Selenium-Containing Heterocycles from Isoselenocyanates: Use of Hydrazine for the Synthesis of 1,3,4-Selenadiazine Derivatives

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Aryl isoselenocyanates **1** react with different phenacyl halides **2** in the presence of hydrazine hydrate in a one-pot reaction to give selenadiazines **3a**–**3f** in good-to-excellent yields.

1. Introduction. – Selenium-containing heterocycles are of remarkable interest because of their antitumor, antibacterial, and other biological and pharmaceutical activities [1]. Among our efforts devoted to the chemistry of selenium in organic synthesis, we were also interested in the preparation of selenadiazines. Several articles deal with the synthesis of 1,3,4- [2–4], 1,3,5- [5][6], and 1,2,6-selenadiazines [7] but, to the best of our knowledge, no synthesis has been described starting from isoselenocyanates. Some selenadiazines are of biological and physical interest, and are found to be cardiotonic [8] or spasmolytic agents [9], but they are also of importance as agrochemicals, dyes, and organic electric conductors [10].

In numerous articles, the synthesis of 1,3,4-selenadiazine derivatives by ring enlargement of other Se-containing heterocycles like selenadiazoles or selenazoles is described [11][12]. However, most of the reports showed the uses of selenoureas [13], selenosemicarbazides [14][15], or phenyl acetyleneselenide as intermediates [16].

As a part of our program aimed at the development of simple new procedures for the synthesis of Se-containing heterocycles [17–24], we have recently reported on the utility of isoselenocyanates as building blocks for the synthesis of 1,3-selenazetidines [25], 1,3-selenazolidines and perhydro-1,3-selenazines [26], 2-methylidene-1,3-selenazolidine derivatives [27], and 1,3-selenazepanes [28]. As an extension of this work, we report here on a novel and efficient synthesis of 1,3,4-selenadiazines.

2. Results and Discussion. – The used isoselenocyanates **1a**–**1e** (see *Table 1*) have been prepared conveniently by a slightly modified procedure of *Barton et al.* [29] from the corresponding *N*-arylformamide by treatment with $COCl_2$ and elemental Se. Then, hydrazine hydrate was added to a mixture of equimolar amounts of **1** and a phenacyl halide **2** in CH_2Cl_2 at room temperature. After stirring for 3–4 h, the reaction was complete (TLC) and the solvent was evaporated. The product was purified by column chromatography on silica gel using a mixture of hexane and AcOEt (ratio from

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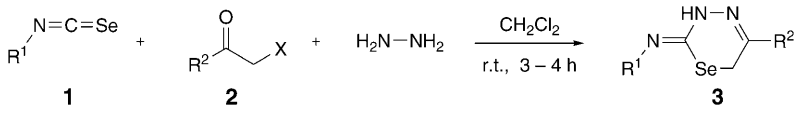
1:0 to 1:1) and recrystallized from AcOEt. The IR spectra (KBr) of the pale-yellow solids showed two characteristic strong absorptions at *ca.* 1590 and 1560 cm^{-1} but no C=O absorption. The NMR spectra revealed the presence of an NH (11.3–11.8 ppm) and a CH_2 group (3.8–3.95 (^1H) and *ca.* 15 ppm (^{13}C)), and the CI-MS and elemental analyses were in accordance with the structure of a 3,6-dihydro-2-imino-2*H*-1,3,4-selenadiazine **3** or its 2-amino tautomer (*Scheme 1*). Finally, the structure of **3a** was established by X-ray crystallography (*Figure*).

Scheme 1



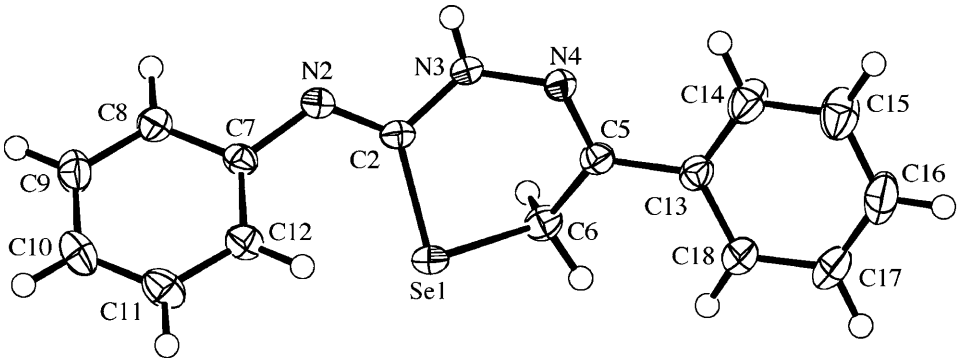


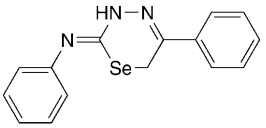
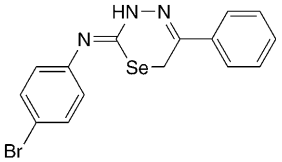
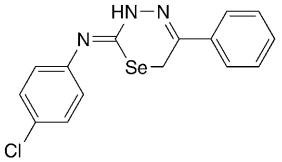
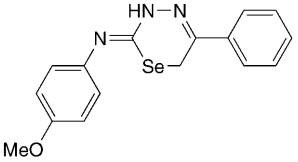
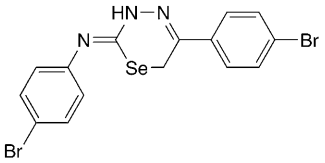
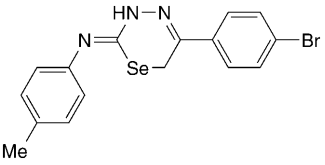
Figure. *ORTEP Plot* [30] *of the molecular structure of* **3a** (arbitrary numbering of the atoms, 50% probability ellipsoids)

In the heterocyclic ring, the unsubstituted C-atom is a CH_2 group, and only one ring N-atom carries an H-atom. The other one is involved in a C=N bond. The heterocyclic ring has a distorted boat conformation. The NH group forms an intermolecular H-bond with the exocyclic imine N-atom of a neighboring molecule. In turn, the acceptor molecule makes an identical H-bond to the original molecule so that pairs of molecules are linked into centrosymmetric dimeric units. The H-bonding can be described by a graph set motif [31] of R (8).

The described one-pot reaction of **1**, **2**, and hydrazine led to the products **3a**–**3f** in 55–80% yield (*Table 1*). Several attempts have been made to carry out this three-component reaction in two consecutive steps. The treatment of **1** with hydrazine hydrate, followed by the addition of a phenacyl halide **2**, did not yield the desired product, but the corresponding selenosemicarbazide was formed. On the other hand, the reaction of the hydrazone, which had been prepared from **2** and hydrazine, with **1** led quickly to decomposition products.

Based on the results described, we propose the reaction mechanism shown in *Scheme 2* for the formation of **3**. We have already demonstrated that isoselenocyanates **1** and bifunctional nucleophiles of type **4**, bearing an electrophilic group, react to give 2-iminoselenaheterocycles **6**. A likely intermediate is the adduct **5**, which undergoes an

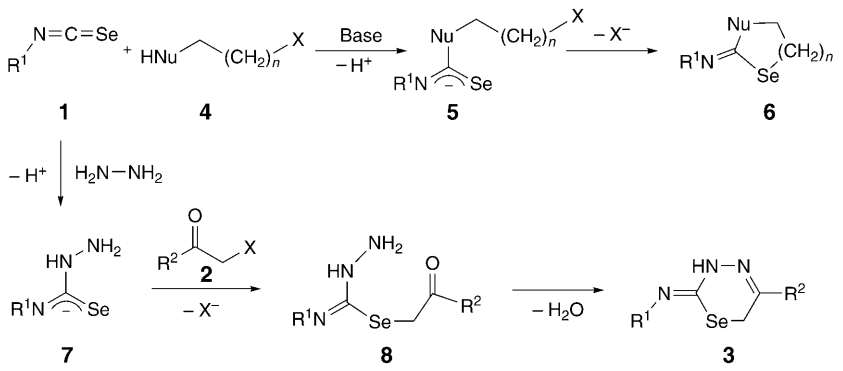
Table 1. *Preparation of Selenadiazines* **3** *from Isoselenocyanates* **1**

Entry	**1**	R^1	**2**	R^2	Selenadiazines **3**	Yield [%]
1	**1a**	Ph	**2a**	Ph	**3a** 	72
2	**1b**	4-BrC_6H_4	**2a**	Ph	**3b** 	68
3	**1c**	4-ClC_6H_4	**2a**	Ph	**3c** 	55
4	**1d**	4-$MeOC_6H_4$	**2a**	Ph	**3d** 	67
5	**1b**	4-BrC_6H_4	**2b**	4-BrC_6H_4	**3e** 	80
6	**1e**	4-MeC_6H_4	**2b**	4-BrC_6H_4	**3f** 	78

exo-trig cyclization [32] to yield five to seven-membered selenaheterocycles [26–28] or heterocyclic selones [33][34]. In the present three-component reaction, the nucleophile (hydrazine) and the electrophile **2** are separated. Addition of hydrazine to **1** leads to the adduct **7**, which immediately reacts with the third component **2** to give **8**. Finally, an intramolecular condensation by elimination of H_2O, *i.e.*, the formation of a hydrazone, leads to the selenaheterocycles **3**.

In conclusion, we have shown that the three-component reaction of isoselenocyanates **1**, phenacyl halides **2**, and hydrazine is a very convenient and useful procedure for the preparation of 1,3,4-selenadiazines **3**.

Scheme 2



We thank the analytical units of our institute for spectra and elemental analyses. Financial support of this work by the *Dr. Helmut Legerlotz Foundation* and *F. Hoffmann-La Roche AG,* Basel, is gratefully acknowledged.

Experimental Part

1. *General.* TLC: Silica gel *60 F_{254}* plates (0.25 mm; *Merck*). Column chromatography (CC): silica gel *60* (0.040–0.063 mesh; *Merck*). M.p.: *Büchi B-540* apparatus, in capillaries; uncorrected. IR Spectra: *Perkin-Elmer 1600-FT-IR* spectrometer, in KBr; absorptions in cm^{-1}. ^{1}H- (300 MHz) and ^{13}C-NMR (75.5 MHz) spectra: *Bruker ARX-300* instrument, in (D_6)DMSO; chemical shifts in ppm, *J* in Hz; multiplicities of C-atoms from DEPT spectra. EI- and CI-MS: *Finnigan SSQ-700* or *MAT-90* instrument; EI mode: 70 eV; CI mode: NH_3 as carrier gas.

2. *Starting Materials.* α-Halogeno acetophenones and hydrazine hydrate are commercially available (*Fluka*). Isoselenocyanates **1a**–**1e** were prepared according to a slightly modified procedure of *Barton et al.* [29] starting from a formamide. Formanilide is commercially available (*Fluka* and *Aldrich*). *N*-(4-Chlorophenyl)-, *N*-(4-bromophenyl)-, *N*-(4-methylphenyl)-, and *N*-(4-methoxyphenyl)formamide were prepared from the corresponding aniline and 95% HCOOH. The soln. was heated to reflux for 30 min and evaporated to dryness *in vacuo*. The residue was dissolved in Et_2O and washed with diluted AcOH (5%), H_2O, and aq. $NaHCO_3$ (5%). The aq. layer was extracted with Et_2O, and the combined org. extracts were dried ($MgSO_4$) and evaporated. The crude products were purified by recrystallization from EtOH/H_2O.

3. *General Procedure for the Preparation of Selenadiazines* **3a**–**3f**. A 25-ml round-bottom flask equipped with a magnetic stirrer and condenser was charged with a mixture of an isoselenocyanate (1.0 mmol) and a phenacyl halide (1.0 mmol) in CH_2Cl_2 (20 ml). Then, $NH_2NH_2 \cdot H_2O$ (0.05 ml, 1.0 mmol) was added in one portion, and the mixture was stirred for 3 to 4 h at r.t. and concentrated to dryness *i.v.* The crude product was purified by CC (silica gel; hexane/AcOEt 100:0 to 50:50).

*(3,6-Dihydro-5-phenyl-2*H*-[1,3,4]selenadiazin-2-ylidene)(phenyl)amine* (**3a**). Yield: 226.3 mg (72%). Yellowish crystals. M.p. 186–188° (AcOEt). IR: 3443*m* (br.), 3150*w*, 3060*w*, 3034*w*, 2921*m* (br.), 1621*m*, 1580*s*, 1556v*s*, 1494*m*, 1471*w*, 1404*w*, 1303*w*, 1251*w*, 1209*m*, 1172*w*, 1137*w*, 1112*w*, 1075*w*, 1004*w*, 899*w*, 845*w*, 798*w*, 766*w*, 753*m*, 687*m*, 632*m*. ^{1}H-NMR: 3.95 (*s*, CH_2); 6.95–7.25 (br. *m*, *t*-like at 7.12, $J = 7.4$, 3 arom. H); 7.37 (*t*-like, $J = 7.7$, 2 arom. H); 7.45–7.55 (*m*, 3 arom. H); 7.91 (*d*-like, $J = 7.7$, 2 arom. H); 11.28 (br. *s*, NH). ^{13}C-NMR: 15.1 (*t*, CH_2); 123.1 (*d*, 1 arom. CH); 126.1 (*d*, 2 arom. CH); 128.4 (*d*, 3 arom. CH); 128.5 (*d*, 2 arom. CH); 129.2 (*d*, 2 arom. CH); 135.4, 149.0, 155.2 (3*s*, 2 arom. C, C(5)); 163.5 (*s*, C(2)). CI-MS: 318 (19), 317 (17), 316 (100, $[M(^{80}Se)+1]^+$), 315 (10), 314 (48), 313 (19), 312 (18), 239 (7), 238 (41, $[M-Ph]^+$), 236 (20), 225 (7). Anal. calc. for $C_{15}H_{13}N_3Se$ (314.24): C 57.33, H 4.17, N 13.37; found: C 57.34, H 4.03, N 13.09.

Crystals suitable for the X-ray crystal-structure determination were grown from $CHCl_3$/MeOH by slow evaporation of the solvent.

*(4-Bromophenyl)-(3,6-dihydro-5-phenyl-2*H*-[1,3,4]selenadiazin-2-yliden)amine* (**3b**). Yield: 267.3 mg (68%). Yellowish crystals. M.p. 179–181° (AcOEt). IR: 3443*m* (br.), 3133*w*, 3056*w*, 2917*m* (br.), 1623*m*, 1587v*s*, 1567*s*, 1490*m*, 1472*m*, 1444*m*, 1403*m*, 1297*w*, 1276*w*, 1214*s*, 1173*m*, 1105*w*, 1072*m*, 1003*w*, 889*m*, 841*m*, 827*s*, 759*s*, 693*s*, 658*m*, 632*w*. ^{1}H-NMR: 3.93 (*s*, CH_2); 6.70–7.00 (br. *m*, 2 arom. H); 7.45–7.60 (*m*, 5 arom. H); 7.85–8.00 (*m*, 2 arom. H); 11.71 (br. *s*, NH). ^{13}C-NMR: 15.3 (*t*, CH_2); 121.6 (*s*, 1 arom. C); 126.2 (*d*, 2 arom. CH); 128.5 (*d*, 3 arom. CH); 129.3 (*d*, 2 arom. CH); 131.3 (*d*, 2 arom. CH); 135.3, 148.0, 154.3 (3*s*, 2 arom. C, C(5)); 166.2 (*s*, C(2)). CI-MS: 398 (13), 397 (14), 396 (77), 395 (21), 394 (100, $[M(^{80}Se,^{79}Br)+1]^+$), 393 (21), 392 (47), 391 (14), 390 (14). Anal. calc. for $C_{15}H_{12}BrN_3Se$ (393.15): C 45.83, H 3.08, N 10.69; found: C 45.46, H 3.21, N 10.42.

*(4-Chlorophenyl)-(3,6-dihydro-5-phenyl-2*H*-[1,3,4]selenadiazin-2-yliden)amine* (**3c**). Yield: 191.8 mg (55%). Yellowish crystals. M.p. 178–180° (AcOEt). IR: 3444*m* (br.), 3125*w*, 3047*w*, 2908*m* (br.), 2866*m* (br.), 1623*m*, 1584v*s*, 1568*s*, 1491*s*, 1473*m*, 1444*w*, 1403*m*, 1297*w*, 1277*w*, 1214*s*, 1178*w*, 1172*m*, 1107*w*, 1093*m*, 1071*w*, 1003*w*, 888*m*, 843*w*, 830*m*, 796*w*, 760*m*, 694*m*, 683*w*, 662*w*. ^{1}H-NMR: 3.95 (*s*, CH_2); 6.80–7.05 (br. *m*, 2 arom. H); 7.45 (*d*-like, $J=8.4$, 2 arom. H); 7.50–7.60 (*m*, 3 arom. H); 7.90–8.05 (*m*, 2 arom. H); 11.64 (br. *s*, NH). ^{13}C-NMR: 15.3 (*t*, CH_2); 126.2 (*d*, 2 arom. CH); 128.4 (*d*, 2 arom. CH); 128.5 (*d*, 3 arom. CH); 129.3 (*s*, 2 arom. CH); 135.0, 135.3, 147.5, 155.3 (4*s*, 3 arom. C, C(5)); 163.9 (*s*, C(2)). CI-MS: 354 (6), 353 (8), 352 (44), 351 (18), 350 (100, $[M(^{80}Se,^{35}Cl)+1]^+$), 349 (15), 348 (48), 347 (17), 346 (17). Anal. calc. for $C_{15}H_{12}ClN_3Se$ (348.69): C 51.67, H 3.47, N 12.05; found: C 51.51, H 3.74, N 11.73.

*(3,6-Dihydro-5-phenyl-2*H*-[1,3,4]selenadiazin-2-ylidene)(4-methoxyphenyl)amine* (**3d**). Yield: 229.3 mg (67%). Yellowish crystals. M.p. 132–134° (AcOEt). IR: 3439*m* (br.), 3346*m*, 2912*m* (br.), 2836*w*, 1654*s*, 1638*m*, 1580v*s*, 1544*s*, 1509v*s*, 1447*w*, 1282*m*, 1249*s*, 1211*w*, 1178*w*, 1109*w*, 1077*w*, 1033*w*, 1011*w*, 892*w*, 826*m*, 800*w*, 757*w*, 713*m*, 692*w*. ^{1}H-NMR: 3.82 (*s*, MeO); 3.90 (*s*, CH_2); 6.90–7.20 (br. *m*, *d*-like at 6.92, $J=8.2$, 4 arom. H); 7.30–7.55 (*m*, 2 arom. H); 7.75–8.00 (*m*, 2 arom. H); 11.82 (br. *s*, NH). ^{13}C-NMR: 15.1 (*t*, CH_2); 55.4 (*q*, MeO); 115.6 (*d*, 2 arom. CH); 124.2 (*d*, 2 arom. CH); 128.3 (*d*, 2 arom. CH); 129.2 (*d*, 2 arom. CH); 131.1 (*d*, 1 arom. CH); 133.9, 147.8, 153.7, 158.4 (4*s*, 3 arom. C, C(5)); 166.1 (*s*, C(2)). CI-MS: 350 (8), 349 (12), 348 (65), 347 (21), 346 (100, $[M(^{80}Se)+1]^+$), 345 (19), 344 (52), 343 (15), 342 (14). Anal. calc. for $C_{16}H_{15}N_3OSe$ (344.28): C 55.82, H 4.39, N 12.21; found: C 55.95, H 4.67, N 12.23.

*(4-Bromophenyl)[5-(4-bromophenyl)-3,6-dihydro-2*H*-[1,3,4]selenadiazin-2-yliden]amine* (**3e**). Yield: 377.6 mg (80%). Yellowish crystals. M.p. 176–178° (AcOEt). IR: 3442*m* (br.), 3155*w*, 3051*w*, 2920*m* (br.), 1626*m*, 1590v*s*, 1576*s*, 1554*m*, 1485*m*, 1407*w*, 1299*w*, 1271*w*, 1209*m*, 1172*m*, 1146*w*, 1101*w*, 1070*m*, 1000*m*, 890*w*, 828*m*, 725*w*, 707*w*, 653*w*, 604*w*. ^{1}H-NMR: 3.88 (*s*, CH_2); 6.85–7.10 (br. *m*, 2 arom. H); 7.68 (*d*-like, $J=8.2$, 2 arom. H); 7.80 (*d*-like, $J=8.2$, 2 arom. H); 7.90–8.00 (*m*, 2 arom. H); 11.79 (br. *s*, NH). ^{13}C-NMR: 15.0 (*t*, CH_2); 122.8 (*s*, 2 arom. C); 124.2 (*d*, 2 arom. CH); 128.1 (*d*, 2 arom. CH); 131.3 (*d*, 2 arom. CH); 131.5 (*d*, 2 arom. CH); 134.5, 147.2, 155.5 (3*s*, 2 arom. C, C(5)); 162.9 (*s*, C(2)). CI-MS: 478 (7), 477 (9), 476 (52), 475 (19), 474 (100, $[M(^{80}Se,^{81}Br,^{79}Br)+1]^+$), 473 (23), 472 (85, $[M(^{80}Se,^{79}Br,^{79}Br)+1]^+$), 471 (19), 470 (35), 469 (8), 468 (9). Anal. calc. for $C_{15}H_{11}Br_2N_3Se$ (472.05): C 38.17, H 2.35, N 8.90; found: C 38.01, H 2.54, N 8.60.

*[5-(4-Bromophenyl)-3,6-dihydro-2*H*-[1,3,4]selenadiazin-2-ylidene](4-methylphenyl)amine* (**3f**). Yield: 317.5 mg (78%). Yellowish crystals. M.p. 202–204° (AcOEt). IR: 3441*m* (br.), 2919*m*, 2853*m* (br.), 1623*m*, 1583v*s*, 1554*m*, 1508*w*, 1486*w*, 1406*w*, 1269*w*, 1221*m*, 1173*m*, 1075*m*, 999*w*, 890*w*, 826*m*. ^{1}H-NMR: 2.40 (*s*, Me); 3.93 (*s*, CH_2); 6.90–7.20 (*m*, 2 arom. H); 7.24 (*d*-like, $J=8.1$, 2 arom. H); 7.52 (*d*-like, $J=8.1$, 2 arom. H); 7.66 (*d*-like, $J=8.1$, 2 arom. H); 11.50 (br. *s*, NH). ^{13}C-NMR: 14.8 (*t*, CH_2); 20.3 (*q*, Me); 121.6 (*s*, 1 arom. C); 122.6 (*d*, 2 arom. CH); 128.0 (*d*, 2 arom. CH); 129.0 (*d*, 2 arom. CH); 131.4 (*d*, 2 arom. CH); 134.7, 145.6, 155.0 (3*s*, 3 arom. C, C(5)); 163.2 (C(2)). CI-MS: 412 (13), 411 (15), 410 (77), 409 (33), 408 (100, $[M(^{80}Se,^{79}Br)+1]^+$), 407 (40), 406 (50), 405 (23), 404 (17). Anal. calc. for $C_{16}H_{14}BrN_3Se$ (407.07): C 47.20, H 3.47, N 10.32; found: C 46.72, H 3.51, N 10.15.

Table 2. *Crystallographic Data of Compound* **3a**

Crystallized from		$CHCl_3$/MeOH
Empirical formula		$C_{15}H_{13}N_3Se$
Formula weight [g mol^{-1}]		314.19
Crystal color, habit		pale-yellow, prism
Crystal dimensions [mm]		$0.18\times0.23\times0.28$
Temp. [K]		160(1)
Crystal system		monoclinic
Space group		$P2_1/n$
Z		4
Reflections for cell determination		27519
2θ Range for cell determination [°]		4–60
Unit cell parameters	a [Å]	10.5899(2)
	b [Å]	8.7839(1)
	c [Å]	15.2309(3)
	β [°]	110.2058(9)
	V [Å^3]	1329.60(4)
D_x [g cm^{-3}]		1.569
μ(MoK_α) [mm^{-1}]		2.811
Scan type		ϕ and ω
$2\theta_{(max)}$ [°]		60
Transmission factors (min; max)		0.510; 0.623
Total reflections measured		37327
Symmetry independent reflections		3883
Reflections with $I>2\sigma(I)$		3316
Reflections used in refinement		3882
Parameters refined		177
Final	$R(F)$ [$I>2\sigma(I)$ reflections]	0.0297
	$wR(F^2)$ (all data)	0.0750
Weights:	$w=[\sigma^2(F_o^2)+(0.0359P)^2+0.9122P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$	
Goodness-of-fit		1.033
Secondary extinction coefficient		0.0036(8)
Final Δ_{max}/σ		0.002
$\Delta\rho$ (max; min) [e Å^{-3}]		0.64; −0.50

X-Ray Crystal-Structure Determination of **3a** (see *Table 2* and *Figure*)[2]). All measurements were performed on a *Nonius KappaCCD* diffractometer [35] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. Data reduction was performed with *HKL Denzo* and *Scalepack* [36]. The intensities were corrected for *Lorentz* and polarization effects, and an absorption correction based on the multi-scan method [37] was applied. Equivalent reflections were merged. Data collection and refinement parameters are given in *Table 2*, and a view of the molecule is shown in the *Figure*. The structure was solved by direct methods using *SIR92* [38], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The amine H-atom was placed in the position indicated by a difference electron-density map, and its position was allowed to refine together with an isotropic displacement parameter. All of the remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom. Refinement of

[2]) CCDC-601303 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/data_request/cif.

the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F - F_c^2)^2$. A correction for secondary extinction was applied. One reflection, whose intensity was considered to be an extreme outlier, was omitted from the final refinement. Neutral-atom scattering factors for non-H-atoms were taken from [39a], and the scattering factors for H-atoms were taken from [40]. Anomalous dispersion effects were included in F_c [41]; the values for f' and f'' were those of [39b]. The values of the mass attenuation coefficients are those of [39c]. All calculations were performed using the SHELXL97 [42] program.

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