A New Synthesis of 2-Amino Derivatives of 6-Chloro-4-phenylquinazoline 3-Oxide (1)

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The first preparation of 6-chloro-2-methylamino-4-phenylquinazoline 3-oxide was described by Sternbach (3), but no general route has been reported thus far for the preparation of related 2-amino derivatives. As these derivatives have been our objective, we wish to report here their synthesis by a new and convenient route.

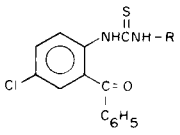
When 2-amino-5-chlorobenzophenone (4) was reacted with phenylisothiocyanate at room temperature, a single compound (5) whose structure corresponded to 5-chloro-2-aminothiocarboxamidobenzophenone (I) was obtained in high yields. The latter, on treatment with hydroxylamine hydrochloride in the presence of a slight excess of the equimolar amount of triethylamine in boiling ethanol, failed to give the classical oxime derivative. Contrary to expectations, the oximation of I proceeded *in situ* with intermolecular cyclization to give 6-chloro-2-phenylamino-4-phenylquinazoline 3-oxide (II) in 87% yield.

The infrared spectrum of the crystalline compound II was consistent with such a structure since this compound showed a strong band in the 1318-1290 cm^{-1} region corresponding to the N-O stretching frequency (6). The molecular weight as determined by mass spectrum was in good agreement with the value calculated for II (7).

Compound II was found to be stable in 50% sulfuric acid or 10% sodium hydroxide and heating under reflux for one half hour. The stability of II in acidic or alkaline medium is in line with its assigned structure. As expected (6), its catalytic hydrogenation over 10% palladium on charcoal, produced the corresponding quinazoline derivative.

Table I

N-Thiocarboxamido Derivatives of 2-Amino-5-chlorobenzophenone

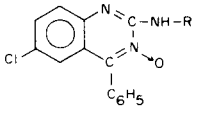


Ia, R = C_6H_5-
Ib, R = $C_6H_5CH_2$-
Ic, R = C_2H_5-
Id, R = $CH_2{=}CHCH_2$-

Compound	Yield	Mol. Formula	M.p., °C	Analysis Caled. C	H	N	Found C	H	N
Ia	90%	$C_{20}H_{15}N_2ClSO$	197	65.47	4.12	7.64	65.47	4.13	7.48
Ib	92%	$C_{21}H_{17}N_2ClSO$	220	66.24	4.50	7.35	66.53	4.20	7.10
Ic	81%	$C_{16}H_{15}N_2ClSO$	215	60.28	4.74	8.78	60.56	4.49	8.63
Id	91%	$C_{17}H_{15}N_2ClSO$	158	61.72	4.57	8.46	61.49	4.50	8.50

Table II

2-Amino Derivatives of 6-Chloro-4-phenylquinazoline 3-Oxide



IIa, R C_6H_5-
IIb, R $C_6H_5CH_2$-
IIc, R C_2H_5-
IId, R $CH_2{=}CHCH_2$-

Compound	Yield	Mol. Formula	M.p., °C	Analysis Calcd. C	H	N	Found C	H	N
IIa	87%	$C_{20}H_{14}N_3ClO$	190	69.06	4.05	12.08	68.74	4.19	12.23
IIb	91%	$C_{21}H_{16}N_3ClO$	156	69.80	4.43	11.63	70.15	4.74	11.90
IIc	77%	$C_{16}H_{14}N_3ClO$	197	64.10	4.67	14.02	63.80	4.58	14.20
IId	52%	$C_{17}H_{14}N_3ClO$	199	65.48	4.49	13.48	65.38	4.49	13.42

(a) Ir: 3290 cm^{-1} (NH), 1300 (N→O), 1600 (C=N); nmr (deuteriochloroform): τ -0.1 (N-H), 2.2 (aromatic H). (b) Ir: 3290 cm^{-1} (NH), 1300 (N→O), 1595 (C=N); nmr (deuteriochloroform): τ -0.1 (N-H), 2.2 (aromatic H). (c) Ir: 3295 cm^{-1} (NH), 1295 (N→O), 1590 (C=N). (d) Ir: 3320 cm^{-1} (NH), 1310 (N→O), 1590 (C=N).

This type of cyclization allows the preparation of 2-amino derivatives of 6-chloro-4-phenylquinazoline 3-oxide from readily available analogs of I (Tables I and II).

EXPERIMENTAL

Melting points were determined on a Gallenkamp capillary apparatus and have not been corrected. Infrared spectra were recorded on a Perkin-Elmer Granting Infrared Spectrophotometer and nmr spectra on a Varian A-60 nmr spectrometer. Microanalyses are by the National Research Foundation.

General Preparation of *N*-Thiocarboxamido Derivatives of 2-Amino-5-chlorobenzophenone (Ia, Ib, Ic, Id).

Solutions of 0.01 mole quantity of 2-amino-5-chlorobenzophenone and 0.01 mole of the appropriate isothiocyanate in 20 ml. of absolute ether were heated under reflux for 10 minutes. The reaction mixtures were allowed to stand at room temperature for 24 hours and the precipitated products were collected by filtration. The yields, melting points, and microanalytical data of the resulting products, after one recrystallization from aqueous ethanol or acetone, are given in Table I.

General Preparation of 2-Amino Derivatives of 6-Chloro-4-phenylquinazoline 3-Oxides (IIa, IIb, IIc, IId).

To stirred suspensions of 0.01 mole of *N*-thiocarboxamido derivatives in 60 ml. of absolute ethanol were added 0.01 mole of hydroxylamine hydrochloride and 1.5 ml. of triethylamine. These mixtures were refluxed for 24 hours in a water-bath and during that time the evolution of hydrogen sulfide ceased. After concentration of the organic layer *in vacuo* the desired products were recrystallized from ethanol (see Table II).

6-Chloro-2-phenylamino-4-phenylquinazoline.

A solution of 0.5 g. of 6-chloro-2-phenylamino-4-phenylquinazoline 3-oxide (IIa) was reduced with hydrogen in the presence of 0.5 g. of 10% palladium on charcoal. After one half hour the catalyst was filtered and the solvent was evaporated to dryness. The residue was precipitated twice from ether-petroleum ether giving a white powder, m.p. 148-150°, in 60% yield. Strong infrared absorption bands in the 1543-1540 and in the 1480-1471 cm^{-1} region were observed.

Anal. Calcd. for $C_{20}H_{14}N_3Cl$: C, 72.40; H, 4.22; N, 12.67. Found: C, 72.10; H, 4.00; N, 12.81.

REFERENCES

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(2) This work is based on part of the thesis presented by A. S. to the School of Natural Sciences, University of Patras, in partial fulfillment of the requirements for the Ph.D. degree.

(3) W. Metlesics, G. Silverman and L. H. Sternbach, *Monatsch. Chem.*, **98**, 633 (1967).

(4) L. Sternbach, E. Reeder, O. Keller and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961).

(5) When phenylisocyanate was used, two products appeared on a thin layer chromatography silica gel plate.

(6) L. H. Sternbach, S. Kaiser and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

(7) Molecular weight (MS) Calcd. 347,5. Found 347. We thank the Laboratory of Organic Chemistry, University of Thessaloniki, for this determination.