propoxyphenyl)pyrimidine	14-14.5; 13-13.5
2-(2-Hydroxy-4-methoxyphenyl)-4-(2,4-dimethoxyphenyl)quinazoline	14.03
2-(2-Hydroxy-4-propoxyphenyl)-4-(2,4-dipropoxyphenyl)quinazoline	14.17
2-(*o*-Hydroxyphenyl)-4-chloroquinazoline	13.00
2-(*o*-Hydroxyphenyl)quinazoline	13.47
2-(*o*-Hydroxyphenyl)-4-phenylquinazoline	13.57
2-(*o*-Hydroxyphenyl)-4-methylquinazoline	13.63
2-(*o*-Hydroxyphenyl)-4-methoxyquinazoline	14.04
2-(*o*-Hydroxyphenyl-4-dimethylaminoquinazoline	14.62
2-(*o*-Hydroxyphenyl)quinoline (b)	14.42

(a) Determined in deuteriochloroform, unless stated otherwise. Chemical shifts in ppm downfield from TMSi. (b) In carbon tetrachloride.

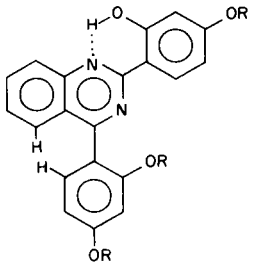
showed both *o*-OH groups to be chelated, but the PMR spectra provided additional information regarding relative strengths of the two hydrogen bonds. This difference in strength of the hydrogen bonds, observed also in the case of 2,4-bis(2-hydroxy-4-propoxyphenyl)pyrimidine (Table II), was undoubtedly due, in the main, to steric effects, to which hydrogen bonding was extremely sensitive. There are dramatic examples in the literature (15) of steric hindrance to planarity weakening an intramolecular hydrogen bond. In particular, severe steric effects result from overcrowding substituents on C-4 and C-5 of the quinazoline nucleus (17). It could readily be seen that a steric strain resulted from attachment of a fairly bulky substituent, such as *o*-hydroxyphenyl, in the 4-position, but not in the 2-position, of either pyrimidine or quinazoline. This steric strain was present in both the ground and the lowest excited singlet states of the enol and the ketone forms arising in a reversible rearrangement (compare I ⇌ II with VI ⇌ VII, shown below). It was due to overcrowding

VI VII

of hydrogens at C-5 and *o'*(C-6'). In VI, the amount of steric strain should be similar to that in biphenyl, in which the corresponding hydrogens are 1.8 Å apart (this compares with a double Van der Waals radius of a hydrogen atom of 2.4 Å, which is a minimum distance necessary for repulsion between two hydrogen atoms to disappear), causing the angle between two phenyl rings to be about 23° in solution (18). In quinazolines carrying a phenyl ring in the 4-position, the distance between hydrogens at C-5 and *o'*(C-6') is even smaller than 1.8 Å, leading to a correspondingly larger twisting of the rings out of plane than 23°. The larger the steric hindrance to planarity, the weaker the intramolecular hydrogen bonding because of an increased distance between the oxygen and nitrogen atoms and a reduced conjugation between the 4-phenyl ring and the heterocycle.

Another factor contributing to a weaker hydrogen bond between the *o*-OH in the 4-phenyl ring and the N-3 atom of the quinazoline nucleus seemed to be basicity of the N-3 atom, which was calculated to be lower than that of the N-1 atom (19).

It was possible, on the basis of the above discussion of chelation, to assign a structure to trialkyl derivatives of 2,4-bis(2,4-dihydroxyphenyl)quinazoline. It seemed reasonable to assume that the *o*-OH group in the 4-phenyl ring was much more susceptible to alkylation as a result of its forming a weaker hydrogen bond to the N-3 atom than the other *o*-OH group chelating to the N-1 atom so that the structure of trialkyl derivatives was as indicated



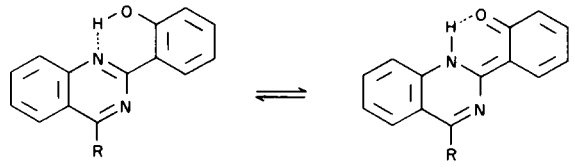
VIIIa, R = CH_3
b, R = *n*-propyl

in VIII. This contention was supported by the PMR spectra. It can be seen from Table II that the introduction of a third alkyl group was accompanied by the disappearance of a higher-field signal around 12.70 ppm which was associated with the *o*-OH group in the 4-phenyl ring of 2,4-bis(2-hydroxy-4-butoxyphenyl)quinazoline. A hydroxyl proton signal around 14 ppm was seen in the spectrum of trimethyl or tripropyl derivatives. It apparently corresponded to the lower-field signal of the dibutoxy derivative at 13.80 ppm associated with the *o*-OH group in the 2-phenyl ring and to those of 2-(*o*-hydroxyphenyl)quinazolines substituted in the 4-position at 13.47-14.62 ppm.

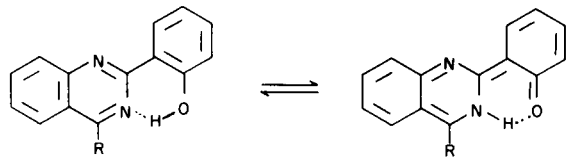
Two possible modes of chelation free of steric hindrance had to be considered for trialkyl derivatives VIII and 2-(*o*-hydroxyphenyl)quinazolines carrying a 4-substituent other than an *o*-hydroxyphenyl group (Va-i): one to N-1 and the other to N-3. Chelation of the OH group to a more basic N-1 (19) to form a stronger hydrogen bond was supported by the PMR spectra (Table II). These showed a large susceptibility of chelation to changes in the basicity of N-1 brought about by the mesomeric, rather than inductive, effects of the 4-substituent of V. For instance, the 4-chloro substituent, which strongly withdraws electrons by induction, caused a much smaller upfield shift in the proton signal of 2-(*o*-hydroxyphenyl)-quinazoline than the downfield shift due to 4-dimethylamino group, which strongly releases electrons in a mesomeric effect (see ref. 9, pp. 332-333). The latter substituent brought up the strength of the intramolecular hydrogen bonding in 2-(*o*-hydroxyphenyl)quinazoline to that in 2-(*o*-hydroxyphenyl)quinoline. The importance of

mesomeric effects transmitting electrons from the 4-substituent to N-1 was underscored also by a rather large change in the signal location when the 4-phenyl group (13.57 ppm) was replaced by the 4-(2,4-dialkoxyphenyl) group (14.03-14.17 ppm) which equalled that obtained on going from 4-H to 4-CH_3O. This indicated that the 4-(2,4-dialkoxyphenyl) group, unlike the 4-phenyl group, conjugated with the quinazoline nucleus and that its conformation was as shown in VIII, the bulky *o*-OR group being away from hydrogen at C-5 to minimize repulsions and to increase conjugation. Evidently, the *p*-OR group in the 4-phenyl substituent was instrumental in bringing about coplanarity of this substituent and the quinazoline nucleus.

It should be pointed out that the probability and the speed of the reversible enol-ketone rearrangement would be predicted on the basis of resonance considerations to be higher for the OH group chelated to N-1 rather than to N-3. It can be seen that the rearrangement V″ ⇌ V‴ would lead to a larger loss in the resonance energy than the rearrangement V ⇌ V′.



V V′



V″ V‴

Examination of the IR and PMR spectra allowed all the important structural and conformational assignments to be made. These could be corroborated in a few instances with the aid of UV spectra which, in addition, served as a valuable criterion of purity for some not so easily purifiable compounds. The UV spectra of 4-(2,4-dihydroxyphenyl)- and 2,4-bis(2,4-dihydroxyphenyl)quinazoline and their alkyl derivatives are listed in Table III. Those of 2-(*o*-hydroxyphenyl)quinazolines substituted in the 4-position are listed in Table IV. All compounds absorbed strongly in the 300-400 mμ region. The lowest transition appeared in most compounds as a shoulder (inflection point) around 350 mμ. Extinction coefficients of the absorption maxima in the spectra of di- and trialkyl derivatives of 2,4-bis(2,4-dihydroxyphenyl)quinazoline (Table III) were much higher (26,000-27,000) than those in the spectra of compounds listed in Table IV (8,000-17,000). Interestingly, the UV spectrum of 2-(*o*-hydroxyphenyl)-4-phenylquinazoline was similar in this respect to other compounds shown in Table IV and carrying such 4-substituents as 4-H, 4-CH_3, 4-OCH_3, etc. It differed drastically from those of the dipropyl and tripropyl derivatives of 2,4-bis(2,4-dihydroxyphenyl)quinazoline (Table III), indicating that the 4-(2-hydroxy-4-propoxyphenyl) and 4-(2,4-dipropoxyphenyl) groups, but not the 4-phenyl group, conjugated with the quinazoline nucleus—in agreement with the PMR data. UV spectral features allowed a distinction to be made between a dialkyl and a trialkyl derivative (Table III). The former showed a very well-developed shoulder above 350 mμ whose extinction coefficient relative to the peak around 339 mμ was very high (0.87 for the dipropyl derivative). The latter showed a much less pronounced shoulder above 350 mμ whose extinction coefficient relative to the peak at 331 mμ was significantly smaller (0.415 for the tripropyl derivative). Regarding the UV spectra of compounds listed in Table IV, an interesting trend was observed as the electron-releasing power of the 4-substituent increased in the order Ph < H < CH_3 < OCH_3 < $N(CH_3)_2$. A small hypsochromic shift occurred in the absorption maximum from 334 to 326 mμ and a larger one in the location of the shoulder from 354 to around 335 mμ. Normally, electronic spectra exhibit bathochromic effects with the increasing electron-donating power of substituents. The data indicated that the 4-phenyl group, due to a strong steric hindrance, was mostly withdrawing electrons by induction and did not conjugate with the quinazoline nucleus—in agreement with the PMR spectra which produced an identical order of substituent effect, *i.e.*, an increase in the strength of chelation at N-1 with an increasing electron-releasing power of the 4-substituent (Table II).

Photostability.

Photostability data (in Nylon or PAN films and in acetonitrile or hexane solutions) listed in Table I correlated well with the steric and resonance effects discussed in the previous sections of this paper. 4-(2-Hydroxy-4-propoxyphenyl)quinazoline showed a very low photostability, lower than that of the corresponding 4-(*o*-hydroxyaryl)pyrimidines, in agreement with a larger steric hindrance to planarity for the 4-aryl substituent in the former than in the latter. Consequently, the photostabilities of 2,4-bis(2,4-dihydroxyphenyl)quinazoline and its dialkyl derivatives were adversely affected and appeared to be only marginally better than those of the corresponding pyrimidine compounds. More complete data for the latter family of compounds indicated that an *o*-hydroxyaryl group in the 2 and 4 positions yielded higher photo-

TABLE III

UV Spectral Data for 2,4-Dihydroxyphenylquinazolines (a)

4-(2,4-Dihydroxyphenyl)quinazoline (b)	400 (c)	(3,500); 359 (9,700); 260 (7,400).
4-(2-Hydroxy-4-propoxyphenyl)quinazoline (d)	400 (c)	(3,600); 367 (16,500). 297 (6,200); 263 (8,100); 255 (8,500).
2,4-bis(2,4-Dihydroxyphenyl)quinazoline (b)	400 (c)	(6,400); 350 (e) (17,700); 327 (23,400); 282 (21,500).
2,4-bis(2-Hydroxy-4-propoxyphenyl)quinazoline (d)	400 (c)	(10,250); 357 (e) (23,800); 339 (27,400); 306 (23,100); 291 (e) (21,400); 267 (15,300); 243 (e) (17,200).
2-(2-Hydroxy-4-propoxyphenyl)-4-(2,4-dipropoxyphenyl)quinazoline (d)	400 (c)	(3,080); 358 (e) (10,700); 331 (25,800); 323 (e) (24,600); 293 (25,000); 287 (e) (24,800); 259 (16,800); 239 (e) (19,900); 222 (e) (42,200).

(a) Values are in mμ; numbers in parentheses are molar extinction coefficients. (b) In 95% ethanol. (c) End absorption. (d) In cyclohexane. (e) Inflection point (shoulder).

TABLE IV

UV Spectral Data for 2-(*o*-Hydroxyphenyl)Quinazolines Substituted in the 4-Position (a)

4-Substituent	
H (b)	400 (c) (475); 348 (d) (7,700); 332 (9,000); 320 (d) (7,700); 284 (d) (15,500); 268 (32,400); 218 (34,400).
CH_3 (b)	400 (c) (260); 343 (d) (8,400); 330 (9,700); 320 (d) (8,200); 282 (d) (16,600); 267 (34,400); 217 (36,000).
C_6H_5	400 (c) (950); 354 (d) (7,050); 334 (11,450); 327 (d) (10,800); 273 (36,600).
OCH_3 (b)	400 (c) (33); 330 (11,000); 294 (14,300); 283 (16,800); 260 (30,200); 218 (33,200).
$N(CH_3)_2$ (b)	400 (c) (18); 326 (17,000); 314 (16,950); 269 (23,200).
COOH (e)	400 (c) (1,470; 327 (7,760).
$COOCH_3$ (b)	400 (c) (2,760); 365 (d) (4,550); 330 (d) (7,600); 276 (25,500); 260 (18,900); 217 (32,900).
$CONH_2$ (f)	400 (c) (1,580); 353 (d) (4,950); 326 (8,200); 274 (28,400).

(a) Values are in mμ; numbers in parentheses are molar extinction coefficients. (b) In cyclohexane. (c) End absorption. (d) Inflection point (shoulder). (e) In acetonitrile. (f) In acetic acid.

stability than one such group in the 2 position, which, in turn, was more effective than that in the 4-position. Alkylation of the photochemically rather labile *o*-OH group in 2,4-bis(2-hydroxy-4-alkoxyphenyl)quinazolines gave highly photostable trialkyl derivatives of 2,4-bis(2,4-dihydroxyphenyl)quinazoline. These were as good as 2-(*o*-hydroxyphenyl)quinazolines carrying such 4-substituents as phenyl, methyl and hydrogen, which appeared to represent the most photostable organic molecules. Only one other compound prepared in this laboratory (6) exhibited a higher photostability. For comparison, the photostability of the well-known 2-hydroxy-4-methoxybenzophenone measured in a Nylon film was found to be 1.1×10^4—three orders of magnitude less than that of 2-(*o*-hydroxyphenyl)-4-phenylquinazoline in the same matrix ($\Phi^{-1} = 1.05 \times 10^7$). Photostabilities of 2-(*o*-hydroxyphenyl)quinazolines having such 4-substituents as carboxamido or acetylamino were also in the range of several million. A strongly electron-releasing group in the 4-position, like amino or dimethylamino, although providing a stronger intramolecular hydrogen bond between OH and N-1 (Table II), had an adverse effect on photostability, probably due to its mesomeric effect, which had to be overcome before the enol-ketone rearrangement could take place.

EXPERIMENTAL

Melting points were determined in a "Uni-melt" capillary melting point apparatus of A. H. Thomas Co., Philadelphia, Pa., and are uncorrected. Elemental analyses were performed by Micro-Analysis, Inc., Marshallton, Wilmington, Del. Infrared spectra were determined in potassium bromide discs on a Perkin-Elmer 621 spectrophotometer. Only absorption bands of strongest intensity are listed at the end of preparations unless stated otherwise. Proton magnetic resonance spectra were determined with a Varian Associates 60-Mc. NMR spectrometer, Model A-60. Chromatographic purifications were carried out in a column (12″ high and 1-3/8″ wide) provided with a built-in, coarse, sintered glass funnel and a "Teflon" stopcock and filled (usually 7″ high) with silicic acid (100 mesh, powder). Nitrogen was used to accelerate the movement of the mobile phase. The column was sufficient to purify up to 1 g. of a substance.

4-(2,4-Dihydroxyphenyl)quinazoline.

A solution of 11.15 g. (0.068 mole) of 4-chloroquinazoline (20) and 8.6 g. (0.078 mole) of resorcinol in 140 ml. of chlorobenzene was cooled to 5°. Anhydrous aluminum chloride, 11.5 g. (0.086 mole), was added in several portions to the stirred solution at 10°. The mixture was heated slowly with stirring until evolution of hydrogen chloride took place at around 70°. It was held at 80-90° for 90 minutes to complete evolution of hydrogen chloride and then 45 minutes longer. The mixture was cooled to room temperature, the solvent was removed by decantation and the residual solid was decomposed with dilute hydrochloric acid and ice. The product was isolated by filtration, dried and crystallized from ethanol to a constant melting point of 235-236°; IR: 1615, 1558, 1497, 1376, 1337, 1210, 1190, 1183, 1117, 837 cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.23; H, 4.38; N, 11.95.

4-(2-Hydroxy-4-propoxyphenyl)quinazoline.

The above 4-resorcinylquinazoline, 2.38 g. (0.01 mole), propyl bromide, 1.30 g. (0.01 + 0.07 g. excess) and potassium hydroxide, 0.57 g. (0.01 mole), in 15 ml. of methyl cellosolve were heated under an efficient reflux condenser with stirring at 68-83° for 30 minutes, at 83-86° for 30 minutes, and at 86-90° for 60 minutes. A precipitate of potassium bromide began to appear at 79°. The solvent was distilled in a water aspirator. The residue was extracted with boiling benzene several times. The combined, cooled extracts were filtered and the filtrate was concentrated under reduced pressure to 20 ml. It was chromatographed on silicic acid using as eluent first 1.5% and then 5% of acetone in benzene. The compound was crystallized twice from a 2:1 mixture of cyclohexane:benzene, m.p. 118°.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.68; H, 5.70; N, 10.11.

2,4-bis(2,4-Dihydroxyphenyl)quinazoline.

Distilled 2,4-dichloroquinazoline (21), 12.0 g. (0.06 mole), and resorcinol, 15.4 g. (0.14 mole), in nitrobenzene, 150 g., were treated with anhydrous aluminum chloride, 20.6 g. (0.154 mole), at 5° with stirring. The mixture was heated at 65-75° for 30 minutes, at 75° for 75 minutes and at 75-80° for 75 minutes. The cooled reaction solution was poured into a stirred mixture of 60 ml. of concentrated hydrochloric acid, 600 ml. of water and 160 g. of ice. An orange precipitate was obtained. The aqueous layer was decanted. The solid was washed with a dilute hydrochloric acid solution and then dissolved in a cold 10% aqueous sodium hydroxide solution. Nitrobenzene was extracted with benzene twice and the aqueous layer was acidified to precipitate the product which was filtered, washed thoroughly with water and dried in vacuum at room temperature (21.1 g.). The compound was dissolved in 350 ml. of boiling dioxane, hot benzene (700 ml.) was added to the solution, which was quickly filtered and left standing for crystallization. A yellow solid, m.p. 288-290°, was obtained. A small amount (1.0 g.) of this material was chromatographed on silicic acid using 15% of ethanol in benzene as eluent. The sample was dried in vacuum at room temperature, m.p. 290-292°; IR: 2.95, 3.03, 6.20, 6.28, 6.38, 6.48, 7.21, 7.99, 8.08, 9.00, 9.05, 10.20, 10.25, 11.51, 11.81, 11.85, 12.96 μ.

Anal. Calcd. for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.09; H, 4.43; N, 8.00.

2,4-bis(2-Hydroxy-4-propoxyphenyl)quinazoline.

2,4-bis(2,4-Dihydroxyphenyl)quinazoline, 1.73 g. (0.005 mole), *n*-propyl bromide, 1.30 g. (0.01 mole + 0.07 g. excess), anhydrous sodium carbonate, 1.08 g. (0.01 mole) and 15 ml. of methyl cellosolve were heated with stirring at 60-70° for 30 minutes, at 70-80° for 30 minutes, at 80-95° for 30 minutes and at 95-110° for 30 minutes. The mixture was then maintained at 110° for 45 minutes. The product crystallized after cooling the reaction solution in an ice bath. The filtered material was suspended in 10% aqueous sodium hydroxide solution and stirred for one hour. It was then filtered, washed with water, dried and crystallized from acetic acid, m.p. 146-148°. A small amount of the product was chromatographed on silicic acid using 5% of acetone in benzene as eluent. This was followed by crystallization from a 3:1 mixture of cyclohexane:benzene, m.p. 149-151°. The dipropyl derivative was insoluble in 5% aqueous sodium hydroxide solution.

Anal. Calcd. for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.50. Found: C, 72.28; H, 6.26; N, 6.73.

2,4-bis(2-Hydroxy-4-butoxyphenyl)quinazoline.

Reaction of 3.46 g. (0.01 mole) of 2,4-bis(2,4-dihydroxyphenyl)quinazoline with 2.75 g. (0.02 mole) of *n*-butyl bromide in the presence of 1.08 g. (0.01 mole) of anhydrous sodium carbonate in 25 ml. of methyl cellosolve under conditions similar to those for the preceding preparation gave 1.30 g. of a product crystallized from the reaction solvent at 0°. This was extracted with 40 ml. of boiling cyclohexane to give 0.75 g. of a material which was insoluble in 5% aqueous sodium hydroxide solution. Chromatography with benzene containing 2.5% acetone was followed by extraction with boiling *n*-hexane to remove any tributylated derivative. The residue was crystallized from cyclohexane to give 0.34 g. of a product, m.p. 142-143°.

Anal. Calcd. for $C_{28}H_{30}N_2O_4$: C, 73.34; H, 6.59; N, 6.11; O, 13.96. Found: C, 73.09; H, 6.66; N, 6.16; O 13.95.

2-(2-Hydroxy-4-methoxyphenyl)-4-(2,4-dimethoxyphenyl)quinazoline.

2,4-bis(2,4-Dihydroxyphenyl)quinazoline, 3.46 g. (0.01 mole), was dissolved in 50 ml. of methyl cellosolve and treated with 150 ml. of an ether solution containing around 0.06 mole of diazomethane (22). A rapid evolution of nitrogen took place and a product precipitated at room temperature in 15 minutes. The material was filtered, washed with a mixture of ether and methyl cellosolve, and dried in vacuum, 2.62 g., m.p. 172-177°. Chromatography on silicic acid using 10% of acetone in benzene was followed by two benzene crystallizations, m.p. 178-179°.

Anal. Calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21; O, 16.48. Found: C, 71.16; H, 4.79; N, 6.88; O, 16.20.

2-(2-Hydroxy-4-propoxyphenyl)-4-(2,4-dipropoxyphenyl)quinazoline.

2,4-bis(2,4-Dihydroxyphenyl)quinazoline, 3.46 g. (0.01 mole), *n*-propyl bromide, 11.07 g. (0.09 mole), potassium hydroxide, 5.56 g. (0.09 mole +) and methyl cellosolve, 50 ml., were heated with stirring under an efficient reflux condenser for 3-1/2 hours, the temperature being gradually raised from 25 to 80° and then maintained at 80° for three additional hours. The product precipitated after the reaction solution was cooled in an ice bath. It was filtered, washed with methyl cellosolve and extracted with 5% aqueous sodium hydroxide solution at 50°. The insoluble material was filtered, washed with water, dried and extracted with hot *n*-hexane. The solution was filtered and the product was allowed to crystallize from the filtrate. Repeated crystallization from *n*-hexane gave the tripropyl derivative, m.p. 143-144.5°.

Anal. Calcd. for $C_{29}H_{32}N_2O_4$: C, 73.70; H, 6.83; N, 5.93. Found: C, 73.84; H, 6.63; N, 5.71.

2-(*o*-Methoxyphenyl)quinazoline.

o-Aminobenzaldehyde (23) reacted with *o*-methoxybenzoyl chloride in pyridine to give *o*-(*o'*-methoxybenzoylamino)benzaldehyde, m.p. 93-95°. The intermediate, 3.28 g., was heated in the presence of about 5 g. of anhydrous ammonia and 25 ml. of absolute ethanol in a sealed, heavy-walled Pyrex glass tube placed in an oil bath maintained at 160° for 16 hours. The tube was opened at −35°, excess ammonia was removed and ethanol was evaporated in a water aspirator. The residue was crystallized from cyclohexane, m.p. 89-90°.

PMR spectrum (in carbon tetrachloride; chemical shifts downfield from TMS as internal standard): methoxy protons (3) at 3.80 ppm, aromatic protons (8) at 6.8-8.3 ppm, and proton in the 4-position at 9.31 ppm.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.23; H, 5.00; N, 11.69.

2-(*o*-Methoxyphenyl)-4-methylquinazoline.

o-Aminoacetophenone reacted with *o*-methoxybenzoyl chloride in pyridine at 10-15° to give *o*-(*o'*-methoxybenzoylamino)acetophenone, m.p. 104-106°. The intermediate, 24.6 g., was heated in the presence of 50 g. of anhydrous ammonia in 600 ml. of absolute ethanol in a stainless-steel autoclave (capacity 1,200 ml.) at 150° (internal temperature) for 24 hours. The product was crystallized from cyclohexane twice, m.p. 89-90°.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.78; H, 5.64; N, 11.48.

2-(*o*-Hydroxyphenyl)quinazoline.

Method A.

2-(*o*-Hydroxyphenyl)quinazoline-4-carboxylic acid, prepared either as described by Bogert and McColm (24) or by saponification of 2-(*o*-hydroxyphenyl)quinazoline-4-carboxamide as described below, 3.06 g., was decarboxylated in 25 ml. of quinoline at 160° during three hours. Quinoline was distilled in vacuum and the residue was sublimed (135°/0.025 mm. Hg.) to give 2.5 g. of a pale yellow material which was crystallized from 60 ml. of ethanol, m.p. 133-134°; IR (Primol D mull): 1620, 1605, 1580, 1560, 1240, 1155, 1035, 837, 774, 765, 756, 744, 701 cm^{-1}. PMR spectrum showed H-4 at 9.19 ppm (in deuteriochloroform) downfield from TMSi as external standard.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.61; O, 7.20. Found: C, 75.65; H, 4.60; N, 12.61; O, 7.28.

Method B.

2-(*o*-Methoxyphenyl)quinazoline, 0.65 g., was dissolved in 35 ml. of methylene chloride and the solution was cooled to 0° in an ice bath. A slow stream of boron trichloride was passed through the cooled and stirred solution until the precipitation of a yellow solid was complete. Excess boron trichloride and solvent were removed by distillation into a trap cooled in dry ice-acetone mixture. The residue was slurried in a solution of 15 g. of sodium acetate in 60 ml. of water, and the mixture was agitated at 0° overnight. The solid was filtered to give 0.55 g. of a pale-yellow substance after drying. It was crystallized from 25 ml. of ethanol to give 0.31 g. of pure 2-(*o*-hydroxyphenyl)quinazoline, m.p. 135-136°, whose IR spectrum was identical to that of the preparation obtained according to Method A.

2-(*o*-Hydroxyphenyl-4-methylquinazoline.

Method A.

o-Salicylaminoacetophenone (24), 1.93 g., was heated in the presence of 8 g. of anhydrous ammonia in 50 ml. of absolute ethanol in a stainless-steel autoclave (capacity 100 ml.) at 180° (internal temperature) for 24 hours. The discharged solution was concentrated to a volume of about 15 ml. and the product was allowed to crystallize. It was collected, slurried and agitated in 5% aqueous sodium hydroxide solution, filtered again, washed with water until neutral and dried. Chromatography on silicic acid (10% of ethanol in benzene was used as eluent) followed by sublimation (120°/0.02 mm. Hg.) and crystallization from ethanol gave the title compound, m.p. 119-120° (dried at 56° in vacuum).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.35; H, 5.03; N, 11.92.

Method B.

2-(*o*-Methoxyphenyl)-4-methylquinazoline, 2.0 g., in methylene chloride, 75 ml., was demethylated with boron trichloride at 0° and the boron complex was hydrolyzed as described above for 2-(*o*-hydroxyphenyl)quinazoline. The product, after crystallization from ethanol, melted at 118-119.5°. Its IR spectrum matched that of the preparation obtained according to Method A.

2-(*o*-Hydroxyphenyl)-4-phenylquinazoline.

o-Salicylaminobenzophenone (prepared from salicyl chloride and *o*-aminobenzophenone), 5.14 g., was heated in the presence of 14 g. of anhydrous ammonia and 150 ml. of absolute ethanol in a stainless-steel autoclave (capacity 250 ml.) at 180° (internal temperature) for 24 hours. The reaction mixture was cooled in an ice bath and filtered. The product was washed with ice-cold ethanol, collected and dried (3.94 g.), m.p. 168-171°. Crystallization from a mixture of 150 ml. of ethanol and 60 ml. of benzene gave m.p. 171-172°.

Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.52; H, 4.73; N, 9.39; O, 5.36. Found: C, 80.59; H, 4.57; N, 9.59; O, 5.41.

2-(*o*-Hydroxyphenyl)quinazoline-4-carboxamide.

The intermediate *N*-(*o*-acetoxybenzoyl)isatin was prepared by reacting equimolar amounts of *o*-acetoxybenzoyl chloride and sodium salt of isatin in benzene at room temperature. The reaction mixture was filtered, benzene was evaporated from the filtrate and the residue was extracted with a large quantity of boiling water for a short time to remove unreacted isatin. The resulting solid had a m.p. of 123-132°. IR spectrum showed no N–H stretching band of isatin, only its three carbonyl bands at 1750-1800 cm^{-1} and one doublet at 1600 cm^{-1}. The presence of a benzoyl group was indicated by an additional carboxyl band at 1675 cm^{-1}.

N-(*o*-Acetoxybenzoyl)isatin, 20 g., was heated in the presence of 50 g. of anhydrous ammonia and 500 ml. of absolute ethanol in a 1200-ml. autoclave at 150° (internal temperature) for five

hours. The discharged reaction mixture was filtered to collect a solid product which was washed with ethanol and dried (8.15 g., m.p. 294-296°). One g. of this rather pure material was sublimed at 280° and 0.02 mm. Hg., the sublimate was crystallized from 100 ml. of acetic acid and dried at 56° in vacuum for 18 hours, m.p. 295-296°; IR (potassium bromide pellet): 3400, 3170, 1686, 1662, 1606, 1590, 1567, 1544, 1496, seven bands between 1200 and 1400, 1155 (doublet), 764 cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84; O, 12.06. Found: C, 67.87; H, 4.10; N, 15.96; O, 12.06.

2-(*o*-Hydroxyphenyl)quinazoline-4-carboxylic Acid.

The 6.74 g. of carboxamide prepared as described in the preceding procedure was saponified in a refluxing mixture of 200 ml. of 5 *N* sodium hydroxide solution and 100 ml. of ethanol in two hours. The reaction solution was filtered and the corresponding carboxylic acid was precipitated from the filtrate after addition of 5 *N* hydrochloric acid solution at room temperature. The carboxylic acid was filtered, washed thoroughly with water and dried in vacuum (>0.02 mm. Hg.) at room temperature. The yield of a compound melting at 174-174.5° with decomposition was 6.85 g. Bogert and McColm (24) reported m.p. 171°, corrected, after five crystallizations. The acid yielded 2-(*o*-hydroxyphenyl)quinazoline following decarboxylation either in quinoline or in bulk.

Methyl 2-(*o*-Hydroxyphenyl)quinazoline-4-carboxylate.

2-(*o*-Hydroxyphenyl)quinazoline-4-carboxylic acid, prepared as described by Bogert and McColm (24), 0.50 g., was dissolved in 20 ml. of methanol and the solution was saturated with gaseous hydrogen chloride. The flask was stoppered and left standing at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was crystallized from cyclohexane. The crystalline material was sublimed at 135° and 0.025 mm. Hg. to give pure methyl ester, m.p. 135-135.5°. IR spectrum (Primal D mull) showed an ester band at 1720 cm^{-1} and four ring-vibration bands between 1540-1610 cm^{-1}.

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00; O, 17.13. Found: C, 68.33; H, 4.18; N, 10.08; O, 17.21.

The above methyl ester was dissolved in methanol and the solution was saturated with gaseous ammonia to precipitate 2-(*o*-hydroxyphenyl)quinazoline-4-carboxamide which, after crystallization from dimethylformamide, gave m.p. 294-295° and IR spectrum matching those of the amide prepared from *N*-(*o*-acetoxybenzoyl)isatin.

2-(*o*-Hydroxyphenyl)-4-aminoquinazoline.

A stainless-steel autoclave having capacity of 1200 ml. was charged with 16.66 g. (0.07 mole) of 2-(*o*-hydroxyphenyl)-4(3*H*)-quinazolinone (13), 200 ml. of *n*-propyl alcohol and 100 g. of anhydrous ammonia and was heated at 250° (internal temperature) for 24 hours. The solvent was removed from the discharged reaction solution under reduced pressure, the residue was suspended in 300 ml. of 5% aqueous sodium hydroxide solution and stirred to dissolve any unreacted quinazolinone. The solid was collected, washed and dried. It weighed 14.2 g. (85% of theory) and melted at 218-222°. A small sample was sublimed at 220° and 0.01 mm. Hg. and then crystallized from ethanol to give m.p. 221.5-222.5°. IR spectrum (potassium bromide pellet showed N–H stretching bands at 3490, 3390, 3335 and 3220 cm^{-1}. A low-intensity, diffuse absorption due to O–H stretching vibrational modes of a strongly chelated type was found in the region of 2400-2800 cm^{-1}. This indicated a strong O–H · · · N hydrogen bonding comparable in strength to that of 2-(*o*-hydroxyphenyl)-quinoline. C=O stretching band, present in the spectrum of the starting quinazolinone at 1667 cm^{-1}, was absent. Other strong peaks were found at 1622, 1604, 1590, 1576, 1547, 1485, 1456, 1361, 1260, 1241 and 757 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71; O, 6.74. Found: C, 70.86; H, 4.67; N, 17.49; O, 6.77.

2-(*o*-Hydroxyphenyl)-4-acetamidoquinazoline.

The 4-amino compound above (3.0 g.) was acetylated with 6.0 g. of acetic anhydride in 3 ml. of acetic acid by refluxing for 15 minutes. The reaction solution was triturated in a dilute aqueous ammonia solution. The solid was collected, dissolved in 150 ml. of ethanol containing 1 ml. of concentrated aqueous ammonia and the solution was heated to boiling for a few minutes. The solvent was removed under reduced pressure, the residue was crystallized from ethanol, sublimed at 190-200° (0.01 mm. Hg.) and again crystallized twice from ethanol, m.p. 232-233°. IR spectrum (Nujol mull) showed a broad peak at 3270 cm^{-1}, a sharp doublet at 1700 cm^{-1} and strong absorptions at 1620, 1590, 1565, 1230, 845 and 755 cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.04; O, 11.46. Found: C, 68.88; H, 4.76; N, 14.90; O, 11.50.

2-(*o*-Hydroxyphenyl)-4-chloroquinazoline.

A slow stream of phosgene was passed through a vigorously stirred mixture of 7.14 g. (0.03 mole) of 2-(*o*-hydroxyphenyl)-4(3*H*)-quinazolinone (13), 6.57 g. (0.09 mole) of dimethylformamide and 150 ml. of *o*-dichlorobenzene at room temperature for a period of two hours. Subsequently, a stream of sulfur dioxide was passed to decompose the chlorinated complex (a considerable portion of the solid went into solution). The excess phosgene and sulfur dioxide were purged with dry nitrogen, the mixture was filtered and the solvent was removed from the filtrate by distillation under reduced pressure. The residue and the solid collected by filtration were combined and triturated in a dilute hydrochloric acid solution at 0°. The solid was isolated by filtration, dried in vacuum at room temperature and then extracted with a large quantity of boiling cyclohexane. The mixture was filtered and the filtrate was concentrated to allow the product to crystallize. Repeated crystallization from cyclohexane gave a sample melting at 157-158°. IR spectrum (Nujol mull) showed four-ring vibrational bands between 1550 and 1625 cm^{-1}. Other strong peaks were present at 1253, 1162, 988, 830, 820, 775, 762 and 754 cm^{-1}.

Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.91; O, 6.23; Cl, 13.81. Found: C, 65.53; H, 3.44; N, 11.06; O, 6.30; Cl, 14.02.

2-(*o*-Hydroxyphenyl)-4-dimethylaminoquinazoline.

2-(*o*-Hydroxyphenyl)-4(3*H*)-quinazolinone (13) was chlorinated with phosgene as described above. Excess phosgene was purged with dry nitrogen. A stream of dimethylamine was passed through the reaction mixture maintained at 22° by external cooling. Most of the solid went into solution. The solvent was removed by distillation under reduced pressure. The residue was suspended in 5% aqueous sodium hydroxide solution and stirred at room temperature to dissolve any unreacted quinazolinone. The solid was filtered, washed with water and dried to give 6.87 g. of a material showing only a very weak absorption around 6 μ in the IR spectrum. The product was dissolved in 300 ml. of boiling ethanol, the solution was filtered through a layer of Celite, the filtrate was concentrated to 150 ml. and left standing for crystallization. The collected solid weighed 5.08 g. (64% of theory) after drying and melted at 147-148.5°. A small sample, recrystallized from ethanol, gave the same melting point. IR spectrum (potassium bromide

pellet), when heavily screened, showed a weak and diffuse chelated O–H stretching band centered around 2560 cm^{-1}. Strong bnads were present at 1600, 1565, 1520, 1486, 1465, 1378, 960, 890, 762, 698 and 677 cm^{-1}. PMR spectrum (in deuteriochloroform) showed six protons of the dimethylamino group at 3.15 ppm downfield from TMSi as internal standard.

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84; O, 6.03. Found: C, 72.50; H, 5.81; N, 15.89; O, 6.05.

2-(*o*-Hydroxyphenyl)-4-methoxyquinazoline.

Method A.

2-(*o*-Hydroxyphenyl)-4(3*H*)-quinazolinone (13), 2.38 g. (0.01 mole), in dimethylformamide, 50 ml., was treated with diazomethane (22), approximately 0.04 mole of the reagent in 75 ml. of ether, at room temperature. The solvent was distilled in vacuum, a residue was extracted with 80 ml. of boiling ethanol, the ethanol solution was concentrated after filtration and the product was allowed to crystallize at room temperature. It was chromatographed on silicic acid using 3% of ethanol in benzene as eluent. The compound was crystallized from methanol, m.p. 117-118°. IR spectrum (Nujol mull) showed neither N–H nor C=O stretching bands. Strong peaks were at 1620, 1580, 1560, 1308, 1262, 1199, 1155, 1105, 1034, 980, 930, 872, 834, 766, 752, 700 and 679 cm^{-1}. PMR spectrum (in deuteriochloroform) showed three protons of the 4-OCH_3 group at 4.03 ppm downfield from TMSi as internal standard.

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.11; O, 12.68. Found: C, 71.06; H, 4.80; N, 10.89; O, 12.65.

Method B.

A mixture of 19.1 g. (0.08 mole) of 2-(*o*-hydroxyphenyl)-4(3*H*)-quinazolinone (13), 17.1 g. (0.12 mole) of methyl iodide and 16.6 g. (0.12 mole) of anhydrous potassium carbonate in 600 ml. of acetone was refluxed 48 hours. After filtration and evaporation of the solvent, the residue was extracted with 150 ml. of boiling cyclohexane, the solution was filtered, the filtrate was concentrated to 75 ml. and left standing for crystallization. The separated solid was recrystallized from methanol to give essentially pure 2-(*o*-hydroxyphenyl)-4-methoxyquinazoline whose IR spectrum matched that of the compound prepared according to Method A. The yield was 7.33 g. The cyclohexane-insoluble portion was stirred in a large volume of water to remove inorganics, the residue was filtered, washed with water and dried to give 7.74 g. of a colorless material, m.p. 184-186°. It was crystallized from methanol to give m.p. 186-187°. The compound was identified as 2-(*o*-methoxyphenyl)-3-methyl-4(3)-quinazolinone (13) on the basis of the PMR spectrum (lacking O–H proton signal; showing the presence of two methyl groups: N–CH_3 at 3.42 and O–CH_3 at 3.82 ppm in deuteriochloroform downfield from TMSi as internal standard).

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