Tetrahedron Vol 49, No 31, pp 6899-6912, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Reactions of Hydroxyglycines. New Synthetic Routes to 4-Phenylquinazoline Derivatives

Anthonius J. Hoefnagel[a*], Henk van Koningsveld[a], Frank van Meurs[b], Joop A. Peters[a], Anton Sinnema[a] and Herman van Bekkum[a]

[a] Laboratory of Organic Chemistry and Catalysis, Delft University of Technology,
Julianalaan 136, 2628 BL Delft, The Netherlands

[b] Delft Instruments X-Ray Diffraction B.V, Rontgenweg 1, 2624 BD Delft, The Netherlands

(*Received in UK* 2 *June* 1993)

Abstract: Reaction of hydroxyglycine with 2-aminobenzophenones gives 1,2-dihydro-4-phenyl-quinazoline-2-carboxylic acids in high yields and under mild conditions. These can be smoothly converted into the corresponding 3,4-dihydro isomers and into quinazoline derivatives via rearrangement and oxidation by air, respectively. The X-ray crystallographic structure of 6-chloro-1,2-dihydro-1-methyl-4-phenylquinazoline-2-carboxylic acid shows the carboxylate group at C(2) and the methyl group at N(1) to be in axial positions.

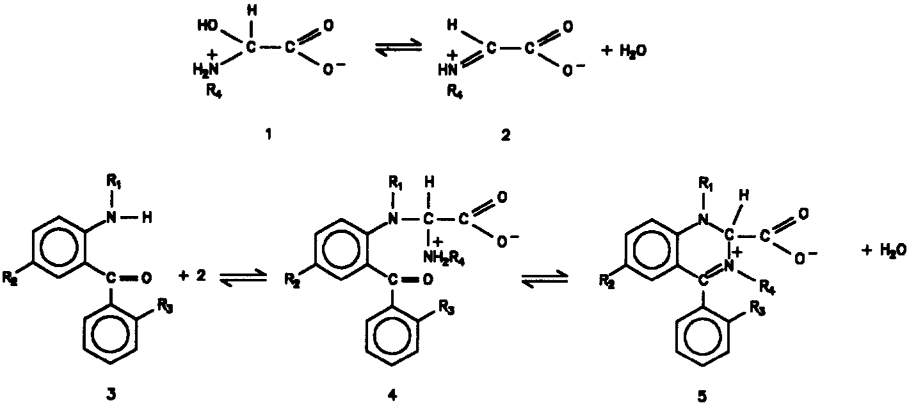
INTRODUCTION

Hydroxyglycine can easily be prepared from glyoxylic acid and ammonia, and is stable as a solid.[1] In aqueous solution at pH > 6, however, it forms the highly reactive iminoacetate, and therefore hydroxyglycines may be versatile reagents in organic syntheses. The observation of Han et al.[2] that hydroxyglycine is a degradation product of the tranquillizer Oxazepam (7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one), induced us to investigate the reverse conversion: reaction between hydroxyglycine and N-substituted derivatives with 2-aminobenzophenones. It appeared that substituted 1,2-dihydro-4-phenylquinazoline-2-carboxylic acids are formed. Here we report on these reactions, as well as on subsequent conversions of these primary products, such as isomerization, decarboxylation, and aromatization reactions, leading to products that are identical with or related to degradation products of Oxazepam and other tranquillizers from the diazepine family.

RESULTS AND DISCUSSION

Addition of an aqueous solution of a hydroxyglycine (**1**), or of glyoxylic acid and the appropriate amine, to an alcoholic solution of a 2-aminobenzophenone (**3**) immediately gave an intensely orange-red coloured reaction mixture. From these reaction mixtures 1,2-dihydro-4-phenylquinazoline-2-carboxylic acids (**5**)(see Scheme I) could be isolated in high yields (71-96%).

A comparable reaction, starting from 2-aminoacetophenone, produces 1,2-dihydro-4-methylquinazoline-2-carboxylic acid (**5h**).



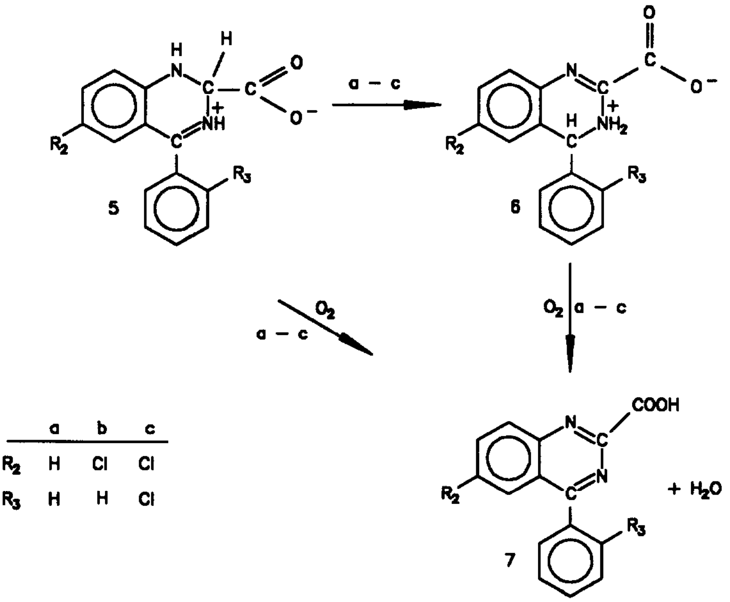
Compound	a	b	c	d	e	f	g
R_1	H	H	H	H	H	CH_3	CH_3
R_2	H	Cl	Cl	Cl	Cl	Cl	Cl
R_3	H	H	Cl	H	H	H	H
R_4	H	H	H	CH_3	CH_2Ph	H	CH_3

Scheme I

The structure of the N(1)-Me compound **5f** was elucidated with X-ray diffraction (see below). From the ^{13}C NMR shifts for the C(2) atoms (69-78.9 ppm), it could be concluded that all products obtained were the 1,2-dihydro isomers. This is in agreement with the observation of Schöpf and Oechler[3] that reaction of 2-aminobenzaldehyde with formaldehyde and allylamine under neutral conditions gives the orange-yellow 3-allyl-1,2-dihydroquinazolinium hydroxide. The products obtained are probably formed via an attack of iminoacetate on the amino function of **3** to form intermediate **4**, which is converted into **5** by cyclization and dehydration. A similar mechanism has been shown[1] to be operative in the cyclotrimerization of iminoacetate (**2**).

All products **5** are stable as solids, but in solution there is a tendency to return to compound **3**, probably because the hydroxyglycines are withdrawn from the equilibrium with **3**, via decomposition into glyoxylic acid and the corresponding amine, followed by condensation reactions and evaporation, respectively. These decompositions are especially found, according to UV-measurements, with the inner salts **5d-e** and **5g**. Compounds **5a-c** easily isomerize to the corresponding yellow coloured 3,4-dihydroquinazolines **6a-c** (see Scheme II); heating of **5b** with 2 N NaOH in ethanol afforded **6b** in 82% yield. Compound **6b** has been identified as a degradation product of Oxazepam and can also be obtained by treating Oxazepam with an alcoholic NaOH solution.[4] The higher stability of the 3,4-dihydroquinazolines is in agreement with the observed exclusive formation of these compounds upon catalytic hydrogenation of quinazolines.[5]

Products **5a-c** also undergo aromatization to give the quinazolines **7a-c**, either directly or via the 3,4-dihydro derivatives **6a-c** (see Scheme II).



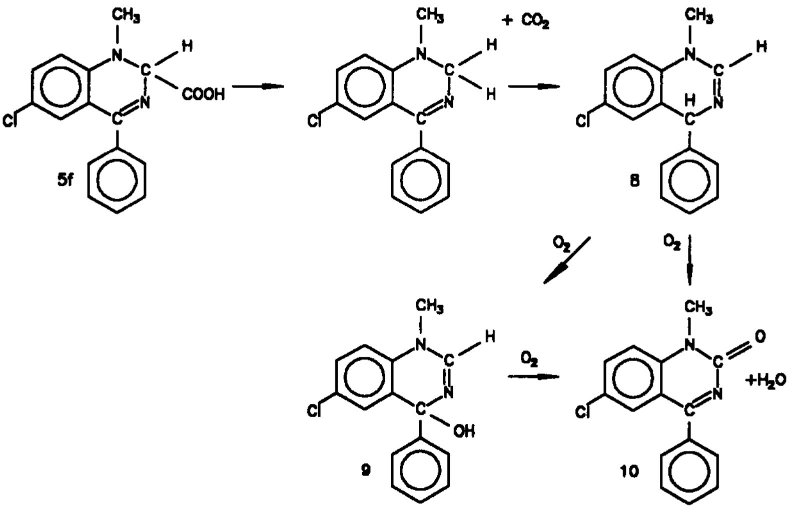
	a	b	c
R_2	H	Cl	Cl
R_3	H	H	Cl

Scheme II

The methyl ester of **5b**[6] was identical with the product, which was obtained by acid catalyzed rearrangement of Oxazepam, followed by esterification of the intermediate with methanol at 40 °C. It may be concluded, that compound **5b** is a degradation product of 7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (Oxazepam). A solution of **5b** in dimethylformamide (DMF) afforded **7b** in 87% yield, after standing in daylight for 3 days. The influence of light is illustrated by the fact that the conversion to **7b** was only 43% when this reaction was performed in the dark.

Formation of 6-chloro-4-phenylquinazoline-2-carboxylic acid (**7b**) can also be accomplished from Oxazepam by a two steps reaction following the directions of Bell et al.[7]. Decarboxylation of **5b** and **7b** can simply be accomplished by heating the compound above the decomposition point, and leads to 6-chloro-3,4-dihydro-4-phenylquinazoline[8] and 6-chloro-4-phenylquinazoline[9], respectively.

The presence of a methyl group on N(1) does not allow these isomerization and aromatization reactions in compound **5f**. Instead, decarboxylation followed by oxidation is observed in this case (see Scheme III).



Scheme III

Upon heating of solid **5f** at 130 °C under nitrogen decarboxylation was observed and the 1,4-dihydro derivative **8** was obtained in about 80% yield. When this reaction was performed in air, a mixture of **8**, and the oxidation products **9** and **10** resulted. These reactions also occur in a solution of **5f** in methanol or ethanol. Compounds **8** and **10** have been identified as photochemical products of Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one).[10]

The reactions of compounds **5** were monitored by UV spectroscopy with diluted solutions in 96% ethanol. The N(3) protonated forms of **5a-f** have an absorption peak at about 450 nm; upon deprotonation the maximum shifts to about 390 nm. The aromatic products **7a-c** have a maximum absorption at about 330 nm. It appears that the pH has a profound influence on the reaction rates (see Table 1).

Table 1. Electronic Spectra and Half-life Data of Compound **5** in 96% Ethanol[a] and Dissociation Constants in 50% Ethanol.

Compound	pH solution	λ_{max}[b]	ε_{max}[c]	$t_{½}$ (min)	pKa[d] 50% EtOH
5a	7.2	448	2380	465	6.82
5b	1.8[e]	450	3440	7800	5.93
	5.5	450^{sh}	1290	277	
	5.5	390	3840	283	
5b (Me-ester)	2.9	450	1631	4100	
5c	5.0	400	2060	642	5.19
5d	7.3	460	2960	47	
5e	6.8	470	2890	213	
5f	5.9	410	2720	∞	5.79
5g	8.0	480	2670	3120	
5h	7.0	430	1980	235	7.21

[a] Conditions: ~10 mg of the compounds in 50 mL of 96% ethanol at 25 °C. The solutions were stored between the measurements in the compartment of the UV-apparatus. [b] λ_{max}:wavelength maximum absorption, in nm. [c] ε_{max} : extinction coefficient, in $M^{-1}.cm^{-1}$ [d] Dissociation constant in 50% ethanol at 25 °C after correction for the small change of the pH caused by decomposition. [e] Acidified with 2 M HCl solution.

At low pH the reactions are very slow, probably as a result of stabilization of **5** by protonation at N(3), which results in a cation stabilized by a diphenylcarbinyl group. At pH values 5-8 the reactions are much faster, which may also be rationalized by rearrangement of **5** into **6** via a mechanism that starts with an abstraction of the proton at C(2). The enhancing effect of light on these reactions may be explained by a rearrangement mechanism via a sigmatropic [1,3]-H shift of the H-atom at C(2) in **5**, which is thermally forbidden, but photochemically allowed.

The dissociation constants in 50% aqueous ethanol solutions of the zwitterionic compounds **5b**, **5c**, **5f** and **5h**, given in Table I, are in agreement with the influences of the substituents on the dissociation constant of **5a**, which is comparable with that of benzophenone imine (7.18 in water[11]).

The half-life data, illustrating the forward and backward conversions (**3** ← **5** → **6**/**7**) of diluted solutions of the compounds **5** in 96% ethanol as obtained by UV spectroscopy, are compiled in Table I. Under these conditions the inner salts **5d-e** are not very stable, but compound **5g** is stabilized by the methyl group at N(1) and the equilibrium (**5g** ⇌ **3g** + **2**) is in favour of the adduct. The stability of **5f** shows the influence of a methyl group on N(1), which can be explained in part by the absence of the isomerization and/or aromatization reactions.

Structure of 6-chloro-1,2-dihydro-1-methyl-4-phenylquinazoline-2-carboxylic acid (**5f**)

For X-ray analysis crystals of **5f** were obtained upon partial evaporation of the solvent from the reaction mixture of **3f** and **2**. A single crystal of $C_{16}H_{13}ClN_2O_2.H_2O$ (**5f**), selected for X-ray analysis, measured along the a, b and c directions, 0.53, 0.43 and 0.20 mm, respectively. The unit-cell contains 4 molecules $C_{16}H_{13}ClN_2O_2$ and 4 molecules H_2O, of which 2 molecules $C_{16}H_{13}ClN_2O_2$, representing the two enantiomers, and 2 molecules H_2O are crystallographically independent.

Figure 1 shows an ORTEP drawing of one of the enantiomers. The phenyl groups are approximately coplanar, while a half-chair model is found for the 1,2-dihydropyrimidine ring with an axial carboxylate anion at C(2) and an axial methyl group at N(1).

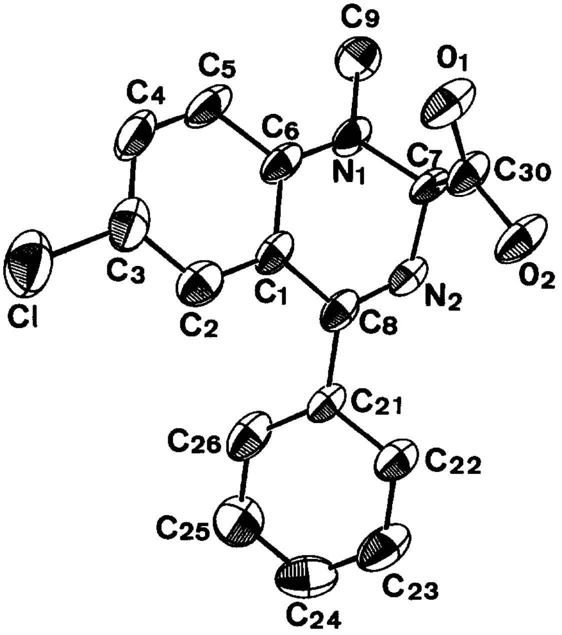


Fig. 1. ORTEP plot of one of enantiomers of **5f**. The first digit of the atomic labels is deleted for the sake of clarity. The atomic numbering differs from the Ring Index numbering, for instance, C(7) instead of C(2) (see text).

EXPERIMENTAL

The starting materials used were commercial products and were used without further purification. The ^{13}C and ^{1}H NMR spectra were recorded with a Varian VXR-400 S or a Nicolet NT-200 WB spectrometer at 25 °C. Chemical shifts are from tetramethylsilane (TMS) as internal reference.

The UV-spectra were measured on a Pye-Unicam SP 8-250 spectrometer and the IR-spectra were obtained from KBr discs using a Beckman IR 4210 infrared spectrophotometer. According to Culbertson et al.[12] characteristic bands are found for the quinazoline structure in the "double bond" region: 1478-1517 cm^{-1} (I), 1566-1581 cm^{-1} (II), and 1612-1628 cm^{-1} (III).

The EI mass spectra were recorded on a VG 70-250 mass spectrometer. The thermodynamic pK_a^* values were determined by the method of Wepster et al.[13].

X-ray crystallographic data were collected on an Enraf-Nonius Turbo CAD-4 diffractometer, using Mo-$K\alpha$ radiation and a graphite monochromator. The red crystal of $C_{16}H_{13}ClN_2O_2.H_2O$ selected for X-ray analysis measured along the a, b and c directions, 0.53, 0.43 and 0.20 mm, respectively. The unit-cell dimensions are a = 8.3531(9) Å, b = 10.155(2) Å, c = 17.721(5) Å, α = 84.31(2)°, β = 87.18(2)°, γ = 89.85(1)° (Mo-$K_{\alpha 1}$ = 0.70926 Å). The space group is P-1. The unit-cell contains 4 molecules $C_{16}H_{13}ClN_2O_2$ and 4 molecules H_2O, of which 2 molecules $C_{16}H_{13}ClN_2O_2$ and 2 molecules H_2O are crystallographically independent.

The formula weight of the independent unit, $C_{32}H_{30}Cl_2N_4O_6$, is 637.52. The density calculated for this compound is 1.417 gcm^{-3}. The crystal was mounted about the a-axis. The orientation, the diffraction symmetry, the Laue group, the data and the absorption correction data have been determined c.q. collected automatically with the CAD4Express program, using $\omega/2\theta$-scan technique. From the 9055 measured reflections 3365 were significantly [$>2.65^* \sigma(I)$] different from the background intensity. The absorption coefficient μ is 2.66 cm^{-1} (Mo-$K\alpha$). Empirical absorption correction was applied to the reduced data.

All computations were done on a VAX Station3520 using the MolEN structure determination package[14]. The structure has been solved by SIR[15]. The positional and thermal parameters and their standard deviations are listed in Table 2, while the bond distances with their e.s.d's, bond angles and their e.s.d's and a survey of torsion angles and their standard deviations are available from the authors on request. All non-hydrogen atoms could be found in the E-map and the hydrogen atoms were located in a difference map. The structure has been refined with, for all the non-hydrogen atoms, positional and anisotropic thermal parameters, and for the hydrogen atoms positional parameters only. The final refinement led to a disagreement factor R ($= \Sigma||F_0| - |F_c|| / \Sigma|F_0| * 100$) of 7.0% for 487 refined parameters and 3365 observations. A final difference Fourier synthesis showed a residual density between -0.14 and +0.40 $eÅ^{-3}$.

Table 2. Positional Parameters and their Estimated Standard Deviation[a]

Atom	x	y	z	B(Å^2)	Atom	x	y	z	B(Å^2)
Cl1	0.0597(3)	0.3494(2)	0.5863(1)	6.31(5)	Cl2	-0.4295(3)	-0.6888(2)	0.5800(1)	6.14(5)
O3	-0.5769(6)	-0.0232(4)	0.8729(4)	6.8(2)	O4	-0.0724(6)	-0.4239(4)	0.8765(4)	6.7(1)
O11	0.1085(5)	0.0294(4)	0.9155(3)	4.4(1)	O12	0.0586(5)	-0.1747(4)	0.8852(3)	4.3(1)
O21	-0.3905(5)	-0.4934(4)	0.9143(3)	4.3(1)	O22	-0.4425(5)	-0.2789(3)	0.8862(3)	4.2(1)
N11	-0.1974(5)	0.1122(4)	0.8811(3)	3.0(1)	N12	-0.2238(5)	-0.0913(4)	0.8301(3)	2.77(9)
N21	-0.6923(5)	-0.5647(4)	0.8764(3)	3.1(1)	N22	-0.7217(5)	-0.3420(4)	0.8285(3)	2.9(1)
C11	-0.1296(6)	0.0924(5)	0.7502(3)	2.6(1)	C12	-0.0678(7)	0.1491(5)	0.6816(4)	3.4(1)
C13	-0.0251(8)	0.2806(5)	0.6717(4)	3.8(1)	C14	-0.0484(8)	0.3564(5)	0.7322(4)	4.2(1)
C15	-0.1103(8)	0.3074(5)	0.7993(4)	3.8(1)	C16	-0.1471(6)	0.1688(5)	0.8134(3)	2.9(1)
C17	-0.1637(6)	-0.0298(5)	0.8944(3)	2.6(1)	C18	-0.1945(6)	-0.0411(5)	0.7621(3)	2.6(1)
C19	-0.2550(9)	0.1824(6)	0.9433(4)	4.9(2)	C21	-0.6217(6)	-0.4952(5)	0.7474(3)	2.8(1)
C22	-0.5576(7)	-0.5252(6)	0.6779(4)	3.6(1)	C23	-0.5147(8)	-0.6532(6)	0.6666(4)	3.9(1)
C24	-0.5422(8)	-0.7530(5)	0.7250(4)	4.5(1)	C25	-0.6028(8)	-0.7279(5)	0.7930(4)	4.1(1)
C26	-0.6409(6)	-0.5956(5)	0.8088(4)	3.1(1)	C27	-0.6620(6)	-0.4283(5)	0.8917(3)	2.8(1)
C28	-0.6912(6)	-0.3665(5)	0.7598(3)	2.8(1)	C29	-0.7501(9)	-0.6586(6)	0.9384(4)	5.0(2)
C111	-0.2369(6)	-0.1169(5)	0.6990(3)	2.8(1)	C112	-0.3063(7)	-0.0619(5)	0.6350(4)	3.8(1)
C113	-0.3463(8)	-0.1363(6)	0.5774(4)	4.4(2)	C114	-0.3083(8)	-0.2692(6)	0.5836(4)	4.3(1)
C115	-0.2394(8)	-0.3239(5)	0.6457(4)	4.5(1)	C116	-0.2025(7)	-0.2534(5)	0.7052(4)	3.6(1)
C130	0.0194(7)	-0.0590(5)	0.8982(4)	3.1(1)	C221	-0.7357(6)	-0.2695(5)	0.6974(3)	2.7(1)
C222	-0.7122(7)	-0.1343(5)	0.7046(4)	3.5(1)	C223	-0.7510(8)	-0.0426(6)	0.6459(5)	4.9(2)
C224	-0.8177(8)	-0.0791(7)	0.5826(5)	5.0(2)	C225	-0.8414(8)	-0.2119(7)	0.5744(4)	4.7(2)
C226	-0.7997(8)	-0.3046(6)	0.6319(4)	4.1(1)	C230	-0.4792(7)	-0.4002(5)	0.8982(4)	3.2(1)
H12	-0.043(6)	0.102(5)	0.645(3)	3.4*	H12n	-0.276(6)	-0.142(5)	0.841(3)	2.8*
H14	-0.019(7)	0.425(5)	0.719(3)	4.2*	H15	-0.138(6)	0.343(5)	0.841(3)	3.8*
H17	-0.225(6)	-0.067(5)	0.950(3)	2.6*	H22n	-0.782(6)	-0.292(5)	0.838(3)	2.8*
H22	-0.538(6)	-0.472(5)	0.641(3)	3.6*	H24	-0.507(7)	-0.824(5)	0.712(3)	4.5*
H25	-0.622(7)	-0.789(5)	0.831(3)	4.1*	H27	-0.723(6)	-0.413(5)	0.944(3)	2.8*
H31o	-0.549(8)	-0.079(7)	0.892(4)	7.0*	H32o	-0.670(8)	-0.025(7)	0.916(4)	7.0*
H41o	-0.176(8)	-0.440(7)	0.901(4)	7.0*	H42o	-0.053(8)	-0.408(7)	0.931(4)	7.0*
H112	-0.329(7)	0.007(5)	0.634(3)	3.8*	H113	-0.384(7)	-0.095(5)	0.532(3)	4.4*
H114	-0.319(7)	-0.311(5)	0.532(3)	4.3*	H115	-0.215(7)	-0.405(5)	0.659(3)	4.5*
H116	-0.149(6)	-0.287(5)	0.749(3)	3.6*	H191	-0.303(7)	0.247(6)	0.922(3)	4.9*
H192	-0.331(7)	0.128(6)	0.989(3)	4.9*	H193	-0.185(7)	0.187(6)	0.985(3)	4.9*
H222	-0.673(6)	-0.110(5)	0.752(3)	3.5*	H223	-0.751(7)	0.027(6)	0.665(3)	4.9*
H224	-0.834(7)	-0.018(6)	0.536(3)	5.0*	H225	-0.885(7)	-0.241(6)	0.522(3)	4.7*
H226	-0.812(7)	-0.378(5)	0.626(3)	4.1*	H291	-0.792(7)	-0.719(6)	0.918(3)	4.9*
H292	-0.679(7)	-0.675(6)	0.979(3)	4.9*	H293	-0.818(7)	-0.620(6)	0.981(3)	4.9*

[a] The temperature factors of the anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(4/3) * [a^2*B(1,1) + b^2*B(2,2) + c^2*B(3,3) + ab(\cos \gamma)*B(1,2) + ac(\cos \beta)*B(1,3) + bc(\cos \alpha)*B(2,3)]$. The starred B's have been assigned on the basis of the isotropic equivalent displacement parameters of the parent atom to which the hydrogen atoms are attached.

SYNTHESES

General procedure. Compound **5a** was synthesized by the dropwise addition of an aqueous solution of 0.92 g (10 mmol) of glyoxylic acid in 10 mL of water to a solution of 2-aminobenzophenone (10 mmol) and ammonium acetate (30 mmol) in 30 mL of 96% ethanol at about 35 °C in 15 min. The orange-red coloured reaction mixture gives a precipitate within 15 minutes. After addition of 20 mL of water the precipitate was isolated by filtration and purified by washing with 96% ethanol and with diethyl ether. Compounds **5b** and **5c** were obtained from the corresponding substituted 2-aminobenzophenones. Compounds **5d-e** were obtained with this procedure from glyoxylic acid (10 mmol) and the appropriate amine (10-12 mmol) in 5 mL of water (or the hydrochloride salt of the amine in combination with a stoichiometric amount of sodium hydroxide solution) and 10 mmol of the substituted 2-aminobenzophenone.

The inner salts were obtained by evaporation of the solvent (< 35°C) from the reaction mixture obtained after 1 day at room temperature, followed by extraction of the residue with diethyl ether and water to remove unreacted starting material. Conversions were corrected for the amount of substituted 2-aminobenzophenone recovered. Compounds **5f** and **5g** were obtained from 5-chloro-2-methylaminobenzophenone (10 mmol in 100 mL of 96% ethanol) and hydroxyglycine or hydroxysarcosine, respectively. After reaction for one day part of the solvent was evaporated, after which **5f** or **5g** precipitated.

1,2-Dihydro-4-phenylquinazoline-2-carboxylic acid (5a). Yield 95% of orange-red crystals, dec 125-126.5 °C. Anal. Calcd for $C_{15}H_{12}N_2O_2.H_2O$: C, 66.66; H, 5.22; N, 10.37. Found: C, 66.50; H, 5.26; N, 10.37. ^{13}C NMR (DMSO-d_6) δ(ppm): 171.52, 165.28, 146.85, 137.40, 132.77, 129.33, 128.68, 127.97, 127.76, 116.62, 115.69, 114.27, 69.08. IR(KBr): 3400-3100, 2800-2600, 1620 (**III**), 1560 (**II**), 1480 (**I**), 1390, 1345, 1260, 1170 cm^{-1}.

6-Chloro-1,2-dihydro-4-phenylquinazoline-2-carboxylic acid (5b). Yield 94% of orange crystals, dec 130-131 °C. Anal. Calcd for $C_{15}H_{11}ClN_2O_2.0.5H_2O$:C, 60.92; H, 4.09; N, 9.47. Found:C, 60.84; H, 4.21; N, 9.62. ^{13}C NMR (DMSO-d_6) δ(ppm): 171.17, 164.22, 145.63, 136.86, 132.46, 129.53, 128.49, 128.15, 126.70, 119.68, 116.56, 116.03, 69.13. IR(KBr): 3400-2400, 1610 (**III**), 1570 (**II**), 1490 (**I**), 1380, 1245, 1175 cm^{-1}.

6-Chloro-4-(2-chlorophenyl)-1,2-dihydroquinazoline-2-carboxylic acid (5c). Yield 94% of orange crystals, dec 141-142 °C. Anal. Calcd for $C_{15}H_{10}Cl_2N_2O_2.0.5H_2O$:C, 54.57; H, 3.36; N, 8.48. Found: C, 54.48; H, 3.44; N, 8.62. ^{13}C NMR (DMSO-d_6) δ(ppm): 172.30, 164.74, 145.93, 137.45, 134.25, 132.41, 132.01, 131.57, 130.80, 128.80, 127.35, 121.07, 117.74, 117.17, 70.69.

6-Chloro-1,2-dihydro-3-methyl-4-phenylquinazoline-2-carboxylic acid (5d). Yield 86% of orange-red crystals, dec 142-143 °C. Anal. Calcd for $C_{16}H_{13}ClN_2O_2.0.5H_2O$: C, 62.04; H, 4.56; N, 9.04. Found: C, 62.14; H, 4.45; N, 9.08. ^{13}C NMR (CD_3OD) δ(ppm): 171.31, 169.07, 147.95, 140.04, 133.73, 131.31, 130.67, 130.61, 129.70, 129.59, 124.92, 118.87, 116.76, 72.75, 44.84.

6-Chloro-1,2-dihydro-3-benzyl-4-phenylquinazoline-2-carboxylic acid (5e). Yield 76% of red crystals, dec 108-109 °C. Anal. Calcd for $C_{22}H_{17}ClN_2O_2.0.75H_2O$: C, 67.69; H, 4.78; N, 7.18. Found: C, 67.67; H, 4.77; N, 7.18. ^{13}C NMR (CD_3OD-DMSO-d_6 ~4:1): 170.30, 168.86, 148.17, 140.25, 134.29, 133.55, 131.19, 130.87, 130.62, 130.48, 130.40, 130.16, 130.00, 129.29, 129.13, 124.52, 118.86, 116.47, 69.56, 59.62.

6-Chloro-1,2-dihydro-1-methyl-4-phenylquinazoline-2-carboxylic acid (5f). Yield 96% of orange-red crystals, dec 120-121.5 °C. Anal. Calcd for $C_{16}H_{13}ClN_2O_2.H_2O$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.49; H, 4.59; N, 9.04. ^{13}C NMR (DMSO-d_6) δ(ppm): 169.91, 164.41, 145.76, 136.90, 132.88, 129.69, 128.61, 128.46, 128.26, 127.00, 119.97, 117.53, 113.47, 75.72, 34.79.

6-Chloro-1,2-dihydro-1,3-dimethyl-4-phenylquinazoline-2-carboxylic acid (5g). Yield 71% of orange crystals, dec 89-90 °C. Anal. Calcd for $C_{17}H_{15}ClN_2O_2.1.75H_2O$: C, 58.96; H, 5.38; N, 8.09. Found: C, 59.14; H, 5.36; N, 8.33. ^{13}C NMR (CD_3OD) δ(ppm): 170.47, 168.44, 148.33, 140.30, 133.82, 131.93, 130.91, 130.63, 130.61, 130.56, 129.90, 124.81, 117.74, 116.90, 78.91, 44.91, 38.83.

1,2-Dihydro-4-methylquinazoline-2-carboxylic acid (5h), obtained from 2-aminoacetophenone using the general procedure, but after evaporation of the solvent from the reaction mixture. Yield 79% of orange powder, dec 152-153 °C. Anal. Calcd for $C_{10}H_{10}N_2O_2.H_2O$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.42; H, 5.84; N, 13.35. ^{13}C NMR (H_2O-D_2O 4 : 1) δ(ppm): 174.48, 173.40, 148.21, 141.06, 134.13, 121.20, 117.45, 114.52, 69.12, 20.11.

Reactions of (1,2-dihydro-)4-phenylquinazoline-2-carboxylic acids

Aromatization. General procedure: An orange-red solution of 50 mmol of **5a-5c** in 10 mL of dimethylformamide was kept in bright daylight for 3 days upon which the colour of the solution changed to light-orange. Addition of 10 mL of water gave a precipitate, which after cooling to 4 °C was isolated by filtration, followed by washing with water and diethyl ether. by filtration.

4-Phenylquinazoline-2-carboxylic acid (7a). Yield 76% of light-yellow crystals, mp 100 °C; Bischer and Barad[16], mp 100-102 °C dec. ^{13}C NMR in DMSO-d_6 δ(ppm) : 168.57, 165.25, 153.15, 150.27, 136.18, 134.83, 130.23, 129.97, 129.82, 129.03, 128.54, 126.91, 122.29.

6-Chloro-4-phenylquinazoline-2-carboxylic acid (7b). Yield 87% of light-yellow crystals, dec 204-206 °C. According to elemental analysis this product contains 1 mole of crystal water. Anal. Calcd for $C_{15}H_9ClN_2O_2.H_2O$: C, 59.52; H, 3.66; N, 9.25. Found: C, 59.42; H, 3.84; N, 9.58. ^{13}C NMR (DMSO-d_6) δ(ppm): 168.73, 165.40, 152.84, 149.61, 136.01, 135.41, 135.36, 131.58, 130.58, 130.06, 128.81, 125.86, 123.73. IR(KBr): 3560, 3410, 3060, 2900-2400, 1750, 1610(III), 1550(II), 1480(I), 1450, 1385, 1310, 1245, 1210, 1150, 1130, 1080 cm^{-1}. UV-spectrum (96% ethanol): max 328 nm ϵ = 6350; 285 nm^{sh} ϵ = 7650; max 240 nm ϵ = 35200. Dissociation constant in 50% aqueous ethanol: 3.77.

The decomposition point of the described product rose to 215-216.5 °C after recrystallization from absolute ethanol, resulting in a product without crystal water. Bell et al.[8] have described 6-chloro-4-phenylquinazoline-2-carboxylic acid with decomposition point 215-216 °C, according to the elemental analysis of their product, a modification without crystal water. The ^{13}C NMR spectra of the two products are identical, while the small differences found in the IR spectra can be explained by the presence of crystal water in the acid with the lower decomposition point.

6-Chloro-4-(2-chlorophenyl)quinazoline-2-carboxylic acid (7c). Yield 78% of light-yellow crystals, mp 215-217 dec; Sellstedt[17], mp 218-220 °C dec. ^{13}C NMR in DMSO-d_6 δ(ppm) : 166.53, 165.27, 154.77, 154.73, 148.38, 135.71, 134.51, 131.60, 131.37, 131.28, 131.14, 129.71, 127.53, 124.86, 123.53.

Isomerization

6-Chloro-3,4-dihydro-4-phenylquinazoline-2-carboxylic acid (6b). A solution of 1.18 g (4 mmol) of **5b** in 10 mL of 96% ethanol and 3 mL of 2 M sodium hydroxide solution was refluxed during 1 h. The clear yellow solution obtained was acidified with 2 M hydrochloric acid to pH 4.5. Cooling to 4 °C, followed by filtration and drying, gave 0.98 g (3.3 mmol, 82%) of 6-chloro-3,4-dihydro-4-phenylquinazoline-2-carboxylic acid (**6b**), yellow powder, dec 166-167.5 °C; Bell et al.[4] described this product with mp 168-169 °C, obtained from Oxazepam after heating with a 4 M sodium hydroxide solution). Anal. Calcd for $C_{15}H_{11}ClN_2O_2$: C, 62.84; H, 3.87, N, 9.77. Found: C, 62.43; H, 4.00; N, 9.77. ^{1}H NMR(DMSO-d_6, NaOD): 7.3 (5, phenyl); 7.1 (2) and 6.9 (1); α-H 5.7 ppm. ^{13}C NMR in DMSO-d_6 δ(ppm) : 164.17, 152.95, 146.18, 128.87, 127.77, 127.62, 126.62, 126.46, 56.34.

Decarboxylation

6-Chloro-3,4-dihydro-4-phenylquinazoline and 6-chloro-4-phenylquinazoline. A solution of 1.48 g (50 mmol) of **5b** in 10 mL of DMF was heated in the dark during 1 hour at 130-140 °C. After evaporation of the solvent, 1.20 g of a 2 : 1 mixture of 6-chloro-3,4-dihydro-4-phenylquinazoline and 6-chloro-4-phenylquinazoline with mp 130-145 °C was obtained. Recrystallization from 50% ethanol gave 0.60 g (50%) of 6-chloro-3,4-dihydro-4-phenylquinazoline with mp 171-172.5 °C. (Bell et al.[4] described this product with mp 173-174 °C, obtained from Oxazepam after heating with a 4 M sodium hydroxide solution, followed by decarboxylation). The mother-liquor, after addition of water, gave a 1 : 2 mixture of 6-chloro-3,4-dihydro-4-phenylquinazoline and 6-chloro-4-phenylquinazoline.

6-Chloro-4-phenylquinazoline. Heating of 0.50 g of 6-chloro-4-phenylquinazoline-2-carboxylic acid (**7b**) during 10 min above the decomposition point (~230 °C) gave 0.35 g (88%) of brown crystals with melting point 132-134 °C. Recrystallization from methanol gave 0.29 g (73%) of 6-chloro-4-phenylquinazoline, mp 137-138.5 °C (ref 10, mp 137-139 °C). ^{13}C NMR ($CDCl_3$) δ(ppm): 167.69, 154.84, 149.62, 136.55, 134.69, 133.51, 130.70, 130.37, 129.83, 128.85, 125.81, 123.70.

Decarboxylation and isomerization

6-Chloro-1,4-dihydro-1-methyl-4-phenylquinazoline (8), 6-chloro-1,4-dihydro-1-methyl-4-hydroxy-4-phenylquinazoline (9), and 6-chloro-1-methyl-4-phenyl-2(1H)-quinazoline (10). Heating of 0.50 g (1.45 mmol) of **5f**, above the decomposition point during 15 min, gave 0.44 g of a yellow-green product which, according to ^{1}H NMR analysis, was a mixture of 3 compounds. Separation of 0.40 g of the mixture was accomplished by chromatography over silica-gel, elution with 50 mL of chloroform-methanol (98:2) followed by 50 mL of chloroform-methanol (95:5). The first fractions gave after evaporation of the solvent 0.22 g of 6-chloro-1-methyl-4-phenyl-2(1*H*)-quinazolinone (**10**). Recrystallization from methanol gave pure **10** with mp 226-227.5 °C (Felix et al.[18] mp 224-226 °C). ^{13}C NMR (DMSO-d_6) δ(ppm): 172.57, 154.13, 142.56, 135.71, 134.93, 130.38, 128.91, 128.39, 127.39, 125.98, 117.11, 115.86, 30.81. MS: *m/z* 270(65), 269(100), 254(9), 241(3), 228(33). IR(KBr): 1660, 1600(III), 1540(II), 1485(I), 1370, 1300, 1285 cm^{-1}. With chloroform-methanol (95:5) as the eluent, the middle fraction gave 40 mg of oil which, after trituration with 2 mL of diethyl ether, gave 20 mg of 6-chloro-1,4-dihydro-1-methyl-4-hydroxy-4-phenylquinazoline (**9**), mp 158-160 °C; Yamada et al.[19], mp 176-178 °C dec. ^{13}C NMR (DMSO-d_6) δ(ppm): 148.63, 144.47, 134.13, 127.60, 127.53, 127.31, 127.07, 126.60, 126.15, 125.24, 113.26(*C7*), 81.53(*C8*), 34.91(*C9*). The assignments were in harmony

with the attach proton test (APT) and with the numbering of Figure 1.
MS: *m/z* 272(3), 271(10), 255(100), 239(56), 205(43), 179(53). IR(KBr): 3070, 1635(**III**), 1575(**II**, small), 1485(**I**), 1360, 1190, 1115 cm^{-1}. The last fractions gave after evaporation of the solvent 80 mg 6-chloro-1,4-dihydro-1-methyl-4-phenylquinazoline (**8**), light-brown crystals with mp 115-117 °C.
^{13}C NMR ($CDCl_3$) δ(ppm): 147.36, 144.43, 135.78, 128.67, 128.57, 127.51, 124.51, 112.18, 60.87, 35.36. MS:*m/z* 256(18), 241(15), 205(5), 179(100). IR(KBr):1645(**III**), 1490(**I**), 1350, 1250, 1120 cm^{-1}.
^{1}H NMR spectroscopy showed, that the same mixture of compounds was obtained after refluxing of a solution of **5f** in methanol during 4 days or after keeping of a solution of adduct **5f** in methanol at ambient temperature during a long period.

Decarboxylation in nitrogen atmosphere: Heating of 0.32 g (1 mmol) of **5f** at 130 °C in nitrogen atmosphere under collecting of the carbon dioxide formed in a barium hydroxide solution, resulted in 160 mg (0.9 mmol) $BaCO_3$ after isolation of the precipitate. The residue gave after recrystallization from 70% methanol 170 mg (0.65 mmol) of **8**, mp 118-120 °C. ^{1}H and ^{13}C NMR spectra were identical with 6-chloro-1,4-dihydro-1-methyl-4-phenylquinazoline (**8**), obtained after decarboxylation of **5f** followed by separation of the mixture by chromatography.

Esterification

Methyl 6-chloro-1,2-dihydro-4-phenylquinazoline-2-carboxylate. A solution of 1.48 g (50 mmol) of **5b** in 50 mL of methanol was saturated with dry hydrogen chloride gas and then refluxed in the dark during 2 h. Evaporation of the solvent, followed by extraction of the residue with diethyl ether, gave 1.64 g (46 mmol, 92%) of hydrochloride salt of methyl 6-chloro-1,2-dihydro-4-phenylquinazoline-2-carboxylate with decomposition point: 181-182.5 °C. Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_2.0.5H_2O$: C, 55.51; H, 4.37; N, 8.09. Found: C, 55.61; H, 4.35; N, 8.25. ^{13}C NMR (CD_3OD) δ(ppm): 171.20, 169.36, 149.06, 141.64, 135.86, 132.27, 131.84, 130.70, 130.37, 126.06, 119.30, 114.28, 63.07, 54.36. IR(KBr): 3200-2400, 1755, 1620 (**III**), 1550 (**II**), 1470 (**I**), 1340, 1240, 1170, 1020 cm^{-1}. The free amine was obtained after addition of 6 mL of a 10% aqueous sodium hydrogen carbonate solution to a suspension of 0.25 g of the HCl salt in 10 mL of diethyl ether, followed by evaporation of the solvent. The residue (0.19 g, mp 185-187 °C, see note 6) was a light-yellow product, which after dissolving in methanol rapidly aromatized, resulting in a precipitate. Filtration gave 0.13 g (72%) of the methyl ester of 6-chloro-4-phenylquinazoline-2-carboxylic acid with mp 194-195 °C (see note 6). No depression of the melting point was obtained after mixing of the obtained product with methyl 6-chloro-4-phenylquinazoline-2-carboxylate.

Methyl 6-chloro-4-phenylquinazoline-2-carboxylate. A solution of 0.75 g (2.5 mmol) of 6-chloro-4-phenylquinazoline-2-carboxylic acid (**7b**) in 20 mL of methanol was saturated with dry hydrogen chloride gas, followed by refluxing for 3 hours. The precipitate was 0.61 g (82%) of methyl 6-chloro-4-phenylquinazoline-2-carboxylate, mp 194-195.5 °C (see note 6).

Reaction of 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (Oxazepam)

Degradation and esterification: 1.00 g (3.5 mmol) of 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (Oxazepam) was added to an ice-cold solution of 1.6 g of hydrogen chloride in 35 mL of methanol. The temperature of the emulsion was brought to 40 °C and after 4 h of stirring a clear orange-red solution was obtained. Evaporation of the solvent, followed by extraction of the residue with diethyl ether, gave 1.10 g (94%) of the hydrochloride salt of methyl 6-chloro-1,2-dihydro-4-phenylquinazoline-2-carboxylate; dec 177-179 °C (see note 8). ^{13}C NMR (CD_3OD) δ(ppm): 171.15, 169.35, 149.04, 141.60, 135.86, 132.26, 131.81, 130.70, 130.44, 126.04, 119.31, 114.28, 63.08, 54.36. The IR and ^{13}C NMR spectra are identical with the ester obtained after esterification of **5b** with MeOH.

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