Monatshefte für Chemie 124, 733–738 (1993)

Monatshefte für Chemie
Chemical Monthly

Amidinoyl Isothiocyanates in the Synthesis of Condensed Heterocycles: Preparation of Quinazolino[3,4-c][1,3,5]-benzotriazepines and Quinazolino[3,4-c][1,2,3,5]-benzotetraazepines

Š. Stankovský[1], **T. Dérer**[2], and **K. Špirková**[1]

[1] Department of Organic Chemistry, Faculty of Chemical Technology, Slovak Technical University, Bratislava, Slovakia
[2] Research Institute of Chemical Technology, Bratislava, Slovakia

Summary. When heated, amidinoyl isothiocyanates (**I**) with 2-nitrophenyl isothiocyanate cyclize to 4-(2′-nitroanilino)quinazolines (**II**) and after reduction to 2′-amino derivatives (**III**). The latter serve as precursors to derivatives of the title compounds.

Keywords. Amidinoyl isothiocyanate, 2-morpholino, 2-piperidino; 6-Bromo-quinazolino[3,4-c]-[1,3,5]-benzotriazepine; Quinazolino[3,4-c][1,2,3,5]-benzotetraazepine.

Amidinoylisothiocyanate als Bausteine in der Synthese von kondensierten Heterozyklen. Darstellung von Chinazolino[3,4-c][1,3,5]-benzotriazepinen und Chinazolino[3,4-c][1,2,3,5]-benzotetraazepinen

Zusammenfassung. Beim Erhitzen cyclisieren Amidinoyl-isothiocyanate (**I**) mit 2-Nitrophenylisothiocyanaten zu 4-(2′-Nitroanilino)chinazolinen (**II**) und nach Reduktion zu 2′-Aminoderivaten (**III**). Die letztgenannten dienen als Ausgangssubstanzen für Derivate der Titelverbindungen.

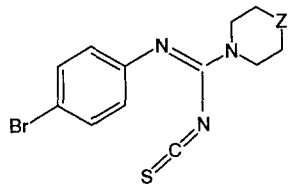
Introduction

Quinazolines, heaving a "c" fused heterocyclic ring, are usually prepared starting from 4-chloroquinazolines and a proper bifunctional reagent.

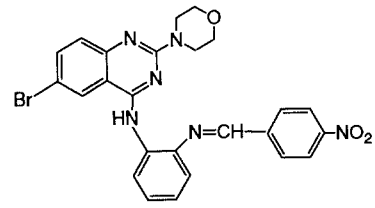
In order to circumvent laborious and lengthy preparations of the derivatives of anthranilic acid leading to 4-chloroquinazolines, easily accessible amidinoyl isothiocyanates (**I**) can be used as convenient starting materials [1, 2].

Results and Discussion

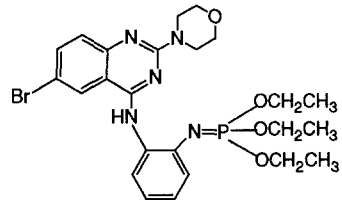
For the preparation of the title compound we used two isothiocyanates, namely N,N-pentamethylene-N′-4-bromophenyl amidinoyl isothiocyanate (**Ia**) and N,N-3-oxapentamethylene-N′-4-bromophenyl amidinoyl isothiocyanate (**Ib**), which were prepared according to a procedure described in Refs. [3, 4].



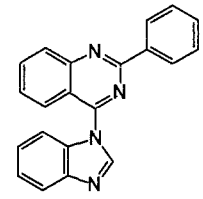
I a Z = CH_2
I b Z = O



IV a, b



IX



VI

Heating of this isothiocyanates (**Ia, b**) with 2-nitrophenyl isothiocyanate in dimethylformamide furnished 2-piperidino-6-bromo-4-(2′-nitroanilino)quinazoline (**IIa**) and 2-morpholino-6-bromo-4-(2′-nitroanilino)quinazoline (**IIb**), respectively.

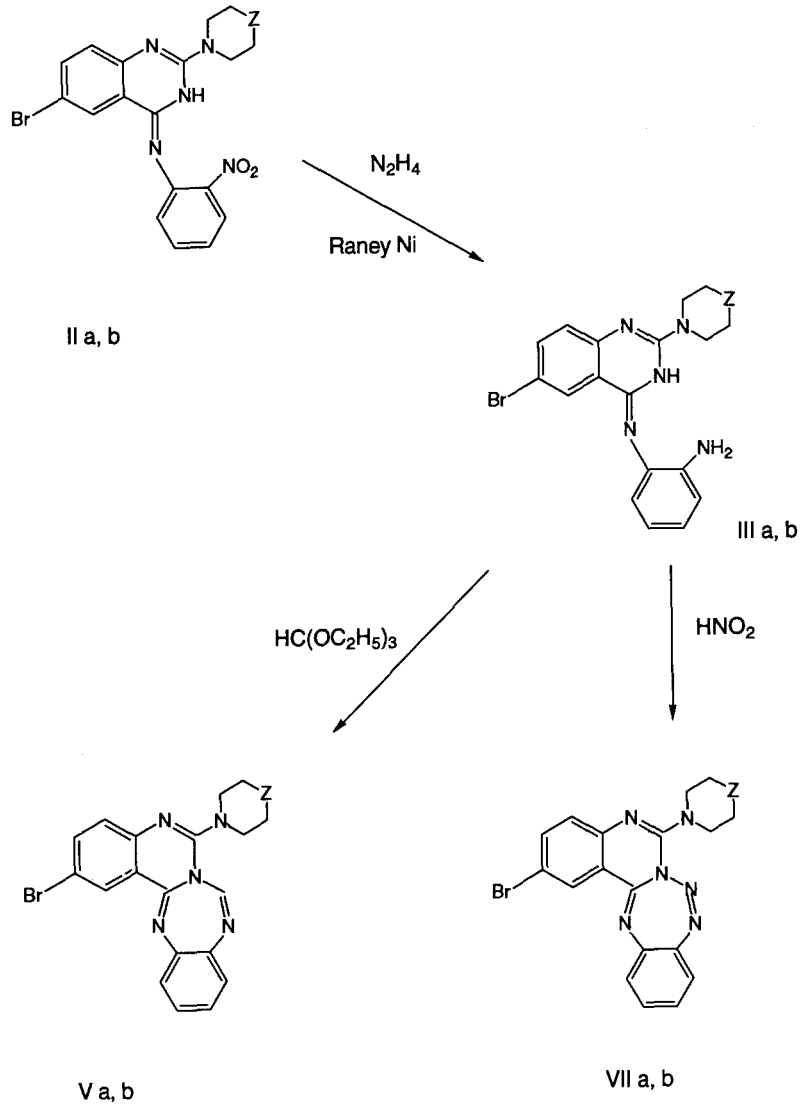
Corresponding 2′-aminoderivatives (**IIIa, b**) were prepared by selective reduction of the nitro group of (**IIa, b**) with conservation of bromine with hydrazine at catalytic amounts of Raney Ni using a procedure described in Ref. [5]. The yields of these amines were almost quantitative and they were characterized as corresponding azomethines with 4-nitrobenzaldehyde (**IVa, b**).

Heating of 2′-aminoderivatives (**IIIa, b**) with ethyl orthoformate in presence of catalytic amounts of 4-toluenesulphonic acid furnished 8-piperidino and 8-morpholino resp. 12-bromoquinazolino[3,4-c][1,3,5]-benzotriazepines (**Va, b**).

Since by reaction of amines (**IIIa, b**) also isomeric 4-(1-benzimidazolyl)quinazolines can be formed, **VI** was prepared as a model compound for this structure by an unambiguous synthesis. Comparison of the spectral properties of this two different structures allow to distinguish the compounds obtained.

Diazotation of aminoderivatives (**IIIa, b**) leads in quantitative yields to the corresponding quinazolino[3,4-c][1,2,3,5]-benzotetraazepines (**VIIa, b**). These yellow compounds, exhibiting fluorescence in solution, present an extensive conjugated planar system which also proves the structure of this four membered ring system.

In an effort to prepare quinazolino[3,4-c][1,2,4]benzotriazine, reactive nitrene from nitroderivate (**IIb**) was generated. However, heating of the 2′-nitroderivate in triethylphosphite gave only an addition product (**IX**).

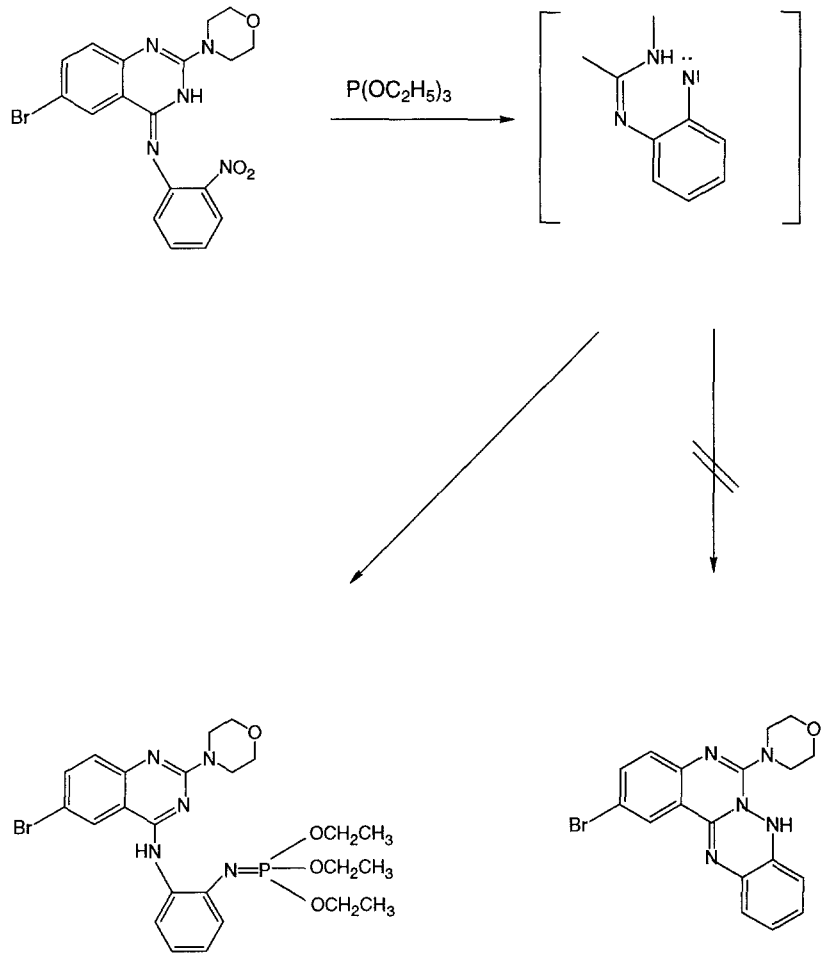


Experimental Part

Infrared spectra (KBr discs) were taken with a double beam Zeiss Jena spectrophotometer, model M-80, ultraviolet spectra with an UV-VIS spectrophotometer M-40 as 10^{-4} *M* solution in dioxane. Proton ^{1}H NMR and carbon ^{13}C NMR spectra (in $CDCl_3$) were taken with a 300 MHz Varian VXR 3000 instrument, mass spectra with a MS 902 S spectrometer (AEI Manchester).

2-Piperidino-6-bromo-4-(2'-nitroanilino)quinazoline (**IIa**)

A solution of 32.4 g (0.1 mol) of (**Ia**) and 18 g (0.1 mol) of 2-nitrophenyl isothiocyanate in 100 ml of absolute dimethylformamide was refluxed 2 h and then concentrated. The product crystallized from a chloroform–ether mixture; yield 15.8 g, 37%, m.p. 205–208 °C. For $C_{19}H_{18}N_5BrO_2$ ($M = 428.29$): 53.28% C, 4.23% H, 16.35% N; found: 53.40% C, 4.20% H, 16.20% N. IR(cm^{-1}): 2940($\nu_{CH_{aliph}}$), 1625($\nu_{C=N}$), 1580($\nu_{C=C}$), 1380(ν_{sNO_2}), 1520(ν_{asNO_2}). Compound (**IIb**) was described in Ref. [1].



2-Piperidino-, and 2-Morpholino- resp. 6-Bromo-4-(2'-aminoanilino)quinazolines (**IIIa, b**)

To a stirred solution of 2.1 g (5 mmol) of the corresponding nitroderivatives (**IIa, b**) and 3 ml of 80% hydrazine hydrate in 300 ml of tetrahydrofurane (**THF**) was added a suspension of 0.1 g freshly prepared Raney Ni in **THF**. The mixture was then refluxed 6–10 h. During this period another 0.1 g Raney Ni was added to the boiling mixture in three portions. After cooling, the catalyst was filtered off and the solution was concentrated. The corresponding aminoderivatives (**IIIa, b**) were obtained after crystallization from **THF**.

2-Piperidino-6-bromo-4-(2'-aminoanilino)quinazoline (**IIIa**)

Yield 98%, m.p. 198–200 °C. For $C_{19}H_{20}N_5Br$ ($M = 398.3$): 57.34% C, 5.06% H, 17.60% N; found: 57.5% C, 4.91% H, 17.90% N. IR (cm^{-1}): 3450(ν_{NH}), 2940, 2855($\nu_{CH_{aliph}}$), 1615($\nu_{C=N}$).

2-Morpholino-6-bromo-4-(2'-aminoanilino)quinazoline (**IIIb**)

Yield 97%, m.p. 205–208 °C. For $C_{18}H_{18}N_5BrO$ ($M = 400.28$): 54.05% C, 4.53% H, 17.50% N; found: 54.37% C, 4.21% H, 17.81% N. IR(cm^{-1}): 3460(ν_{NH}), 2830($\nu_{CH_{aliph}}$), 1612($\nu_{C=N}$).

4-Nitrobenzal-anilines (**IVa, b**) *of Corresponding Anilinoquinazolines*

To the suspension of 1 g (2.5 mmol) of corresponding amine (**IIIa, b**) in 50 ml **THF** was added 0.4 g (2.5 mmol) of 4-nitrobenzaldehyde disolved in 5 ml of **THF**. The reaction mixture was refluxed for 4 h and then cooled. The products were separated as an orange solid.

(**IVa**): yield 96%, m.p. 297–299 °C. For $C_{26}H_{24}N_6BrO_2$ ($M = 532.39$): 58.66% C, 4.54% H, 15.78% N; found: 58.47% C, 4.67% H, 15.98% N.

(**IVb**): yield 98%, m.p. 305–308 °C. For $C_{25}H_{22}N_6BrO_3$ ($M = 534.37$): 56.19% C, 4.15% H, 15.72% N; found: 56.30% C, 4.42% H, 16.10% N.

Substituted Quinazolino[3,4-c][1,3,5]-benzotriazepines (**Va, b**)

To the suspension of 1 g (2.5 mmol) of (**IIIa**) or (**IIIb**) in 20 ml of ethylorthoformate a catalytic amount of 4-toluenesulphonic acid (5–10 μg) was added and the mixture was refluxed for 10 h, then the unreacted components was filtered off and the solution was concentrated in vacuum. The solid residue was dissolved in chloroform, extracted with a 10% solution of sodium carbonate, and after drying and concentration to a small volume the material was separated on a silica gel column eluting with a chloroform–ether mixture (volume ratio = 9:1). The products were crystallized from that mixture.

8-Piperidino-12-bromoquinazolino[3,4-c][1,3,5]-benzotriazepine (**Va**)

Yield 86%, m.p. 180–182 °C. For $C_{20}H_{18}N_5Br$ ($M = 408, 31$): 58.87% C, 4.44% H, 17.16% N; found: 58.32% C, 4.16% H, 16.89% N. Mass: $M^+ = 408$. IR (cm^{-1}): 2940, 2860($\nu_{CH_{aliph}}$), 1615($\nu_{C=N}$), 1575, 1540($\nu_{C=C}$). ^{1}H NMR (δ, ppm): 1.68 (m, 6H, β- and γ-CH_2 of piperidine), 3.93 (t, 4H, α-CH_2 of piperidine), 7.39–7.91 (m, 7H, H_{arom}), 8.43 (s, 1H, H–C_6). ^{13}C NMR (δ, ppm): 24.8 (γ-CH_2), 25.9(β-CH_2), 45.2(α-CH_2), 112.7, 113.5, 115.2, 120.8, 123.8, 124.6, 126.7, 128.2, 133.3, 137.9, 142.7, 144.1, 154.7, 155.1, 158.3.

8-Morpholino-12-bromoquinazolino[3,4-c][1,3,5]-benzotriazepine (**Vb**)

Yield 84%, m.p. 162–164 °C. For $C_{19}H_{16}N_5BrO$ ($M = 410.28$): 55.66% C, 3.93% H, 17.08% N; found: 55.30% C, 4.12% H, 17.30% N. Mass: $M^+ = 410$. IR(cm^{-1}): 2960, 2860($\nu_{CH_{aliph}}$), 1615($\nu_{C=N}$), 1570, 1540($\nu_{C=C}$). UV(λ_{max}, (ε)): 250(5.23.10^3), 285(1.64.10^3), 395(0.18.10^3). ^{1}H NMR (δ, ppm): 3.82(t, 4H, β-CH_2 of morpholine), 3.97(t, 4H, α-CH_2 of morpholine), 7.40–7.92(m, 7H, H_{arom}), 8.44(s, 1H, H–C_6). ^{13}C NMR (δ, ppm): 44.6(β-CH_2), 66.8(α-CH_2), 112.6, 114.0, 116.1, 120.9, 124.0, 124.7, 126.8, 128.3, 133.2, 138.2, 142.6, 144.1, 154.4, 155.3, 158.3.

2-Phenyl-4-(1-benzimidazolyl)quinazoline (**VI**)

To the hot solution of 3 g (12.3 mmol) of 2-phenyl-4-chloroquinazoline in 50 ml of absolute acetonitrile was added 1.7 g (12.3 mmol) of sodium salt of benzimidazole (prepared from 0.33 g (12.3 mmol) Na and 1.5 g (12.3 mmol) of benzimidazole) and then 50 ml of absolute toluene. Reflux was continued during 7 h, then the solid was filtered off. The product crystallized after concentration. Yield 2.7 g, 70%, m.p. 182–185 °C. For $C_{21}H_{14}N_4$ ($M = 322.35$): 78.25% C, 4.37% H, 17.38% N; found: 78.59% C, 4.13% H, 17.58% N. UV(λ_{max}(ε)): 267(1075), 289(460), 351(135). ^{1}H NMR (δ, ppm): 8.5 (s, 1H, H–C2 of imidazole ring), 7.3–8.1 (m, 13H_{arom}).

Substituted Quinazolino[3,4-c][1,2,3,5]-benzotetraazepines (**VIIa, b**)

To a cooled suspension (0 °C) of 1 g (2.5 mmol) of corresponding aminoderivatives (**IIIa**) or (**IIIb**) in 20 ml of concentrated hydrochloric acid was dropped a solution of 0.3 g natrium nitrite in 3 ml of water.

After 1 h of stirring, the mixture was heated to room temperature and then neutralized with aqueous ammonia solution. The precipitated yellow products were extracted with chloroform, after drying diethylether was added and the products crystallized as a yellow, in solution green fluorescing, solid.

8-Piperidino-12-bromoquinazolino[3,4-c][1,2,3,5]-benzotetraazepine (**VIIa**)

Yield 1 g, 95%, m.p. 135–137 °C. For $C_{19}H_{17}N_6Br$ ($M = 409.3$): 56.7% C, 4.18% H, 20.53% N; found: 56.37% C, 4.20% H, 20.43% N. IR(cm^{-1}): 2930, 2860($\nu_{CH_{aliph}}$), 1615($\nu_{C=N}$), 1570, 1540($\nu_{C=C_{arom}}$). ^{1}H NMR (δ, ppm): 1.72(m, 6H of β and γ-CH_2 of piperidine), 3.95(t, 4H of α-CH_2 of piperidine), 7.5–8.24(m, $6H_{arom}$), 8.86(d, $1H_{arom}$, H–C13). ^{13}C NMR (δ, ppm): 24.8(β-CH_2), 25.9(γ-CH_2), 45.4(α-CH_2), 112.7, 113.9, 115.9, 120.2, 125.5, 127.7, 129.2, 129.4, 132.5, 137.8, 145.9, 154.9, 157.6.

8-Morpholino-12-bromoquinazolino[3,4-c][1,2,3,5]-benzotetraazepine (**VIIb**)

Yield 0.9 g, 95%, m.p. 196–199 °C. For $C_{18}H_{15}N_6BrO$ ($M = 411.27$): 53.57% C, 3.67% H, 20.43% N; found: 53.26% C, 3.60% H, 20.30% N. Mass: $M^+ = 411$. IR (cm^{-1}): 2960, 2860($\nu_{CH_{aliph}}$), 1615($\nu_{C=N}$), 1575, 1545($\nu_{C=C}$). UV(λ_{max}, (ε)): 255(4.6.10^3), 280(1.38.10^3), 405(0.23.10^3). ^{1}H NMR (δ, ppm): 3.88(t, 4H, β-CH_2 of morpholine), 3.93(t, 4H, α-CH_2 of morpholine), 7.40–8.28(m, $6H_{arom}$), 8.93(d, $1H_{arom}$, H–C13).

Attempt towards 7-Morpholino-11-bromo-5H-quinazolino[3,4-c][1,2,4]-benzotriazine

The mixture of 4.3 g (10 mmol) of nitroderivate (**IIb**) and 7 ml of triethylphosphite was refluxed in argon atmosphere during 6 h, after cooling a not identified pink solid was filtered off and the solution was evaporated to dryness. The crude product (1.1 g) was crystallized from ethanol and it was identified as the corresponding triethyliminophosphate (**IX**). Yield 1.1 g, 19.5%, m.p. 187–189 °C. Mass: $M^+ = 564$. For $C_{24}H_{31}N_5BrO_4P$ ($M = 564.41$): 51.07% C, 5.54% H, 12.41% N, 14.17% Br; found: 51.36% C, 5.13% H, 12.17% N, 14.31% Br. IR (cm^{-1}): 3280(ν_{NH}), 2950, 2900, 2850($\nu_{CH_{aliph}}$), 1616($\nu_{C=N}$), 1996, 1566($\nu_{C=C}$). ^{1}H NMR (δ, ppm): 1.17(q, 6H, CH_3–CH_2–), 3.67(m, 8H of morpholine), 4.02(t, 6H, CH_3–CH_2–), 7.6–7.02(m, $6H_{arom}$), 8.2(s, 1H, H–C5), 8.77(s, 1H, NH).

References

[1] Stankovský Š., Martvoň A. (1980) Collect. Czech. Chem. Commun. **45**: 1079
[2] Stankovský Š., Bukovská V. (1983) Chemical Papers **37**: 831
[3] Abraham W., Barnikow G. (1973) Tetrahedron **29**: 691, 699
[4] Stankovský Š., Martvoň A. (1980) Chemical Papers **34**: 253
[5] Adams R., Gortatowski M. J. (1957) J. Am. Chem. Soc. **79**: 5526

Received June 24, 1992. Accepted September 9, 1992