Synthesis and Reactivity of 2-(6,7-Diethoxy-3,4-dihydroisoquinolin-1-yl)acetonitrile towards Hydrazonoyl Halides

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The synthesis of 2-(6,7-diethoxy-3,4-dihydroisoquinolin-1-yl)acetonitrile (**1**) has been performed by ring closure of the corresponding amide according to the *Bischler-Napieralski* method (*Scheme 1*). Based on spectroscopic data, the tautomeric 2-(tetrahydroisoquinolin-1-ylidene)acetonitrile is the actual compound. The reactions of **1** with α-oxohydrazonoyl halides **4** in the presence of Et_3N led to 2-(aryldiazenyl)pyrrolo[2,1-*a*]-isoquinoline derivatives **8** (*Scheme 2*), whereas with *C*-(ethoxycarbonyl)hydrazonoyl chlorides **14**, 2-(arylhydrazono)pyrrolo[2,1-*a*]isoquinoline-1-carbonitriles **16** were formed (*Scheme 4*). The structures of the products were established from their analytical and spectroscopic data and, in the case of **8b**, by X-ray crystallography.

Introduction. – Fused isoquinoline derivatives compose a very interesting class of compounds because of their significant biological and pharmaceutical activities [1–3]. As part of our studies aimed at developing simple and efficient syntheses of polyfunctional heteroaromatics from readily obtained starting materials, we have previously reported the synthesis of triazoloisoquinolines and pyrroloisoquinolines from 3,4-dihydroisoquinolines and hydrazonoyl halides [4][5]. However, in many cases, the exact structure of the reaction products could not be established unequivocally, because several closely similar isomeric products could be formed (*cf.* [5]). Whereas 1-unsubstituted and 3,4-dihydro-1-methylisoquinolines in the presence of Et_3N reacted with α-oxo hydrazonoyl halides to give [1,2,4]triazolo[3,4-*a*]isoquinolines [5] *via* a 1,3-dipolar cycloaddition of the *in situ* generated nitrile imines (*cf.* [6] and refs. cit. therein), the reaction course of the 1-cyanomethyl derivative (2-(3,4-dihydroisoquinolin-1-yl)acetonitrile) was obviously quite different.

In the present paper, we report on the investigation of the latter reaction and the elucidation of the structures of the products by spectroscopy and X-ray crystallography.

Results and Discussion. – The starting material 2-(6,7-diethoxy-3,4-dihydroisoquinolin-1-yl)acetonitrile (**1**) was prepared as shown in *Scheme 1* in analogy to [7]: ring closure of 2-cyano-*N*-[2-(3,4-diethoxyphenyl)ethyl]acetamide (**2**), prepared by heating equimolar amounts of ethyl cyanoacetate and 2-(3,4-diethoxyphenyl)ethylamine (**3**) with $POCl_3$ in $CHCl_3$ according to the *Bischler-Napieralski* method [8], led to **1** in 80% yield. The structure of **1** was established on the basis of its elemental analysis and

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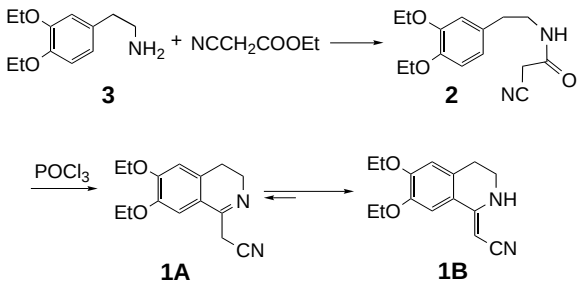
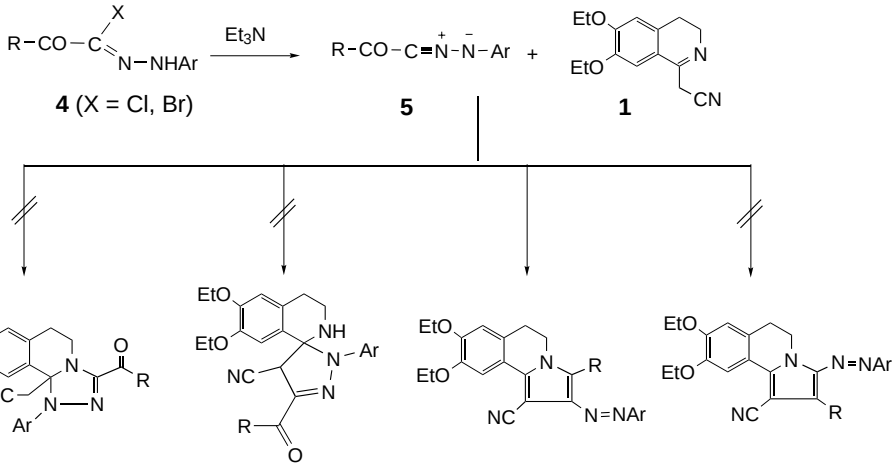
Scheme 1



spectroscopic data. For example, the EI-MS showed an intense molecular-ion peak at *m/z* 258. The IR spectrum (KBr) revealed the C≡N absorption at 2167 cm^{-1}, indicating a conjugated C≡N group. In addition, an absorption for NH appeared at 3348 cm^{-1} in accordance with the enamine structure **1B**. The ^{1}H-NMR spectrum confirmed the existence of the enamine tautomer in $CDCl_3$ solution; it showed a singlet at 4.23 ppm for =CH– and a second one at 5.64 ppm for NH. The latter disappeared on shaking the solution with D_2O.

The reaction of **1** with α-oxohydrazonoyl halides **4** in refluxing THF in the presence of Et_3N afforded, in each case, a single product as evidenced by TLC analysis. Based on the general reactivity of **1A**/**1B** towards **4** and the corresponding nitrile imines **5**, respectively, there are four possible products **6**–**9** (*Scheme 2*, *cf.* [5]).

Scheme 2



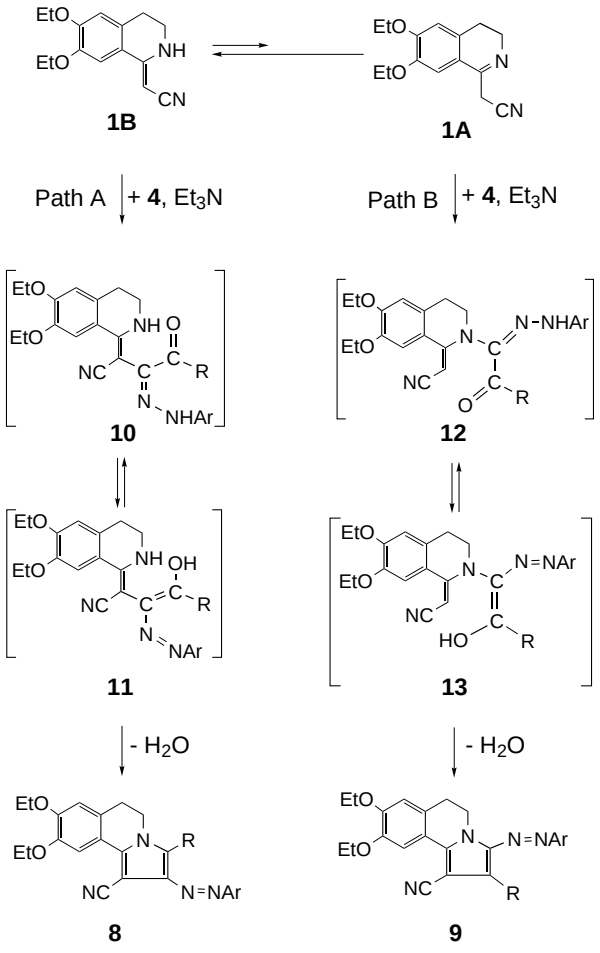
	R / Ar
a	Me / Ph
b	Me / 4-MeC_6H_4
c	Ph / Ph
d	Ph / 4-MeC_6H_4

	R / Ar
e	2-thienyl / Ph
f	2-naphthyl / Ph
g	2-naphthyl / 4-MeC_6H_4

The cycloadducts **6** and **7**, which could be formed *via* 1,3-dipolar cycloadditions of **5** with **1A** and **1B**, respectively (*cf.* [9]), were ruled out on the basis of elemental analysis and the mass spectra of the products, which proved the loss of H_2O. Furthermore, the IR spectra showed the presence of a conjugated C≡N group (2208–2196 cm^{-1}) and the absence of a C=O group. All data were in agreement with structures **8** and **9**, which are cyclocondensation products. The electronic absorption spectra were characterized by three maxima at 420–390, 340–320, and 255–240 nm, corresponding to the –N=N– chromophore [10]. Unfortunately, despite all these data, one cannot distinguish between the isomeric structures **8** and **9**.

Two mechanistic pathways *A* and *B* that account for the formation of **8** and **9**, respectively, are proposed in *Scheme 3*. In route *A*, the reaction involves an initial nucleophilic substitution of the halide of **4** by the enamine C-atom of **1B** to give intermediate **10**, which is in equilibrium with the tautomer **11**. Alternatively, **1B** reacts

Scheme 3



with nitrile imine **5** *via* protonation and nucleophilic addition (1,3 addition with 1,3-dipoles, *cf.* [6][11–14]) to give **10**. Then, cyclization *via* elimination of H_2O affords **8**. In route *B*, the corresponding nucleophilic substitution/addition occurs at the imine N-atom of **1A**, leading to **12** and **13** and, *via* elimination of H_2O, to the isomeric compound **9**.

In the case of the reaction of **1** with **4b** (R = Me, Ar = 4-MeC_6H_4, X = Cl), the structure of the orange product has been established by X-ray crystallography to be **8b** (*Fig.*). In the structure, the Et group of the EtO substituent at C(9)[3]) is disordered over two approximately equally occupied orientations. The central fused six-membered ring shows a screw-boat conformation. All other rings are planar. The torsion angle between the azo group and both the pyrrole and toluene rings is *ca.* 9°.

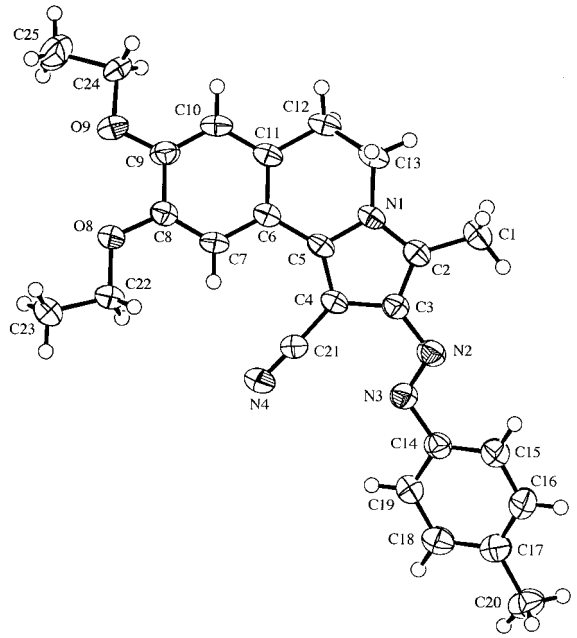


Figure. *ORTEP Plot* [15] *of the molecular structure of* **8b***: disordered conformation A* (arbitrary numbering of the atoms; 50% probability ellipsoids)

Next, we studied the reaction between **1** and ethyl 2-(arylhydrazono)-2-chloroacetates **14a–e**. Treatment of **1** with **14a** (Ar = Ph) in THF in the presence of Et_3N under reflux afforded a single product **16a** in 80% yield. The same product was obtained from **1** and methyl 2-chloro-2-(phenylhydrazono)acetate (**17a**) under similar conditions and by stirring equimolar amounts of **1** and **14a** in ethanolic EtONa solution at room temperature. The structure of the isolated product was assigned to be 8,9-diethoxy-5,6-dihydro-3-oxo-2-(phenylhydrazono)pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile (**16a**; *Scheme 4*) on the basis of its elemental analysis and spectroscopic data.

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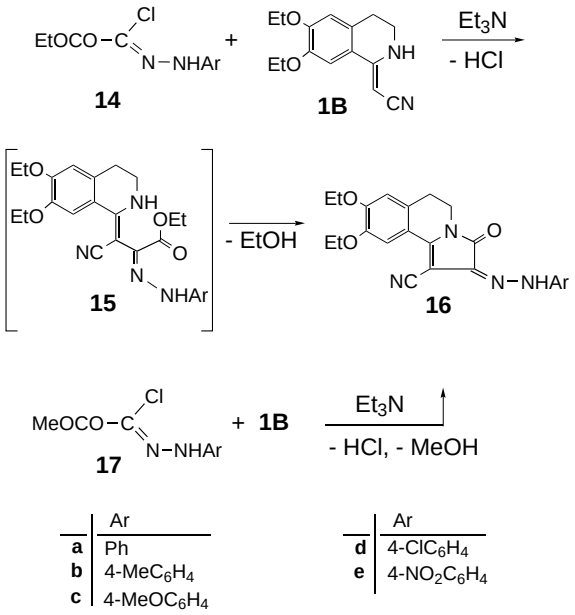
[3]) Arbitrary numbering of the atoms according to the *Figure*.

Scheme 4



	Ar
a	Ph
b	4-MeC_6H_4
c	4-$MeOC_6H_4$
d	4-ClC_6H_4
e	4-$NO_2C_6H_4$

Analysis and CI-MS indicated its molecular formula as $C_{23}H_{22}N_4O_3$, *i.e.*, a condensation product has been formed by elimination of HCl and EtOH. The ^{1}H-NMR spectrum revealed the absence of signals characteristic for the EtOCO group, and there was no absorption due to an ester C=O group (*ca.* 1735 cm^{-1}) in the IR spectrum (KBr). Rather it showed two absorption bands at 2206 and 1674 cm^{-1}, which can be assigned to the conjugated CN and the lactam groups, respectively.

Similarly, the ethyl 2-(arylhydrazono)-2-chloroacetates **14b**–**e** reacted with **1** to give the corresponding pyrrolo[2,1-*a*]isoquinolin-3-ones **16b**–**e** in excellent yield. The proposed reaction mechanism (*Scheme 4*) that seems to account for the formation of **16** is analogous to path *A* in *Scheme 3*. Nucleophilic substitution of chloride in **14** by the enamine C-atom of **1B** (or nucleophilic addition onto the corresponding nitrile imine) gives **15,** which undergoes ring closure by elimination of EtOH to afford **16**.

We thank the analytical units of our institutes for spectra and analyses. *E. M. A.* thanks the *Swiss Federal Government* for the provision of a *National Scholarship for Foreign Students.*

Experimental Part

1. *General*. M.p.: *Gallenkamp* melting-point apparatus; uncorrected. UV/VIS spectra: *Perkin-Elmer Lambda 4B* spectrometer. IR spectra: *Pye Unicam SP-300 IR* spectrophotometer and *Testscan Shimadzu FTIR 8000* series; in KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR spectra: *Varian Gemini* (200 MHz) and *Varian EM* (390 MHz) instruments; in $CDCl_3$ with TMS as an internal standard; chemical shifts δ in ppm, coupling constants *J* in Hz. EI-MS: *GCMS-QP 1000-EX Shimadzu* instrument; 70 eV. Elemental analyses were carried out at the Center of Microanalysis, Cairo University, Giza. The X-ray crystallographic analysis was carried out at the University of Zürich. Compounds **4a**,**b** (chlorides) [16], **4c**,**d** (bromides) [17], **4e** (chloride) [18], **4f**,**g** (chlorides) [19], **13a**–**c**

(chlorides) [20], **13d,e** (chlorides) [21], and **16a** (chloride) [22] were prepared according to the reported procedures.

2. *Synthesis of 2-(6,7-Diethoxy-3,4-dihydroisoquinolin-1-yl)acetonitrile* (**1**). A mixture of *2-(3,4-diethoxyphenyl)ethylamine* (**3**; 20.9 g, 100 mmol) and ethyl cyanoacetate (11.3 g, 100 mmol) was refluxed for 3 h. The mixture was cooled to r.t., at which it solidified. The solid was washed with EtOH and crystallized from EtOH to give *2-cyano*-N-*[2-(3,4-diethoxyphenyl)ethyl]acetamide* (**2**). The latter product was cyclized to give **1** by the *Bischler-Napieralski* method [8]: 20.7 g (80%) of **1**. M.p.: 167°. IR: 3348 (NH), 2167 (CN). ^{1}H-NMR: 1.32–1.52 (*m*, 2 Me); 2.75–2.89 (*m*, CH_2); 3.30–3.46 (*m*, CH_2N); 3.98–4.16 (*m*, 2 CH_2O); 4.23 (*s*, =CH–); 5.64 (*s*, NH); 6.63, 7.01 (2*s*, 2 arom. H). EI-MS: 258 (100, $M^{+\cdot}$), 230 (13), 201 (23), 173 (26), 149 (44), 91 (16), 81 (33), 69 (68), 57 (53), 55 (41). Anal. calc. for $C_{15}H_{18}N_2O_2$ (258.32): C 69.74, H 7.02, N 10.84; found: C 69.54, H 6.81, N 10.74.

3. *Synthesis of 5,6-Dihydropyrrolo[2,1-*a*]isoquinoline Derivatives* **8a**–**g**. *General Procedure.* To a soln. of **4** (5 mmol) and **1** (1.29 g, 5 mmol) in THF (40 ml) was added Et_3N (1.4 ml, 10 mmol) at r.t. The mixture was refluxed for 6 h, then the solvent was evaporated under reduced pressure, and the residue was triturated with MeOH (10 ml), under which it solidified. The crude product was crystallized from DMF. The prepared compounds **8a**–**g** are listed below.

*8,9-Diethoxy-5,6-dihydro-3-methyl-2-(phenyldiazenyl)pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**8a**): Yield 1.442 g (72%). M.p. 254° (DMF). IR: 2196 (CN). ^{1}H-NMR: 1.45 (*m*, 2 Me); 2.42 (*s*, Me); 3.01–3.23 (*m*, CH_2); 3.41–3.60 (*m*, CH_2N); 4.15 (*m*, 2 CH_2O); 7.80–8.25 (*m*, 7 arom. H). EI-MS: 401 (100, $[M+1]^+$), 400 (90, $M^{+\cdot}$), 371 (21), 296 (42), 240 (9), 77 (45), 51 (13). Anal. calc. for $C_{24}H_{24}N_4O_2$ (400.48): C 71.98, H 6.04, N 13.99; found: C 72.30, H 6.23, N 13.82.

*8,9-Diethoxy-5,6-dihydro-3-methyl-2-[(4-methylphenyl)diazenyl]pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**8b**): Yield 1.617 g (78%). M.p. 259° (DMF). IR: 2200 (CN). ^{1}H-NMR: 1.43 (*t*, $J=7$, Me); 1.51 (*t*, $J=7$, Me); 2.40 (*s*, Me); 2.58 (*s*, Me); 3.01 (*m*, CH_2); 4.00 (*m*, CH_2N); 4.10 (*q*, $J=7$, CH_2O); 4.21 (*q*, $J=7$, CH_2O); 6.68 (*s*, 1 arom. H); 7.25–7.78 (*m*, 4 arom. H); 7.90 (*s*, 1 arom. H). EI-MS: 416 (27), 415 (100, $[M+1]^+$), 414 (3, $M^{+\cdot}$), 385 (19), 358 (9), 296 (35), 239 (10), 193 (9), 91 (43), 77 (5), 65 (15). Anal. calc. for $C_{25}H_{26}N_4O_2$ (414.51): C 72.45, H 6.32, N 13.52; found: C 72.40, H 6.43, N 13.32.

8,9-Diethoxy-5,6-dihydro-3-phenyl-2-(phenyldiazenyl)pyrrolo[2,1-a]isoquinoline-1-carbonitrile (**8c**): Yield 1.804 g (78%). M.p. 275° (DMF). IR: 2204 (CN). ^{1}H-NMR: 1.43 (*m*, 2 Me); 2.40–2.62 (*m*, CH_2); 2.81–3.43 (*m*, CH_2N); 4.18 (*m*, 2 CH_2O); 7.01–8.04 (*m*, 12 arom. H). EI-MS: 464 (30), 463 (100, $[M+1]^+$), 462 (80, $M^{+\cdot}$), 405 (13), 330 (18), 301 (18), 283 (11), 255 (13), 91 (15), 77 (46), 51 (12). Anal. calc. for $C_{29}H_{26}N_4O_2$ (462.56): C 75.31, H 5.67, N 12.11; found: C 75.13, H 5.61, N 12.32.

*8,9-Diethoxy-5,6-dihydro-3-phenyl-2-[(4-methylphenyl)diazenyl]pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**8d**): Yield 1.787 g (75%). M.p. 275° (DMF). R: 2198 (CN). ^{1}H-NMR: 1.45 (*m*, 2 Me); 2.53 (*s*, Me); 2.81–3.03 (*m*, CH_2); 3.22–3.44 (*m*, CH_2N); 4.18 (*m*, 2 CH_2O); 7.11–8.04 (*m*, 11 arom. H). EI-MS: 478 (32), 477 (100, $[M+1]^+$), 476 (33, $M^{+\cdot}$), 463 (17), 447 (13), 420 (11), 358 (13), 301 (14), 273 (13), 255 (11), 243 (10), 91 (46), 77 (10), 65 (16), 51 (5). Anal. calc. for $C_{30}H_{28}N_4O_2$ (476.58): C 75.61, H 5.92, N 11.76; found: C 75.34, H 5.65, N 11.48.

*8,9-Diethoxy-5,6-dihydro-2-(phenyldiazenyl)-3-(2-thienyl)pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**8e**): Yield 1.898 g (81%). M.p. 243° (DMF). IR: 2208 (CN). EI-MS: 469 (100, $[M+1]^+$), 468 (91, $M^{+\cdot}$), 440 (14), 439 (6), 412 (10), 363 (15), 307 (10), 280 (6), 261 (7), 77 (44), 51 (10). Anal. calc. for $C_{27}H_{24}N_4O_2S$ (468.58): C 69.21, H 5.16, N 11.96, S 6.84; found: C 69.18, H 5.32, N 11.68, S 6.63.

*8,9-Diethoxy-5,6-dihydro-3-(naphthalen-2-yl)-2-(phenyldiazenyl)pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**8f**): Yield 1.922 g (75%). M.p. 282° (DMF). IR: 2208 (CN). EI-MS: 513 (37, $[M+1]^+$), 512 (100, $M^{+\cdot}$), 483 (10), 455 (21), 407 (14), 362 (8), 334 (8), 322 (14), 305 (10), 293 (8), 292 (7), 77 (9). Anal. calc. for $C_{33}H_{28}N_4O_2$ (512.62): C 77.32, H 5.51, N 10.93; found: C 77.43, H 5.42, N 10.64.

*8,9-Diethoxy-5,6-dihydro-2-[(4-methylphenyl)diazenyl]-3-(naphthalen-2-yl)pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**8g**): Yield 2.159 g (82%). M.p. 298° (DMF). IR: 2206 (CN). EI-MS: 526 (100, $M^{+\cdot}$), 469 (9), 407 (17), 351 (23), 322 (29), 305 (26), 293 (22), 235 (15), 152 (7), 91 (88), 65 (21), 55 (21). Anal. calc. for $C_{34}H_{30}N_4O_2$ (526.64): C 77.54, H 5.74, N 10.64; found: C 77.69, H 5.77, N 10.41.

4. *Synthesis of 5,6-Dihydro-3-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile Derivatives* (**16a**–**e**). *General Procedure 1.* Compounds **16** were prepared by the same method described for the synthesis of **8**, but using **1** and **14** in place of **4**.

General Procedure 2. To a stirred ethanolic soln. of EtONa, prepared from Na (0.1 g, 5 mmol) and abs. EtOH (30 ml), was added **1** (1.29 g, 5 mmol). Then the appropriate hydrazono acetate **14** (5 mmol) was added at r.t. The mixture was stirred for 1 h, during which **14** was dissolved and the crude product was precipitated. The

latter was washed with H_2O, dried, and crystallized from a suitable solvent. The prepared compounds **16a**–**e** are listed below.

*8,9-Diethoxy-5,6-dihydro-3-oxo-2-(phenylhydrazono)pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**16a**): Yield 1.611 g (80%). M.p. 248° (DMF). IR: 3258 (NH), 2207 (CN), 1667 (CO). ^{1}H-NMR: 1.34 (*m*, 2 Me); 3.02 (*m*, CH_2); 3.83 (*m*, CH_2N); 4.11 (*m*, 2 CH_2O); 7.12 (*s*, 1 arom. H); 7.15–7.53 (*m*, 5 arom. H); 7.74 (*s*, 1 arom. H); 12.64 (*s*, NH). EI-MS: 402 (100, $M^{+\bullet}$), 374 (13), 345 (17), 317 (8), 241 (5), 77 (33), 65 (16), 51 (8). Anal. calc. for $C_{23}H_{22}N_4O_3$ (402.46): C 68.64, H 5.51, N 13.92; found: C 68.50, H 5.41, N 13.72.

*8,9-Diethoxy-5,6-dihydro-2-[(4-methylphenyl)hydrazono]-3-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**16b**): Yield 1.688 g (81%). M.p. 245° (DMF). IR: 3363 (NH), 2211 (CN), 1670 (CO). ^{1}H-NMR: 1.34 (*m*, 2 Me); 2.34 (*s*, Me); 3.03 (*m*, CH_2); 3.82 (*m*, CH_2N); 4.14 (*m*, 2 CH_2O); 7.11 (*s*, 1 arom. H); 7.20–7.43 (*m*, 4 arom. H); 7.74 (*s*, 1 arom. H); 12.61 (*s*, NH). EI-MS: 416 (100, $M^{+\bullet}$), 359 (14), 282 (15), 194 (6), 180 (9), 106 (39), 91 (45), 77 (18), 55 (15). Anal. calc. for $C_{24}H_{24}N_4O_3$ (416.48): C 69.22, H 5.80, N 13.45; found: C 69.01, H 5.73, N 13.22.

*8,9-Diethoxy-5,6-dihydro-2-[(4-methoxyphenyl)hydrazono)]-3-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**16c**): Yield 1.688 g (78%). M.p. 253° (DMF). IR: 3286 (NH), 2205 (CN), 1676 (CO). ^{1}H-NMR: 1.49 (*t*, $J = 7$, Me); 1.53 (*t*, $J = 7$, Me); 3.00 (*m*, CH_2); 3.82 (*s*, MeO); 3.90 (*m*, CH_2N); 4.13 (*q*, $J = 7$, CH_2O); 4.21 (*q*, $J = 7$, CH_2O); 6.71 (*s*, 1 arom. H); 6.86–7.40 (*m*, 4 arom. H); 7.85 (s, 1 arom. H); 12.75 (*s*, NH). EI-MS: 434 (5), 433 (35, $[M+1]^+$), 432 (100, $M^{+\bullet}$), 122 (5). Anal. calc. for $C_{24}H_{24}N_4O_4$ (432.48): C 66.65, H 5.59, N 12.96; found: C 66.60, H 5.32, N 12.71.

*2-[(4-Chlorophenyl)hydrazono]-8,9-diethoxy-5,6-dihydro-3-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**16d**): Yield 1.638 g (75%). M.p. 260° (DMF). IR: 3315 (NH), 2202 (CN), 1685 (CO). EI-MS: 439 (35), 438 (29, $[M+1]^+$), 437 (100, $M^{+\bullet}$), 408 (21), 379 (19), 35 (6), 241 (6), 213 (5), 128 (7), 111 (22), 99 (13), 77 (5). Anal. calc. for $C_{23}H_{21}N_4O_3Cl$ (436.90): C 63.23, H 4.85, N 12.82; found: C 63.52, H 4.56, N 12.61.

*8,9-Diethoxy-5,6-dihydro-2-[(4-nitrophenyl)hydrazono]-3-oxopyrrolo[2,1-*a*]isoquinoline-1-carbonitrile* (**16e**): Yield 1.790 g (80%). M.p. 278° (DMF). IR: 3280 (NH), 2206 (CN), 1681 (CO). ^{1}H-NMR: 1.44 (*m*, 2 Me); 3.02 (*m*, CH_2); 3.83 (*m*, CH_2N); 4.12 (*m*, 2 CH_2O); 7.14 (*s*, 1 arom. H); 7.53 (*s*, 1 arom. H); 7.71–8.20 (*m*, 4 arom. H); 12.62 (*s*, NH). EI-MS: 449 (28), 448 (100, $[M+1]^+$), 447 (72, $M^{+\bullet}$), 390 (21). Anal. calc. for $C_{23}H_{21}N_5O_5$ (447.46): C 61.74, H 4.73, N 15.65; found: C 61.51, H 4.52, N 15.40.

5. *Crystal-Structure Determination of* **8b** (see *Table* and *Fig.*)[4]). All measurements were made on a *Rigaku AFC5R* diffractometer with graphite-monochromated MoK_α radiation (λ 0.71069 Å) and a 12-kW rotating-anode generator. The $\omega/2\theta$ scan mode was employed for data collection. The intensities were corrected for *Lorentz* and polarization effects but not for absorption. Data collection and refinement parameters are given in the *Table*, and a view of the molecule is shown in the *Figure*. The structure was solved by direct methods with SHELXS97 [23], which revealed the position of all non-H-atoms. The Et group of one EtO substituent is disordered over two orientations. Two sets of atoms for this Et group were defined and their site occupation factors were initially refined, then held fixed at a ratio of 0.574 : 0.426. The non-H-atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom. Refinement of the structure was carried out on F by means of full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. A correction for secondary extinction was applied. Neutral-atom-scattering factors for non-H-atoms were taken from [24a] and the scattering factors for H-atoms from [25]. Anomalous dispersion effects were included in F_c [26]; the values for f' and f'' were those of [24b], and the values of the mass-attenuation coefficients were those of [24c]. All calculations were performed with the *teXsan* crystallographic software package [27].

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[4]) Crystallographic data (excluding structure factors) for the structure **8b** reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication Nr. CCDC-145107. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table 1. *Crystallographic Data of Compound* **8b**

Crystallized from	DMF
Empirical formula	$C_{25}H_{26}N_4O_2$
Formula weight [g mol^{-1}]	414.51
Crystal color, habit	orange, plate
Crystal dimensions [mm]	$0.13 \times 0.40 \times 0.40$
Temp. [K]	233(1)
Crystal system	monoclinic
Space group	*C*2/*c*
Z	8
Reflections for cell determination	25
2θ Range for cell determination [°]	33 – 40
Unit-cell parameters *a* [Å]	32.563(2)
b [Å]	7.425(8)
c [Å]	18.394(1)
β [°]	98.972(6)
V [Å^3]	4392(4)
D_x [g cm^{-3}]	1.254
$\mu(\mathrm{Mo}K_\alpha)$ [mm^{-1}]	0.0814
$2\theta_{(\max)}$ [°]	55
Total reflections measured	5532
Symmetry-independent reflections	5042
Reflections used [$I > 2\sigma(I)$]	2617
Parameters refined	299
Final *R*	0.0514
wR ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$)	0.0444
Goodness-of-fit	1.643
Secondary extinction coefficient	$2.1(1) \times 10^{-7}$
Final $\Delta_{\max}/\sigma$	0.0002
$\Delta\rho$ (max; min) [e Å^{-3}]	0.19; −0.16

REFERENCES

[1] J. R. Geigy AG, Neth. Appl. 6,614,979, 1967 (*Chem. Abstr.* **1968**, *68*, 69003).
[2] C. J. Cavallito, A. P. Gray, Malinckrodt Chemical Works, Fr. Demande 2,135,297, 1973 (*Chem. Abstr.* **1973**, *79*, 96989j).
[3] B. E. Maryanoff, D. F. McComsey, M. J. Costanzo, P. E. Setler, J. F. Gardocki, R. P. Shank, C. R. Schneider, *J. Med. Chem.* **1984**, *27*, 943.
[4] H. A. Abdelhadi, N. M. Elwan, T. A. Abdallah, H. M. Hassaneen, *J. Chem. Res., Synop.* **1996**, 292.
[5] N. M. Elwan, H. A. Abdelhadi, T. A. Abdallah, H. M. Hassaneen, *Tetrahedron* **1996**, *52*, 3451.
[6] P. Caramella, P. Grünanger, in '1,3-Dipolar Cycloaddition Chemistry', Ed. A. Padwa, J. Wiley & Sons, New York, 1984, Vol. 1, p. 291.
[7] J. M. Osbond, *J. Chem. Soc.* **1951**, 3464.
[8] A. Bischler, B. Napieralski, *Ber. dtsch. chem. Ges.* **1893**, *26*, 1903; *cf.* W. M. Whaley, T. R. Govindachari, *Org. React.* **1951**, *6*, 74; T. J. Kametami, K. Fukumoto, *Chem. Heterocycl. Compd.* **1981**, *38*, 139.
[9] M. Škof, J. Svete, B. Stanovnik, L. Golič, S. Golič-Grdadolnik, L. Selič, *Helv. Chim. Acta* **1998**, *81*, 2332.
[10] A. Buraway, A. G. Salem, A. R. Thompson, *J. Chem. Soc.* **1952**, 4793.
[11] H.-J. Hansen, H. Heimgartner, in '1,3-Dipolar Cycloaddition Chemistry', Ed. A. Padwa, J. Wiley & Sons, New York, 1984, Vol. 1, p. 177.
[12] G. Tennant, in 'Comprehensive Organic Chemistry', Eds. D. Barton, W. D. Ollis, Pergamon Press, Oxford, 1979, Vol. 2 (Ed. I. O. Sutherland), p. 562 ff.
[13] A. F. Hegarty, *Acc. Chem. Res.* **1980**, *13*, 448.
[14] G. Mlostoń, H. Heimgartner, *Pol. J. Chem.* **2000**, *74*, 1503.

[15] C. K. Johnson, 'ORTEP II.' Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
[16] N. F. Eweiss, A. Osman, *J. Heterocycl. Chem*. **1980**, *17*, 1713.
[17] A. S. Shawali, A. O. Abdelhamid, *Bull. Chem. Soc. Jpn*. **1976**, *49*, 321.
[18] A. M. Farag, M. S. Algharib, *Org. Prep. Proced. Int*. **1988**, *20*, 521.
[19] H. M. Hassaneen, A. S. Shawali, N. M. Elwan, N. M. Abounada, *Sulfur Lett.* **1992**, *13*, 273.
[20] A. S. Shawali, N. F. Eweiss, H. M. Hassaneen, M. Sami, *Bull. Chem. Soc. Jpn.* **1975**, *48*, 365.
[21] R. Huisgen, H.-J. Koch, *Liebigs Ann. Chem*. **1955**, *591*, 200.
[22] R. Fusco, P. Dalla Croce, *Gazz. Chim. Ital*. **1971**, *101*, 703.
[23] G. M. Sheldrick, 'SHELXS97, Program for the Solution of Crystal Structures', University of Göttingen, Germany, 1997.
[24] a) E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, 1992, Vol. C, Table 6.1.1.1, p. 477; b) D. C. Creagh, W. J. McAuley, *ibid.* Table 4.2.6.8, p. 219; c) D. C. Creagh, J. H. Hubbell, *ibid.* Table 4.2.4.3, p. 200.
[25] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.
[26] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr*. **1964**, 17, 781.
[27] 'teXsan: Single Crystal Structure Analysis Software', Version 1.10, Molecular Structure Corporation, The Woodlands, Texas, 1999.

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