Cyclic Hydroxamic Acids Derived from Quinazoline

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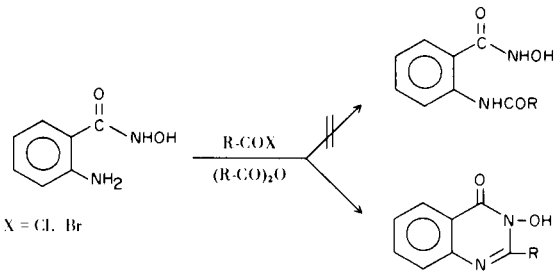
The action of various acylating agents on 2-aminobenzohydroxamic acid afforded 3-hydroxy-4(3*H*)quinazolinones (hydroxamic acids) as well as several ethers and esters from them were prepared and their spectroscopic properties analyzed. Secondary amines, as well as one equivalent of alkali, on 2-halomethyl-3-hydroxy-4(3*H*)quinazolinone lead to the formation of a dimer (XI). In this respect the behaviour of secondary amines is different from that of primary amines. Some new 3-hydroxy-2-4(1*H*,3*H*)-quinazolidinediones are described.

Cyclic hydroxamic acids (*N*-hydroxylactams) derived from various heterocyclic systems are well known. Thus, cyclic hydroxamic acids have been prepared in the pyridine (1), pyrimidine (2), quinoline (3) and pyrazine (4) series. The study of the chemistry of cyclic hydroxamic acids began when White and Hill (5) isolated the antibiotic known as aspergillic acid from cultures of certain strains of Aspergillus Flavus, and Dutcher and Wintersteiner (6) established the structure of a cyclic hydroxamic acid derived from pyrazine (1-hydroxy-3-isobutyl-6-*sec*-butyl-2(1*H*)pyrazinone).

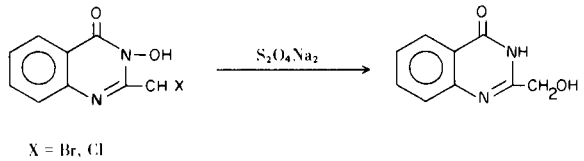
Another natural derivative with a cyclic hydroxamic acid structure is Norcardamine, isolated in 1948 from the mycelium of strains of *Penicillum Griseofulvum*. The structure of this compound was studied by Stoll *et al.* (7).

Cyclic hydroxamic acids derived from 4(3*H*)quinazolinone were prepared by Legrand and Lozac'h by the action of hydroxylamine on 1,3-benzothiazin-4-one (8); by Harrison and Smith by treatment of *N*-acylanthranilic esters with hydroxylamine under alkaline conditions and in an alternative route by heating the *o*-aminobenzohydroxamic acid with acetic anhydride, benzoic anhydride or formic acid (9). Dornow and Fischer prepared 3-hydroxy-4(3*H*)quinazolinones (hydroxamic acid) by the action of hydroxamoyl chlorides on methyl anthranilate (10). Mamalis, Rix and Sarsfield obtained some ethers of 3-hydroxy-4(3*H*)quinazolinones by treatment of anthranils or isatoic anhydride with *o*-alkylhydroxylamines and subsequent cyclization of the intermediate *o*-aminobenzohydroxamate (11).

In this work, the behaviour of the *o*-aminobenzohydroxamic acid with several acylating agents was studied. In all cases under different conditions, the cyclic hydroxamic acid (Table I), not the acyclic product was obtained.



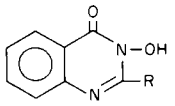
All of the products have high melting points, and are readily soluble in dilute alkali; the cyclic hydroxamic acid structure was supported by the dark red colour given with aqueous-alcoholic ferric chloride (an acyclic hydroxamic acid gives a "permanganate" colour with ferric chloride). Furthermore, by reduction with sodium dithionite, 4(3*H*)-quinazolinone was obtained and in the case of the 2-chloro and 2-bromomethyl derivative, the substitution of the halogen by the hydroxyl group was produced at the same time.



The preparation of hydroxamic acids was carried out by two routes: with an excess of the acid chloride as solvent or using the stoichometric amount of the acylating agent in adequate solvent. Thus 2-aminobenzohydroxamic acid with an excess of benzoyl chloride gave very good yields of 2-phenyl-3-benzoyloxy-4(3*H*)quinazolinone (XIV).

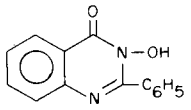
TABLE I

2 Substituted 3-Hydroxy-4(3*H*)quinazolinones

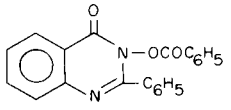


Compound	R	M.p. °C	Recryst. Solvent	Yield %	Formula	Anal.	C%	H%	N%	Halog. %
I	$-CH_2Cl$	210	EtOH-AcOEt	85	$C_9H_7ClN_2O_2$	Calcd.	51.30	3.32	13.30	16.86
						Found	51.30	3.45	13.30	16.83
II	$-CH_2Br$	188	EtOH-AcOEt	84	$C_9H_7BrN_2O_2$	Calcd.	42.36	2.74	10.98	31.37
						Found	42.09	2.97	10.71	30.90
III	$-C_6H_4-CO_2H(o)$	288-289	EtOH	78	$C_{15}H_{10}N_2O_4$	Calcd.	63.81	3.54	9.92	
						Found	63.68	3.44	9.80	
IV	$-CH_2-CH_2-CO_2H$	210	EtOH 50%	75	$C_{11}H_{10}N_2O_4$	Calcd.	56.41	4.27	11.96	
						Found	56.60	4.41	11.88	
V	$-CH_2NHCH_3$	188	DMF	80	$C_{10}H_{11}N_3O_2$	Calcd.	58.53	5.37	20.48	
						Found	58.8	5.54	20.60	
VI	$-CH_2NHC_2H_5$	175	DMF	78	$C_{11}H_{13}N_3O_2$	Calcd.	60.27	5.93	19.17	
						Found	60.30	6.22	18.90	
VII	$-C_6H_5$	177	EtOH	80	$C_{14}H_{10}N_2O_2$	Calcd.	70.58	4.19	11.76	
						Found	70.81	4.03	11.59	
VIII	$-C_6H_4NO_2(p)$	283	Dioxane	82	$C_{14}H_9N_3O_4$	Calcd.	59.34	3.18	14.84	
						Found	59.12	3.00	14.55	
IX	$-CH=CH-CO_2H$	230-231	H_2O	75	$C_{11}H_8N_2O_4$	Calcd.	56.89	3.44	12.06	
						Found	56.61	3.71	11.90	
X	$-CH_2OH$	180	(a)	57	$C_9H_8N_2O_3$	Calcd.	56.25	4.16	14.58	
						Found	56.50	4.04	14.68	

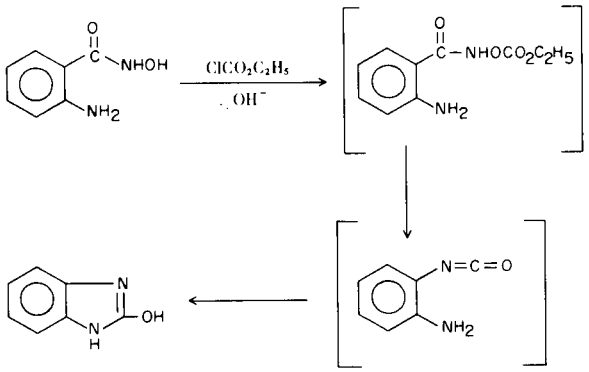
(a) Was purified by preparative layer chromatography.



VII



XIV



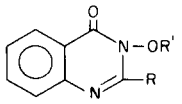
When working with equimolar amounts, 2-phenyl-3-hydroxy-4(3*H*)quinazolinone (VII) was obtained.

The structures of the hydroxamic acids listed in Table I were verified by analysis, and their ir and nmr spectra. The nmr spectrum of I in DMSO exhibited a singlet at 4.8 δ integrating for 2 protons ($-CH_2$) and a multiplet from 7.4-8.3 δ integrating for 4 aromatic protons and 1 hydroxyl proton. The acylation of the *o*-aminobenzohydroxamic acid in alkaline medium under the conditions of a Schotten-Baumann reaction followed another course; thus ethylchloroformate afforded 2-hydroxybenzimidazole identified by ir spectral comparison with an authentic sample. The reaction follows a Lossen rearrangement with formation of an intermediate isocyanate, which immediately cyclizes.

Likewise, small amounts of the cyclic hydroxamic acid (XXIV), 3-hydroxy-2-4(1*H*,3*H*)quinazolinedione, was obtained, which was separated by tlc on silica gel G.F. 254. It has been postulated that the cyclic hydroxamic acids exist in tautomeric equilibrium between the *N*-hydroxy and *N*-oxide structure as was shown in the case of the *N*-hydroxyphthalimidine (12). In order to determine the

TABLE II

3-*O*-Substituted-4(3*H*)quinazolinones

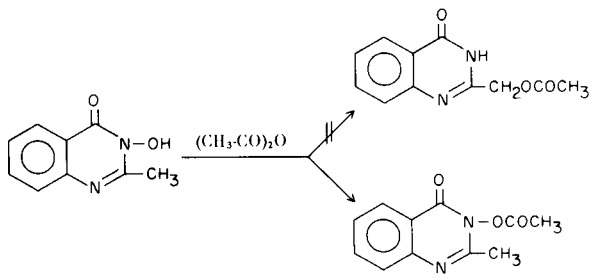


Compound	R	R′	Method	Yield %	M.p. °C	Recryst. Solvent	Formula	Anal.	C%	H%	N%
XII	$-CH_2Cl$	$-COCH_3$	B	80	148	Benzene	$C_{11}H_9ClN_2O_3$	Calcd.	52.3	3.56	11.08
								Found	52.2	3.80	11.23
XIII	$-CH_3$(a)	$-CH_3$	A	73	91-92	Cyclohexane	$C_{10}H_{10}N_2O_2$	Calcd.	63.15	5.26	14.73
								Found	63.3	5.52	14.72
XIV	$-C_6H_5$	$-COC_6H_5$	B	79	152	Ethanol	$C_{21}H_{15}N_2O_3$	Calcd.	73.6	4.3	8.16
								Found	73.8	4.33	8.35
XV	$-CH_3$(a)	$-COCH_3$	B	80	117	Cyclohexane	$C_{11}H_{10}N_2O_3$	Calcd.	60.55	4.58	12.84
								Found	60.80	4.48	13.05
XVI	$-CH_2Cl$	$-COC_6H_5$	A	70	134-135	Ethanol	$C_{16}H_{11}ClN_2O_3$	Calcd.	61.04	3.49	8.90
								Found	61.00	3.66	8.90
XVII	$-CH_3$(a)	$-COC_6H_5$	A	75	160	Methanol	$C_{16}H_{12}N_2O_3$	Calcd.	68.57	4.28	10.00
								Found	68.71	4.40	9.95
XVIII	-H(a)	$-COC_6H_5$	A	70	158	Methanol	$C_{15}H_{10}N_2O_3$	Calcd.	67.66	3.75	10.52
								Found	67.70	3.57	10.42
XIX	$-CH_2Cl$	$-CH_3$	A	63	127	Cyclohexane	$C_{10}H_9ClN_2O_2$	Calcd.	53.45	4.04	12.47
								Found	53.60	4.17	12.56
XX	$-CH_2Cl$	$-CO_2C_2H_5$	A	60	120	Cyclohexane	$C_{12}H_{11}ClN_2O_4$	Calcd.	50.97	3.89	9.91
								Found	51.00	4.02	9.80
XXI	$-CH_3$(a)	$-CO_2C_2H_5$	A	59	81	Cyclohexane	$C_{12}H_{12}N_2O_4$	Calcd.	58.06	4.83	11.29
								Found	58.24	5.08	11.47
XXII	-H(a)	$-CO_2C_2H_5$	A	65	124-125	Benzene/ Cyclohexane	$C_{11}H_{10}N_2O_4$	Calcd.	56.40	4.27	11.96
								Found	56.60	4.22	11.80

(a) 3-Hydroxy-4(3*H*)quinazolinone and 2-methyl-3-hydroxy-4(3*H*)quinazolinone were prepared according to ref. (9).

existence of this equilibrium in the 3-hydroxy-4(3*H*)-quinazolinones some characteristic reactions of the *N*-oxides were assayed and the ir solid state spectra were studied. Although they give a deep red colour with ferric chloride solution and form copper salts, which are typical properties of the hydroxamic acids, the *N*-oxide tautomeric structure might exhibit a similar behaviour because the C-OH ionization is facilitated by the positively charged *N*.

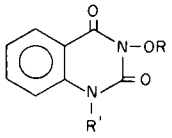
A typical reaction of *N*-oxides is the known conversion of α-picoline *N*-oxide into acetoxymethylpyridine by the action of acetic anhydride (13). However, 2-methyl-3-hydroxy-4-quinazolone with acetic anhydride gave 2-methyl-3-acetoxy-4(3*H*)quinazolinone and not 2-acetoxy-methyl-4(3*H*)quinazolinone as would be expected for the tautomeric *N*-oxide structure. Furthermore all of the 3-hydroxy-4-quinazolones studied are chemically very stable in acid and alkali at the boiling point; in this aspect they differ from the *N*-oxides.



The ir in the solid phase (see Table IV) shows two strong bands in the regions of the double bonds. The strongest between 1,690-1,700 cm^{-1} corresponds to the

TABLE III

3-Hydroxy-2,4(1*H*,3*H*)quinazolinediones and Derivatives



Compound	R	R′	M.p. °C	Recryst. Solvent	Yield %	Formula	Anal.	C%	H%	N%
XXIII	H	$-CH_3$	227	EtOH	78	$C_9H_8N_2O_3$	Calcd.	56.25	4.16	14.53
							Found	56.42	4.30	14.62
XXIV	H	H	320	D.M.F.	83	$C_8H_6N_2O_3$	Calcd.	53.93	3.37	15.72
							Found	54.15	3.50	15.67
XXV	$-COCH_3$	$-CH_3$	155-156	Benzene/ Cyclohexane	84	$C_{11}H_{10}N_2O_4$	Calcd.	56.40	4.27	11.96
							Found	56.60	3.98	11.83
XXVI	$-COCH_3$	H	260	EtOH	77	$C_{10}H_8N_2O_4$	Calcd.	54.54	3.63	12.72
							Found	54.69	3.80	12.82
XXVII	$-COC_6H_5$	$-CH_3$	198	Benzene	81	$C_{16}H_{12}N_2O_4$	Calcd.	64.86	4.05	9.45
							Found	65.10	4.27	9.20
XXVIII	$-COC_6H_5$	-H	275	EtOH	80	$C_{15}H_{10}N_2O_4$	Calcd.	63.82	3.54	9.92
							Found	63.95	3.55	9.73
XXIX	$-CO_2C_2H_5$	$-CH_3$	128	Benzene/ Cyclohexane	72	$C_{12}H_{12}N_2O_5$	Calcd.	54.54	4.54	10.60
							Found	54.41	4.70	10.50
XXX	$-CO_2C_2H_5$	-H	185	Benzene	70	$C_{11}H_{10}N_2O_5$	Calcd.	52.80	4.03	11.30
							Found	52.72	4.20	11.14

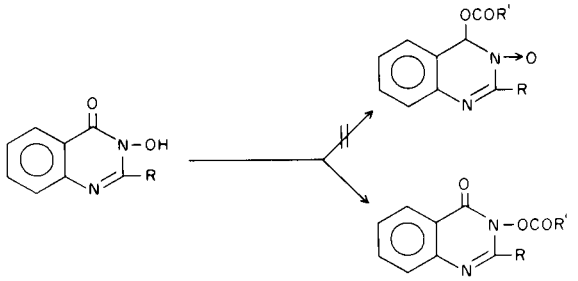
TABLE IV

Infrared Spectral Data of 2-Substituted-3-hydroxy-4(3*H*)quinazolinones

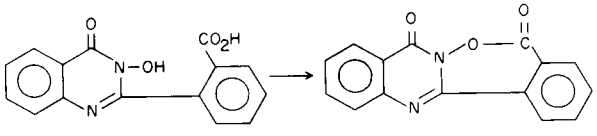
Compound													
I	2800-2000 (w-b)	1700 (v-s)	1590 (s)	1450 (s)	1410 (s)	1290 (s)	1180 (v-s)	1110 (m)	930 (s)	860 (s)	750 (s)	680 (s)	
II	2800-2000 (w-b)	1700 (v-s)	1590 (s)	1450 (s)	1410 (m-s)	1295 (m-s)	1180 (v-s)	1110 (m)	925 (m-s)	850 (s)	755 (s)	680 (s)	
III	2800-2000 (w-b)	1700 (v-s)	1590 (s)	1470 (s)	1400 (m-s)	1295 (s)	1180 (s)	1120 (m)	920 (s)	850 (s)	760 (s)	680 (s)	
IV	3200-2000 (s)	1710 (v-s)	1685 (v-s)	1600 (s)	1450 (s)	1400 (s)	1295 (s)	1190 (s)	1110 (m)	940 (m-s)	845 (m-s)	760 (s)	690 (s)
V	3050 (s)	2600-2000 (w-b)	1650-1640 (v-s)	1600 (s)	1470 (s)	1420 (s)	1300 (m-s)	1180 (s)	1130 (m)	950 (s)	860 (s)	760 (s)	690 (s)
VI	3050 (s)	2600-2000 (w-b)	1645-1635 (v-s)	1590 (s)	1475 (s)	1420 (m-s)	1290 (m-s)	1180 (s)	1135 (m)	940 (s)	860 (s)	770 (s)	700 (s)
VII	2800-2000 (w-b)	1695 (v-s)	1600 (s)	1460 (s)	1390 (s)	1280 (m-s)	1170 (s)	1110 (m)	930 (s)	850 (s)	760 (s)	680 (s)	
VIII	2800-2000 (w-b)	1695 (v-s)	1600 (s)	1450 (s)	1410 (m-s)	1300 (m)	1180 (s)	1110 (m)	920 (s)	865 (s)	770 (s)	680 (s)	
IX	3200-2000 (s)	1710 (s)	1685 (s)	1600 (s)	1450 (s)	1410 (m-s)	1300 (s)	1180 (s)	1110 (m)	940 (s)	860 (s)	780 (s)	680 (s)
X	2800-2000 (w-b)	1700 (v-s)	1590 (s)	1455 (s)	1410 (s)	1295 (s)	1180 (s)	1110 (m)	935 (s)	860 (s)	750 (s)	685 (s)	

Data in cm^{-1}; w: weak; m: medium; s: strong; b: broad.

absorption of the C=O group; the second band, between 1,580-1,600 cm^{-1} is associated with the presence of the phenyl group. The characteristic band of the hydroxy group is absent, and instead, a wide band with a maximum at 2,500 cm^{-1} appears which can be attributed to a chelate type structure; this agrees with the observation by Coutts *et al.* (14) for some quinolinhydroxamic acids and with that by Reed and Ruby for derivatives of 4-hydroxy-5,6-dihydropyrone (15). Although an absorption at 1,290-1,300 cm^{-1} is observed, which would agree with that pointed out by Sternbach *et al.*, for quinazoline *N*-oxides (16), the intense absorption of the C=O group and the chemical properties shows that the 3-hydroxyquinazol-4-ones do not exist as *N*-oxide but as *N*-hydroxy. As a confirmation, 3-*O*-substituted derivatives (see Table II) were easily obtained, the spectra of which are particularly characteristic for the 3-*O*-acylated derivatives, which present two C=O bands instead of one which would take place if the 4-*O*-acyl compounds were formed:

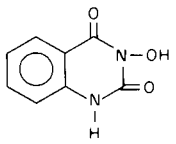


It is of interest that the ester carbonyl frequency of the 3-acyloxy derivatives is extraordinarily high (1,820 cm^{-1} for the 3-acetyloxy, 1,790 cm^{-1} for the 3-benzoyloxy derivatives). The 3-*O*-substitution takes place by a Schotten-Baumann reaction; on the other hand, a greater yield is obtained (for the acetyl derivative) by heating with an excess of acetic anhydride. In the case of 2-(*o*-carboxyphenyl)-3-hydroxy-4(3*H*)quinazolinone (III), heating with an excess of acetic anhydride afforded a lactone instead of the expected 3-*O*-acetyl derivative. The IIIa structure was confirmed by analysis, ir spectrum and hydrolysis.

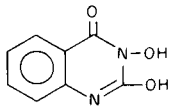


III IIIa

The reaction of the 2-aminobenzohydroxamic acid with ethyl chloroformate leads to a cyclic hydroxamic acid, which may have the quinazolindione structure (XXIV) or a tautomeric (XXIVa).

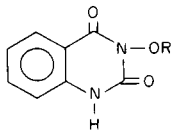


XXIV



XXIVa

The study of the ir spectrum shows a wide band in the range from 3,400 cm^{-1} to 2,000 cm^{-1} with several submaxima. The presence of the -NH group cannot be assigned here, and this absorption at such low frequencies can be attributed to the 3-OH group, which has already been observed in the 3-hydroxy-4(3*H*)quinazolinones. In the "double bond" region the two C=O groups of the XXIV structure are not readily distinguished; two additional bands also appear: one at 1,500 cm^{-1} and another one at 1,615 cm^{-1} which have been associated to the quinazolindione system by Culberston *et al.* (17). As a confirmation to these structural consideration, the 3-acetyl and 3-benzoyl derivatives of XXIV were prepared in order to eliminate the absorption in the infrared spectrum of the

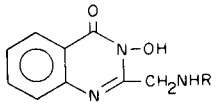


R CH_3 (XXVI)
R C_6H_5 (XXVII)

3-hydroxy group. The study of these spectra shows that they are esters derived from XXIV with a net absorption of the -NH group at 3,250 cm^{-1}, and show 3 bands of the carbonyl groups between 1,695-1,820 cm^{-1}.

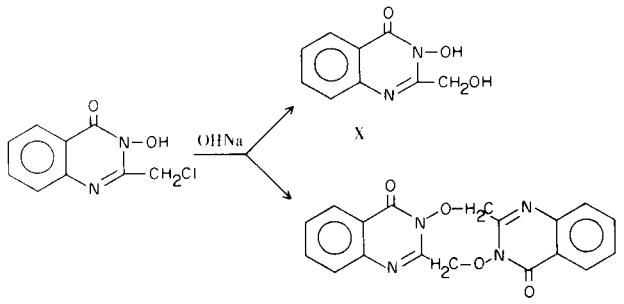
Finally, we prepared 1-methyl-3-hydroxy-2,4-quinazolindione (XXIII), in which there is no possibility for tautomerism, XXIV ⇌ XXIVa. The infrared spectrum is similar to XXIV and the two characteristic bands of the quinazolidindiones at 1,500 and 1,615 cm^{-1} are also observed.

It was also of interest to study the behaviour of 2-chloromethyl-3-hydroxy-4(3*H*)quinazolinone (I) with amines, since the -N → O form, if it exists even in a minimum proportion as 2-chloromethyl-4-hydroxy-quinazoline 3-oxide, is a structure which is able to undergo ring expansion similar to that of Sternbach and Reeder in obtaining 1,4-benzodiazepine *N*-oxides. However, with methyl and ethylamine, the product obtained was apparently that of normal nucleophilic substitution.



V: R CH_3
VI: R C_2H_5

The nmr spectra of 2-(N-methylaminomethyl)-3-hydroxy-4(3*H*)quinazolinone in deuteriohydrochloric acid (20% of DCl in deuterium oxide) exhibited a singlet at 3.3 δ integrating for 3 protons ($-CH_3$); a singlet at 5.2 δ integrating for 2 protons ($-CH_2$) and a multiplet from 8-8.6 δ integrating for 4 aromatic protons. The ir spectrum does not show important variations with the starting material. On this account we assume there was no ring expansion. With secondary amines, such as dimethylamine, diethylamine, morpholine and piperidine, the reaction follows a different course; within a few hours, at room temperature, in the alcoholic medium of the reaction, a white precipitate, m.p. 263° (XI) was produced; it is insoluble in acid and alkali, organic solvents, and it does not give the reaction of hydroxamic acids with ferric chloride. Its infrared spectrum is similar to that of the 2-chloromethyl-3-hydroxy-4(3*H*)quinazolinone (I), except that the characteristic absorption of the OH group at 2,500 cm^{-1} and of the chlorine at 700 cm^{-1}, is not observed. Its molecular weight as determined by mass spectrometry is 348, the calculated value for a "dimer" (XI) of formula $C_{18}H_{12}N_4O_4$: analysis confirmed the structure. The same product was obtained in aqueous solution with one equivalent of sodium hydroxide. On the other hand, if the reaction was carried out with two equivalents of sodium hydroxide, small amounts of XI were obtained and if the alkaline solution was acidified, the normal substitution product replacing the halogen by the OH group (X), having all the properties of the hydroxamic acids, precipitated. Treatment of XI with sodium hydroxide under the



XI

same conditions as those used to obtain X, did not alter the reaction; for this reason it is concluded that XI is not an intermediate in obtaining X.

With primary amines of greater molecular weight (propyl, isopropylamine) the dimer was also obtained as the principal product, and it may be supposed that, in these cases, the amine acts as a base or dehydrohalogenating agent.

EXPERIMENTAL

All melting points are uncorrected and were taken on a Büchi Capillary melting point apparatus. Ir spectra were determined with a Perkin-Elmer Model 21 spectrometer using potassium bromide pellets of the compounds. Nmr spectra were measured on a Varian A-60 instrument and chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. The mass spectra was determined on an AEI M59 mass spectrometer operating at seventy e.v. Thin layer chromatography (TLC) and thick layer chromatography were run on Merck Silica Gel GF 254.

2-Chloromethyl-3-hydroxy-4(3*H*)quinazolinone (I).

Chloroacetyl chloride (22 ml.) was added dropwise with stirring into 2-aminobenzohydroxamic acid (7.6 g., 0.05 mole). The pasty solid was heated under reflux for 10 minutes, cooled, and 100 ml. of cold water was added with caution. The solid which precipitated was collected, washed with cold water and dissolved in 5% sodium hydroxide. The solution was filtered and precipitated with dilute hydrochloric acid.

2-Bromomethyl-3-hydroxy-4(3*H*)quinazolinone (II).

To a solution of 2-aminobenzohydroxamic acid (4.56 g., 0.03 mole) in 20 ml. of dry dimethylformamide was added dropwise with stirring and cooling bromoacetyl bromide (8 g., 0.04 mole). The mixture was allowed to stand 30 minutes at room temperature and then heated in a water bath until all the hydrobromic acid was removed. The solvent was evaporated *in vacuo*, 100 ml. of cold water was added and the residue was dissolved in 5% sodium hydroxide. The solution was quickly filtered to remove any insoluble material and precipitated with dilute hydrochloric acid. The same product was obtained from 2-methyl-3-hydroxy-4(3*H*)quinazolinone (9) and *N*-bromosuccinimide.

2-(*o*-Carboxyphenyl)-3-hydroxy-4(3*H*)quinazolinone (III).

2-Aminobenzohydroxamic acid (5.016 g., 0.033 mole) was dissolved in ethanol (80 ml.); phthalic anhydride (5.18 g., 0.035 mole) was added and the mixture was heated at reflux temperature for 5 hours (the reaction was monitored by tlc). Ethanol was removed *in vacuo* to 25 ml. After cooling the precipitate was collected by filtration. The solid was dissolved in 5% sodium hydroxide, filtered, and the solution precipitated with dilute hydrochloric acid.

2-(β-Carboxyethyl)-3-hydroxy-4(3*H*)quinazolinone (IV).

The compound was prepared in an identical manner; however, the starting materials were 2-aminobenzohydroxamic acid (1.52 g., 0.01 mole) and succinic anhydride (1.5 g., 0.015 mole). The reaction mixture was heated 4 hours at reflux temperature.

2-(methylaminomethyl)-3-hydroxy-4(3*H*)quinazolinone (V).

To a solution of I (1.26 g., 0.006 mole) in 200 ml. of cold methanol, 10 ml. of 20% methanolic methylamine was added. The mixture was allowed to stand 48 hours at room temperature after which it was filtered and evaporated to 10 ml. under reduced pressure. The residue was collected and washed twice with 25 ml. of cold water.

2-(Ethylaminomethyl)-3-hydroxy-4(3*H*)quinazolinone (VI).

This compound was prepared in an identical manner to that described for the above analog except ethylamine (2.58 g., 0.06 mole) was employed.

2-Phenyl-3-hydroxy-4(3*H*)quinazolinone (VII).

2-Aminobenzohydroxamic acid (3.04 g., 0.02 mole) was dissolved in dry dioxane (25 ml.); benzoyl chloride (2.81 g., 0.02 mole) was added and the mixture was heated on a water bath for 1 hour. The dioxane was evaporated *in vacuo*, the residue was

extracted with ether (10 ml.) and ice water (30 ml.) was added. After 1 hour at room temperature, the solid was collected, dissolved in 5% sodium hydroxide, filtered, and acidified with dilute hydrochloric acid.

2-(*p*-Nitrophenyl)-3-hydroxy-4(3*H*)quinazolinone (VIII).

This compound was prepared in an identical manner to that described for the above analog, except *p*-nitrobenzoyl chloride (5.56 g., 0.03 mole) was employed.

2-(β-Carboxyvinyl)-3-hydroxy-4(3*H*)quinazolinone (IX).

2-Aminobenzohydroxamic acid (1.52 g., 0.01 mole) was dissolved in dry dioxane (20 ml.); maleic anhydride (1.47 g., 0.015 mole) was added and the mixture was heated at reflux temperature for 3 hours. The solvent was evaporated *in vacuo*, 50 ml. of water was added and the mixture was allowed to stand at 5° overnight. The solid was collected, dissolved in 5% sodium hydroxide and acidified with acetic acid.

Action of Sodium Hydroxide upon 2-Chloromethyl-3-hydroxy-4-(3*H*)quinazolinone (X-XI).

a) With Two Equivalents of Sodium Hydroxide.

A solution of I (2.1 g. 0.01 mole) in 5% sodium hydroxide (20 ml.) was allowed to stand for 24 hours at room temperature. A small amount of insoluble material (XI) was removed by filtration. The solution upon acidification with acetic acid, gave 1.1 g. of X. The product was purified by thick layer chromatography and extracted with ethanol.

b) With One Equivalent of Sodium Hydroxide.

A solution of I (2.1 g., 0.01 mole) in 10% sodium hydroxide (4 ml.) was allowed to stand for 4 hours at room temperature. The white precipitate was collected, washed with water and dried to give 1.3 g. of XI. An analytical sample was prepared by two recrystallizations from dimethylformamide m.p. 263° dec.; ir 1700, 1600, 1450, 1420, 1240, 950, 750 and 680 cm^{-1}.

Anal. Calcd. for $C_{18}H_{12}N_4O_4$: C, 62.06; H, 3.41; N, 16.09; Mol. Wt., 348. Found: C, 61.90; H, 3.70; N, 16.05; Mol. Wt., 348 (mass spectroscopy).

The aqueous filtrate, acidified with acetic acid, gave a small amount of X as shown by tlc.

Action of Ethyl Chloroformate upon Sodium 2-Aminobenzohydroxamic.

To a stirred cooled solution of 2-aminobenzohydroxamic acid (2.28 g., 0.015 mole) in 5% sodium hydroxide (25 ml.) was added dropwise ethyl chloroformate (1.94 g., 0.018 mole). After 30 minutes, the mixture was filtered. The solid was washed with water, dried, and recrystallized from ethanol to give 1.5 g. (75%) of 2-hydroxybenzimidazole identified by ir spectral comparison with an authentical sample.

2-Chloromethyl-3-acetoxy-4(3*H*)quinazolinone (XII).

Method A.

A stirred cooled solution of I (2.1 g., 0.01 mole) in 5% sodium hydroxide (25 ml.) was treated dropwise with acetic anhydride (2.04 g.). After 10 minutes, the white precipitate was collected, washed until neutral and dried.

Method B.

Compound I (2.1 g.) and acetic anhydride (15 ml.) was heated under reflux for 2 hours. The solution was evaporated *in vacuo* to dryness and washed until neutral.

2-Methyl-3-methoxy-4(3*H*)quinazolinone (XIII).

A stirred cooled soltuion of 2-methyl-3-hydroxy-4(3*H*)quinazolinone (1.76 g., 0.01 mole) (9) in 5% sodium hydroxide (25 ml.) was treated dropwise with dimethyl sulphate (2.4 g.) and stirring was continued until there was no reaction with 10% ferric chloride. The solution was acidified with acetic acid, filtered and extracted with benzene. The extracts were dried and evaporated *in vacuo* to dryness.

2-Phenyl-3-benzoyloxy-4(3*H*)quinazolinone (XIV).

A mixture of 2-aminobenzohydroxamic acid (3.04 g., 0.02 mole) and benzoyl chloride (8 ml.) was heated in a water bath for 2 hours. After cooling, the mixture was extracted with ether (20 ml.); ice water was added and left 2 hours. The precipitate was collected and washed until neutral. Compound XIV was hydrolyzed with 20% sodium hydroxide and the resulting compound was found to be identical with VII.

2-Methyl-3-acetoxy-4(3*H*)quinazolinone (XV).

This compound was prepared in a manner identical to that for compound XII (method B).

2-Chloromethyl-3-benzoyloxy-4(3*H*)quinazolinone (XVI); 2-Methyl-3-benzoyloxy-4(3*H*)quinazolinone (XVII); 3-Benzoyloxy-4(3*H*)quinazolinone (XVIII).

These compounds were prepared in a manner identical to that described for compound XII (method A) with the respective quinazolinone and benzoyl chloride.

2-Chloromethyl-3-methoxy-4(3*H*)quinazolinone (XIX).

A stirred cooled solution of I (2.1 g., 0.01 mole) in 5% sodium hydroxide was treated dropwise with dimethyl sulphate (2.52 g., 0.02 mole). Stirring was continued for 10 minutes, acidified with dilute hydrochloric acid and left at room temperature overnight. The precipitate was collected and washed until neutral.

2-Chloromethyl-3-carbethoxyoxy-4(3*H*)quinazolinone (XX); 2-Methyl-3-carbethoxyoxy-4(3*H*)quinazolinone (XXI); 3-Carbethoxyoxy-4(3*H*)quinazolinone (XXII).

These compounds were prepared in an identical manner to that described for XIX with the respective 3-hydroxy-4(3*H*)quinazolinone (0.01 mole) and ethyl chloroformate (0.02 mole).

Action of Acetic Anhydride on 2-(*o*-Carboxyphenyl)-3-hydroxy-4(3*H*)quinazolinone (IIIa).

A mixture of III (4.23 g., 0.015 mole) and acetic anhydride (15 ml.) was heated under reflux for 2 hours while being protected from moisture. Excess reactant was removed *in vacuo* to 5 ml. and the residue was cooled. The precipitate was collected and recrystallized from dry acetone to yield 2.85 g. (70%) of the lactone IIIa, m.p. 288°. Heating with water or ethanol hydrolyzed IIIa to III; ir 1760, 1700, 1600-1580, 1360, 1280, 1140, 1020, 760 and 680 cm^{-1}.

Anal. Calcd. for $C_{15}H_8N_2O_3$: C, 68.13; H, 3.03; N, 10.60. Found C, 68.20; H, 3.28; N, 10.70.

1-Methyl-3-hydroxy-2,4(1*H*,3*H*)quinazolinedione (XXIII).

a) 2-(*N*-Methylamine)benzohydroxamic Acid.

To a cooled solution of sodium hydroxide (36 g.) in water (300 ml.) was added with stirring hydroxylamine hydrochloride (27.7 g.). To this solution methyl (*N*-methyl)anthranilate (35 g.) in 300 ml. of methanol was added. The solution was left at room temperature for three days and then evaporated *in vacuo* to 100 ml. Cooling caused the sodium salt of the hydroxamic acid to pre-

cipitate. The salt was collected, washed with ether and dissolved in 200 ml. of water. The solution was acidified with acetic acid and the hydroxamic acid precipitated. The product was recrystallized twice from water to yield 28 g. (80%), m.p. 127°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.02; N, 16.86. Found: C, 57.80; H, 6.22; N, 16.93.

b) A mixture of 2-(*N*-methylamino)benzohydroxamic acid (3.32 g., 0.02 mole) in 20 ml. of dry dioxane and ethyl chloroformate (3.25 g., 0.03 mole) was heated under reflux for 1 hour. After cooling, 100 ml. of ice water was added and the mixture was left at 5° overnight. The solid was filtered and washed twice with ice water; ir 3150-2000, 1740, 1695, 1615, 1500, 1270, 860 and 750 cm^{-1}.

3-Hydroxy-2,4(1*H*,3*H*)quinazolinedione (XXIV).

This compound was prepared in an identical manner to that described for XXIII but employing 2-aminobenzohydroxamic acid; ir 3400-2000, 1750, 1695, 1615, 1500, 1290, 800 and 750 cm^{-1}.

1-Methyl-3-acetoxy-2,4(1*H*,3*H*)quinazolinedione (XXV).

A mixture of XXIII (1.34 g., 0.007 mole) and acetic anhydride (15 ml.) was heated under reflux for 2 hours. The solution was concentrated *in vacuo* and 15 ml. of cold water was added. The solid was collected, washed with 5% sodium hydroxide and water until neutral; ir 2980-1820, 1750, 1695, 1615, 1500, 1270, 850 and 750 cm^{-1}.

3-Acetoxy-2,4(1*H*,3*H*)quinazolinedione (XXVI).

The compound was prepared in an identical manner to that described for XXV but employing XXIV; ir 3250, 1820, 1750, 1695, 1615, 1500, 1270, 860 and 750 cm^{-1}.

1-Methyl-3-benzoyloxy-2,4(1*H*,3*H*)quinazolinedione (XXVII).

A stirred cooled solution of XXIII (1.92 g., 0.01 mole) in 24 ml. of 5% sodium hydroxide was treated dropwise with benzoyl chloride (2.18 g., 0.02 mole). Stirring was continued until no reaction with 10% ferric chloride occurred. The precipitate was collected, and washed with water until neutral; ir 1985, 1780, 1750, 1695, 1615, 1500, 1260, 860 and 750 cm^{-1}.

3-Benzoyloxy-2,4(1*H*,3*H*)quinazolinedione (XXVIII).

This compound was prepared in an identical manner to that described for XXVII but employing XXIV; ir 3240, 1780, 1745, 1695, 1615, 1500, 1275, 860 and 745 cm^{-1}.

1-Methyl-3-carbethoxyoxy-2,4(1*H*,3*H*)quinazolinedione (XXIX); 3-Carbethoxyoxy-2,4(1*H*,3*H*)quinazolinedione (XXX).

These compounds were prepared in an identical manner to that described for XXVII with the respective 3-hydroxy-2,4(1*H*,3*H*)-quinazolinedione (0.01 mole) and ethyl chloroformate (0.015 mole) and recrystallized from the solvents indicated in Table III.

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REFERENCES

(1) E. Shaw, *J. Am. Chem. Soc.*, **71**, 67 (1949).

(2) W. A. Lott and E. Shaw, *ibid.*, 71, 70 (1949).

(3) K. G. Cunningham, G. T. Newbold, F. S. Spring and J. Stark, *J. Chem. Soc.*, 2091 (1949).

(4) S. R. Safir and J. H. Williams, *J. Org. Chem.*, 17, 1298 (1952).

(5) E. C. White and T. H. Hill, *J. Bacteriol.*, **45**, 433 (1943).

(6) J. D. Dutcher and O. Wintersteiner, *J. Biol. Chem.*, 155, 359 (1944).

(7) A. Stoll, J. Renz and A. Brack, *Helv. Chem. Acta*, 34, 862 (1951).

(8) L. Legrand and N. Lozac'h, *Bull. Soc. Chim. France*, 618 (1961).

(9) D. H. Harrison and A. C. B. Smith, *J. Chem. Soc.*, 2157 (1960).

(10) A. Dornow and K. Fischer, *Chem. Ber.*, **99**, 72 (1966).

(11) P. Mamalis, M. J. Rix and A. A. Sarsfield, *J. Chem. Soc.*, 6278 (1965).

(12) J. P. Griffiths and C. K. Ingold, *ibid.*, 127, 1639 (1925).

(13) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, 76, 1286 (1956).

(14) R. T. Coutts, K. W. Hindmarsh, S. J. Powell, J. L. Pound and E. M. Smith, *Can. J. Pharm. Sci.*, 2, 49 (1968).

(15) E. B. Reid and W. R. Ruby, *J. Am. Chem. Soc.*, 73, 1054 (1951).

(16) L. H. Sternbach, S. Kaiser and E. Reeder, *ibid.*, 82, 475 (1960).

(17) H. Culbertson, J. C. Decius and B. G. Christensen, *ibid.*, 74, 4834 (1952).