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SYNTHESES AND CHEMICAL REACTIONS OF NEW AZIDE DERIVATIVES

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Abstract: 4-Azido-2-dialkylamino-6-oxo-6H-1,3-oxazin-5-carbonitriles obtained from the 4-chloro-compounds are used for the syntheses of N-(1,3-oxazin-4-yl)iminophosphoranes. The triphenyliminophosphoranes are then hydrolized to heterocyclic amines.

In relation to previous reports about alkyl dicyanoacetates as inexpensive and easily accessible synthetic starting materials for a lot of different heterocycles[1-11] we reported a short time ago the syntheses of 4-chloro-2-dialkylamino-6-oxo-6H-1,3-oxazin-5-carbonitriles[12-13] **3** which were prepared from the salts of alkyl dicyanoacetates[13-14] **1** and N-(dichloromethylene)dialkyliminium chlorides[15] **2**.

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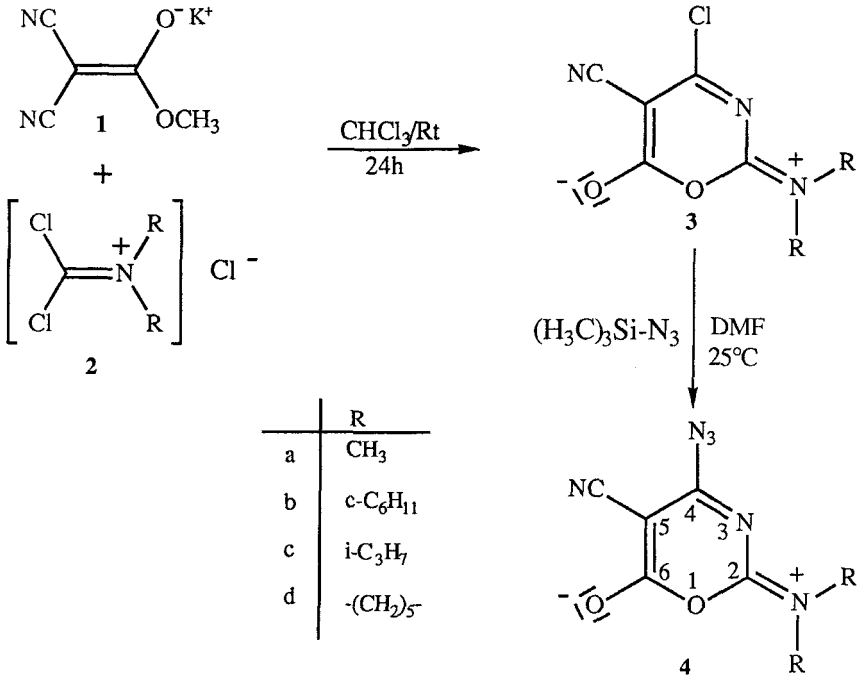
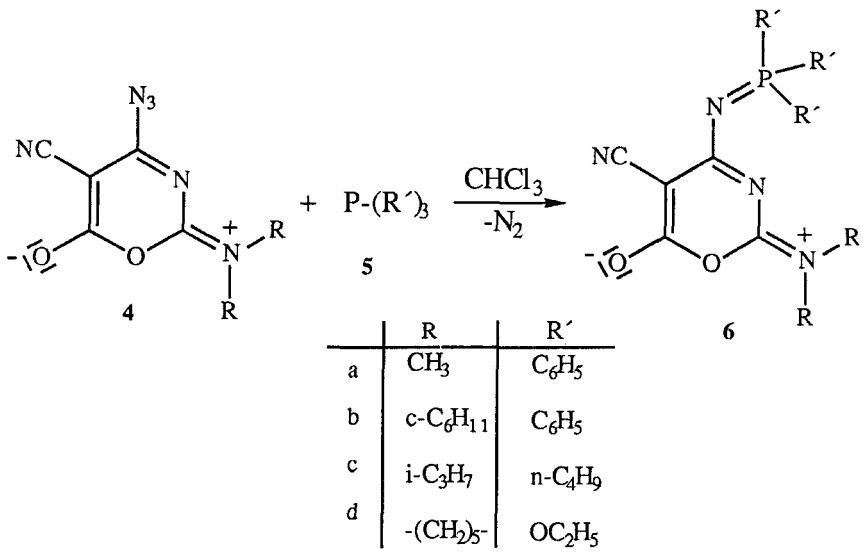


Scheme 1

In continuation of our studies with 4-chloro-2-dialkylamino-6-oxo-6H-1,3-oxazin-5-carbonitriles[16] **3** we have found that trimethylsilylazide reacts at carbon atom 4 which is part of an imidchloride structure. The replacement of the chloro atom leads to 4-azido-2-dialkylamino-6-oxo-6H-1,3-oxazin-5-carbonitriles (**4a-d**) (Scheme 1), which must be stored in the dark and at low temperatures, otherwise they slowly decompose. The reactions of imidchlorides with organic azides also often give tetrazoles or an equilibrium of the two isomers. Our spectroscopic results clearly demonstrate that in case of the new 4-azido-1,3-oxazines (**4a-d**) no isomeric tetrazoles arised.



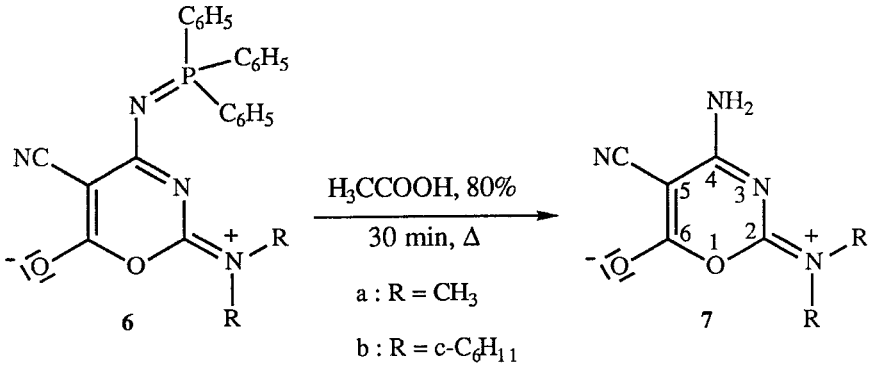
	R	R´
a	CH_3	C_6H_5
b	c-C_6H_{11}	C_6H_5
c	i-C_3H_7	n-C_4H_9
d	-$(CH_2)_5$-	OC_2H_5

Scheme 2

A chemical proof for the existence of the azido form is the reaction with organic phosphorus(III) compounds after the mechanism found by Staudinger[17]. The 4-azido-1,3-oxazines **4** react with the phosphorus atom to form first intermediate phosphazo compounds that extrude nitrogen and result in the oxazin substituted iminophosphoranes **6** (Scheme 2).

While the reaction with triphenylphosphine **5a** or tri-n-butylphosphine **5c** can be carried out at room temperature, triethylphosphite **5d** must be added to the 4-azido-1,3-oxazine at -70 °C due to the greater reactivity.

The conversion of the light sensitive 4-azido-1,3-oxazines to stable iminophosphoranes offers a possibility to obtain 4-amino-1,3-oxazines **7a**, **b** (Scheme 3).



Scheme 3

For that purpose the iminophosphoranes **6a, b** are refluxed with acetic acid (80%) for 30 min[18]. The oxazine ring system is stable towards acids but unstable towards bases.

The o-aminonitriles **7a, b** are expected to offer possibilities for the syntheses of new heterocyclic systems.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer ir-spectrophotometer 283 using potassium bromide and are given as cm^{-1}. ^1H- and ^{13}C-Nmr spectra were recorded on either a Bruker WM-250 (^1H-NMR: 250.13 MHz, ^{13}C-Nmr: 62.89 MHz) or a Varian XL 300 (^1H-NMR: 299.95 MHz, ^{13}C-NMR: 75.43 MHz) spectrometer in $CDCl_3$ or DMSO-d6. The chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane; coupling constants *J* are given in Hz.

Ultraviolet spectra were measured with a Perkin-Elmer 320 uv-spectrophotometer in acetonitrile and are given as λ_{max} (lg ε) in nm. Electron impact mass spectra were obtained on a Varian MAT 311A instrument. Element analyses were performed on a Heraeus Vario EL CHNS apparatus. P-analyses were conducted by the Department of Chemistry of the University of Heidelberg.

General procedure for the preparation of 4-azido-2-dialkylamino-6-oxo-6H-1,3-oxazin-5-carbonitriles **4a-d**: To a solution of 2 mmol 4-chloro-2-dialkylamino-6-oxo-6H-1,3-oxazin-5-carbonitriles **3** in 15 ml dimethylformamide was added 0.5 ml (3.9 mmol) of trimethylsilylazide. After stirring for 48h in the dark double the volume of ice-water was added. The precipitate was isolated by filtration, washed with water and dried.

4-Azido-2-dimethylamino-6-oxo-6H-1,3-oxazin-5-carbonitrile **4a**

From 400 mg **3a**, 320 mg (77.7%) **4a** were obtained. Mp: 161°C. UV/VIS: λ_{max}(lgε)= 238 (4.304), 325 (4.246). IR (KBr): ν = 2220 (C≡N), 2160 (N_3), 1765 (C=O) cm^{-1}. ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 3.25 (s, 3H, CH_3), 3.30 (s, 3H, CH_3). ^{13}C-NMR (62.89 MHz, $CDCl_3$,): δ = 36.9 (-, s, CH_3), 37.9 (-, s, CH_3), 68.2 (+, s, C-5), 112.5 (+, s, CN), 156.6 (+, s, C-6), 158.0 (+, s, C-2), 168.9 (+, s, C-4). $C_7H_6N_6O_2$ (206.16) calcd.: C 40.78 H 2.93 N 40.76; found: C 40.82 H 2.88 N 40.87.

4-Azido-2-dicyclohexylamino-6-oxo-6H-1,3-oxazin-5-carbonitrile **4b**

From 670 mg **3b**, 590 mg (86.1%) **4b** were obtained. Mp: 192 °C. UV/VIS: λ_{max}(lgε)= 238 (4.076), 325 (4.019). IR (KBr): ν = 2220 (C≡N),

2170 (N_3), 1765 (C=O), 1550 (C=N) cm^{-1}. ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.03-1.49 (m, 6H, CH_2), 1.60-2.20 (m, 14H, CH_2), 3.60-4.09 (m, 2H, CH). ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 24.8 (+, s, C-4´), 25.0 (+, s, C-4´), 25.7 (+, s, C-3´), 25.8 (+, s, C-3´), 29.6 (+, s, C-2´), 30.2 (+, s, C-2´), 57.7 (-, s, C-1´), 58.4 (-, s, C-1´), 68.5 (+, s, C-5), 112.6 (+, s, CN), 156.8 (+, s, C-6*), 157.1 (+, s, C-2*), 168.6 (+, s, C-4) * = attachment changeable.

$C_{17}H_{22}N_6O_2$ (342.40) calcd.: C 59.63 H 6.48 N 24.54; found: C 59.71 H 6.49 N 24.63.

4-Azido-2-diisopropylamino-6-oxo-6H-1,3-oxazin-5-carbonitrile **4c**

From 510 mg **3c**, 465 mg (88.7%) **4c** were obtained after recrystallisation from ethyl acetate. Mp: 188 °C. UV/VIS: λ_{max}(lgε)= 237 (4.284), 326 (4.233). IR (KBr): ν = 2220 (C≡N), 2150 (N_3), 1765 (C=O), 1530 (C=N) cm^{-1}. ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.38 (d, J_{HH}=7.0 Hz, 6H, CH_3), 1.41 (d, J_{HH}=6.8 Hz, 6H, CH_3), 4.07 - 4.25 (m, 1H, CH), 4.41- 4.60 (m, 1H, CH). ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 19.8 (-, s, CH_3), 20.4 (-, s, CH_3), 48.3 (-, s, CH), 49.3 (-, s, CH), 68.8 (+, s, C-5), 112.6 (+, s, CN), 156.7 (+, s, C-6), 157.3 (+, s, C-2), 168.8 (+, s, C-4). $C_{11}H_{14}N_6O_2$ (262.27) calcd.: C 50.38 H 5.38 N 32.04; found: C 50.34 H 5.26 N 31.77

4-Azido-6-oxo-2-piperidino-6H-1,3-oxazin-5-carbonitrile **4d**

From 480 mg **3d**, 395 mg (80.2%) **4d** were obtained after recrystallisation from ethyl acetate. Mp: 123 °C. UV/VIS: λ_{max}(lgε)= 236 (4.215), 322 (4.134). IR (KBr): ν = 2210 (C≡N), 2140 (N_3), 1770 (C=O), 1540 (C=N)

cm^{-1}. ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.52 - 1.82 (m, $6H_{piper.}$), 3.60 - 3.90 (m, 4H, NCH_2). ^{13}C-NMR (75.43 MHz, $CDCl_3$,): δ = 23.6 (+, s, C-3′), 25.3 (+, s, C-2′), 25.6 (+, s, C-2′), 45.7 (+, s, C-1′), 46.5 (+, s, C-1′), 68.2 (+, s, C-5), 112.4 (+, s, CN), 156.2 (+, s, C-6*), 156.4 (+, s, C-2*), 168.8 (+, s, C-4) * = attachment changeable. $C_{10}H_{10}N_6O_2$ (246.23) *calcd.*: C 48.78 H 4.09 N 34.13; found: C 49.00 H 4.43 N 33.71.

General procedure for the preparation of N-(1,3-oxazin)-triphenylimino-phosphoranes **6a,b**:

To a suspension of 1 mmol 4-azido-2-dialkylamino-6-oxo-6H-1,3-oxazin-5-carbonitrile **4** (**4a**: 206 mg, **4b**: 342 mg) in 10 ml $CHCl_3$ was added 393 mg (1.5 mmol) of triphenylphosphine in 10 ml $CHCl_3$. After stirring for 3h the solvent is removed under reduced pressure. The residue is recrystallized from ethyl acetate; white crystals.

2-Dimethylamino-6-oxo-4-triphenylphosphoranylidenamino-6H-1,3-oxazin-5-carbonitrile **6a**: yield 408 mg (92.8%), mp: 247 °C. UV/VIS: $\lambda_{max}(lg\varepsilon)$= 227 (4.562), 264 (4.405), 302 (4.270). IR (KBr): ν = 2205 (C≡N), 1735 (C=O), 1490 (C=N), 1435 (P-Aryl) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 7.42 - 7.81 (m, $15H_{arom.}$). ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 36.2 (-, s, CH_3), 36.7 (-, s, CH_3), 67.9 (+, d, $^3J_{PC}$=21.3 Hz, C-5), 118.1 (+, s, CN), 127.7 (+, d, $^1J_{PC}$= 101.2 Hz, C-1′), 128.7 (-, d, $^3J_{PC}$=12.3 Hz, C-3′), 132.5 (-, d, $^4J_{PC}$= 2.8 Hz, C-4′), 132.8 (-, d, $^2J_{PC}$= 10.3 Hz, C-2′), 156.7 (+, s, C-6), 160.3 (+, d, $^4J_{PC}$= 6.2 Hz, C-2), 171.0 (+, d, $^2J_{PC}$=6.1 Hz, C-4). $C_{25}H_{21}N_4O_2P$ (440.44) calcd.: C 68.18 H 4.81 N 12.72 P 7.03; found: C 68.06 H 4.90 N 12.69 P 7.00.

2-Dicyclohexylamino-6-oxo-4-triphenylphosphoranylidenamino-6H-1,3-oxazin-5-carbonitrile **6b**: 522 mg (90.5%), mp: 307 °C. UV/VIS: λ_{max}(lgε) = 228 (4.561), 270 (4.453), 304 (4.259). IR (KBr): ν = 2205 (C≡N), 1735 (C=O), 1490 (C=N), 1435 (P-Aryl) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.66 - 2.35 (m, $20H_{cyclohex.}$), 2.89 - 3.15 (m, 1H, NCH), 3.60- 3.87 (m, 1H, NCH), 7.42 - 8.00 (m, $15H_{ar}$). ^{13}C-NMR (62.89 MHz, $CDCl_3$,): δ = 24.9 (+, s, C-4´), 25.3 (+, s, C-3´), 26.4 (+, s, C-3´), 29.7 (+, s, C-2´), 30.9 (+, s, C-2´), 56.2 (-, s, C-1´), 56.3 (-, s, C-1´), 68.4 (+, d, $^3J_{PC}$=24.6 Hz, C-5), 118.3 (+, s, CN), 127.8 (+, d, $^1J_{PC}$=101.7 Hz, C-1"), 128.6 (-, d, $^3J_{PC}$=12.5 Hz, C-3"), 132.5 (-, d, $^4J_{PC}$=2.3 Hz, C-4"), 132.7 (-, d, $^2J_{PC}$=10.1 Hz, C-2"), 157.0 (+, s, C-6), 159.9 (+, d, $^4J_{PC}$=5.5 Hz, C-2), 171.0 (+, d, $^2J_{PC}$=6.6 Hz, C-4). $C_{35}H_{37}N_4O_2P$ (576.68) calcd.: C 72.90 H 6.47 N 9.72 P 5.37; found C 72.68 H 6.49 N 9.74 P 5.38.

2-Dimethylamino-6-oxo-4-triethoxyphosphoranylidenamino-6H-1,3-oxazin-5-carbonitrile **6c**: To a suspension of 310 mg (1.5 mmol) **4a** in 10 ml $CHCl_3$ is added 0.3 ml (1.8 mmol) of triethylphosphite in 1 ml $CHCl_3$ at -70 °C. After stirring for 2h at room temperature the solvent is removed, 10 ml of n-hexane is added and the residue is recrystallized from n-hexane/ethyl acetate (2:1); white crystals 502.5 mg (97.3%), mp: 133 - 134 °C. UV/VIS: λ_{max}(lgε)= 236 (4.559), 298 (4.296). IR (KBr): ν = 2210 (C≡N), 1755 (C=O), 1505 (C=N), 1020 (P-OAlk.) cm^{-1}. ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.38 (t, $^3J_{HH}$ = 7.1 Hz, 9H, $CH_2C\underline{H}_3$), 3.14 (s, 6H, NCH_3), 4.19 - 4.29 (m, 6H, OCH_2). ^{13}C-NMR (75.43 MHz, $CDCl_3$): δ = 16.0 (-, d, $^3J_{PC}$ = 6.8 Hz, $CH_2\underline{C}H_3$), 36.3 (-, s, NCH_3), 37.2 (-, s, NCH_3), 65.4 (+, d, $^2J_{PC}$ = 7.0 Hz, OCH_2), 68.3 (+, d, $^3J_{PC}$=26.1 Hz, C-5), 117.1

(+, s, CN), 157.4 (+, s, C-6), 159.7 (+, d, $^4J_{PC}$=6.1 Hz, C-2), 170.2 (+, s, C-4). $C_{13}H_{21}N_4O_5P$ (344.31) calcd.: C 45.35 H 6.15 N 16.27 P 9.00; found: C 45.19 H 6.01 N 16.20 P 9.15.

2-Dimethylamino-6-oxo-4-tributylphosphoranylidenamino-6H-1,3-oxazin-5-carbonitrile **6d**: To a suspension of 412 mg (2 mmol) **4a** in 10 ml $CHCl_3$ is added 0.8 ml (3 mmol) of tri-n-butylphosphine in 4 ml $CHCl_3$. After stirring for 12h the solvent is removed, the residue is recrystallized from ethyl acetate/$CHCl_3$ (3:1). White crystals, 672 mg (88.4%), mp: 160 °C. UV/VIS: $\lambda_{max}(lg\varepsilon)$= 240 (4.474), 257 (4.345), 291 (4.267). IR (KBr): ν = 2200 (C≡N), 1740 (C=O), 1490 (C=N), 1030 (P-OAlk.) cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, $^3J_{HH}$=7.1 Hz, 9H, $CH_2C\underline{H}_3$), 1.39-1.57 (m, 12H, $CC\underline{H}_2C\underline{H}_2$), 1.98-2.07 (m, 6H, PCH_2), 3.08 (s, 3H, NCH_3), 3.13 (s, 3H, NCH_3). ^{13}C-NMR (75.43 MHz, $CDCl_3$): δ = 13.5 (-, s, $CH_2\underline{C}H_3$), 23.8 (+, d, $^2J_{PC}$=3.8 Hz, $PCH_2\underline{C}H_2$), 24.0 (+, d, $^3J_{PC}$=14.5 Hz, $PCH_2CH_2\underline{C}H_2$), 24.6 (+, d, $^1J_{PC}$=60.8 Hz, PCH_2), 36.5 (-, s, NCH_3), 37.3 (-, s, NCH_3), 66.6 (+, d, $^3J_{PC}$=23.3 Hz, C-5), 118.1 (+, s, CN), 156.7 (+, s, C-6), 160.1 (+, d, $^4J_{PC}$=4.9 Hz, C-2), 170.8 (+, d, $^2J_{PC}$=7.9 Hz, C-4). $C_{19}H_{33}N_4O_2P$ (380.70) calcd.: C 59.98 H 8.74 N 14.73 P 8.14; found: C 59.75 H 8.54 N 14.74 P 7.97.

General procedure for the preparation of 4-amino-2-dialkylamino-6-oxo-6H-1,3-oxazin-5-carbonitriles **7a, b**: 0.5 mmol of N-(1,3-oxazin)-triphenyliminophosphorane **6a, b** (**5a**: 190 mg, **5b**: 288 mg) were refluxed in 5 ml acetic acid (80%) for 30 min. To the cooled solution was added 10 ml of water and 5 ml of ethyl acetate whereupon the product precipitated in analytical quality.

4-Amino-2-dimethylamino-6-oxo-6H-1,3-oxazin-5-carbonitrile **7a**:
54 mg (59.6%) 226 °C (subl.). UV/VIS: $\lambda_{max}(lg\varepsilon)$= 226 (4.524), 284 (4.223). IR (KBr): ν = 3370 (N-H), 3320 (N-H), 3210 (N-H), 2200 (C=N), 1720 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, DMSO[D6]): δ = 3.03 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 7.72 (s, 1H, NH), 8.06 (s, 1H, NH). ^{13}C-NMR (75.43 MHz, DMSO[D6]): δ = 35.8 (-, s, CH_3), 36.9 (-, s, CH_3), 57.2 (+, s, C-5), 115.9 (+, s, CN), 157.3 (+, s, C-6), 158.3 (+, s, C-2), 165.3 (+, s, C-4). $C_7H_8N_4O_2$ (180.16) calcd.: C 46.67 H 4.48 N 31.10; found: C 46.64 H 4.50 N 30.74.

4-Amino-2-dicyclohexylamino-6-oxo-6H-1,3-oxazin-5-carbonitrile **7b**:
89 mg (56.3%), mp: 233 °C. UV/VIS: $\lambda_{max}(lg\varepsilon)$= 227 (4.561), 286 (4.328). IR (KBr): ν = 3370 (N-H), 3340 (N-H), 3220 (N-H), 2220 (C≡N), (C=O), 1575 (C=N) cm^{-1}. ^{1}H-NMR (250.13 MHz, $CDCl_3$): δ = 1.00 - 2.13 (m, $20H_{cyclohex.}$), 3.30-3.70 (m, 1H, NCH), 3.90-4.30 (m, 1H, NCH), 5.50-6.20 (broad, 2H, NH_2). ^{13}C-NMR (62.89 MHz, $CDCl_3$): δ = 25.0 (+, s, C-4′), 25.2 (+, s, C-4′), 25.8 (+, s, C-3′), 26.1 (+, s, C-3′), 29.7 (+, s, C-2′), 30.7 (+, s, C-2′), 56.9 (-, s, C-1′), 57.4 (-, s, C-1′), 59.6 (+, s, C-5), 116.0 (+, s, CN), 158.1 (+, s, C-6), 158.7 (+, s, C-2), 166.4 (+, s, C-4). $C_{17}H_{24}N_4O_2$ (316.40) calcd.: C 64.53 H 7.65 N 17.71; found: C 64.31 H 7.46 N 17.55.

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