Reactions with 4-Hydroxy-2-methylbutananilides: Unexpected Formation of a Cyclopropanecarboxamide

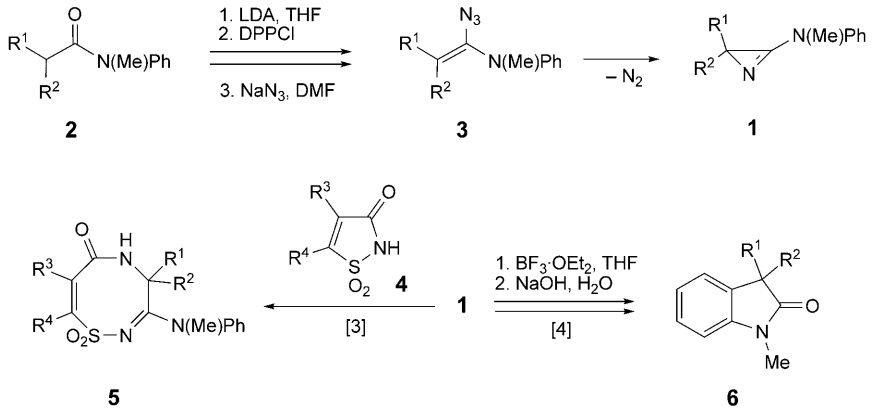
by **Maged K. G. Mekhael**[1]), **Anthony Linden**, and **Heinz Heimgartner***

Organisch-Chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich (phone: +41-44-6354282; fax: +41-44-6356812; e-mail: heimgart@oci.uzh.ch)

The successive treatment of the *N,N*-disubstituted 4-hydroxy-2-methylbutanamide **2a** with lithium diisopropylamide (LDA) and diphenyl phosphorochloridate (DPPCl) led to the 1-methylcyclopropanecarboxamide **10** in good yield. This base-catalyzed cyclization offers a new approach to cyclopropanecarboxamides. Under similar conditions, the *N*-monosubstituted 4-hydroxy-2-methylbutanamide **2b** gave the 3-methylpyrrolidin-2-one **11**. The structure of the cyclopropanecarboxamide **10** was established by X-ray crystallography.

Introduction. – In the last four decades, it has been demonstrated that 2,2-disubstituted 2*H*-azirin-3-amines of type **1** are attractive building blocks for the introduction of 2,2-disubstituted glycines into peptides, as well as for the synthesis of heterocycles [1]. The *N*-methyl-*N*-phenyl derivatives are conveniently accessible *via* successive treatment of anilides **2** with lithium diisopropylamide (LDA), diphenyl phosphorochloridate (DPPCl), and NaN_3 [2] (*Scheme 1*). It is assumed that 1-azido

Scheme 1



[1]) Part of the Ph.D. thesis of *M. K. G. M.*, University of Zürich, 2003; present address: National Research Center, Chemistry of Natural Compounds Dept., Tahrir Street, Dokki, Cairo, Egypt.

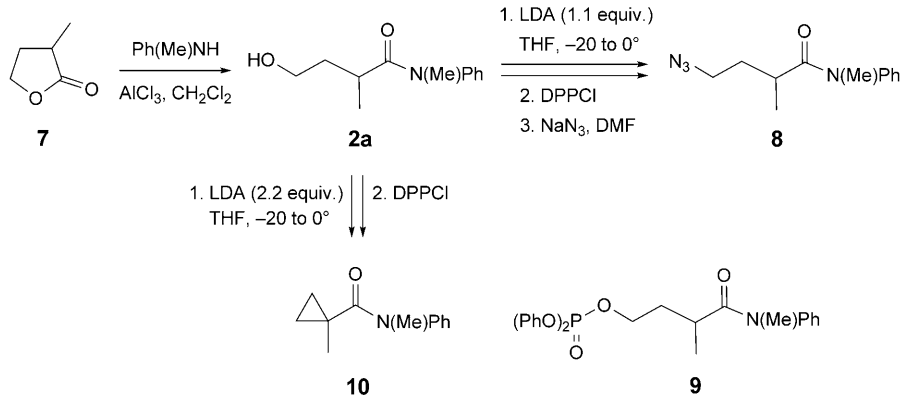
enamines **3** are intermediates, which spontaneously cyclize *via* elimination of N_2 to give 2*H*-azirines **1**.

Two typical examples for ring-enlargement reactions with **1** are shown in *Scheme 1*. The reaction with N*H*-acidic isothiazol-3(2*H*)-one 1,1-dioxides **4** leads to eight-membered 1,2,5-thiadiazocine derivatives **5** *via* cleavage of the N(1)=C(3) bond of **1** [3], whereas treatment of **1** with $BF_3 \cdot OEt_2$ and subsequent hydrolysis gives 2-oxindoles (=2,3-dihydro-1*H*-indol-2-ones) **6** *via* cleavage of the N(1)–C(2) bond [4]. In the second example, a 2-allyl-substituted azirine **1** (R^1 = allyl, R^2 = Me) has been used for the preparation of a 3-allyloxindole **6** (R^1 = allyl, R^2 = Me), which was further transformed into (±)-desoxynoreseroline [5][2]). This example demonstrates that azirines of type **1** with a functionalized side chain R^1 are of high interest for the synthesis of more complex heterocycles[3]).

For this reason, the synthesis of 2*H*-azirin-3-amines **1** with an OH group in the residue R^1 was undertaken. These attempts led to unexpected results, which are presented in this report.

Results and Discussion. – The desired precursor **2a** for the azirine synthesis was obtained by the $AlCl_3$-catalyzed amination of α-methyl-γ-butyrolactone **7** with *N*-methylaniline according to the protocol described in [8] (see also [7a]). The reaction proceeded smoothly, and the known **2a** [7a][8] was obtained in 84% yield as colorless crystals with a m.p. of 78–78.8°. All attempts to synthesize the 2*H*-azirin-3-amine **1a** ($R^1 = HOCH_2CH_2$, R^2 = Me) according to the method described in [2] (see *Scheme 1*) by using *ca.* 1.1 equiv. of LDA failed, and only the azido derivative **8** was isolated in 48% yield as a yellow oil (*Scheme 2*). The structure determination was based on the

Scheme 2



[2]) The 3-allyloxindol **6** (R^1 = allyl, R^2 = Me) [4a] was transformed into 3-(2-hydroxyethyl)-1,3-dimethyloxindole *via* ozonolysis and subsequent $NaBH_4$ reduction [6]. Subsequent treatment with $SOCl_2$ and NH_3 yielded 3-(2-aminoethyl)-1,3-dimethyloxindole, a precursor for the cyclization to (±)-desoxynoreseroline.

[3]) For the synthesis of 2*H*-azirin-3-amines with a functionalized side chain, see also [7].

analytical and the IR, ^{1}H- and ^{13}C-NMR data. The presence of the N_3 group was evidenced by the strong IR absorptions at 2096 and 1266 cm^{-1} for the asymmetric and symmetric stretching vibration. The base peak in the CI-MS appeared at *m*/*z* 233 ($[M+1]^+$), corresponding to the formula $C_{12}H_{16}N_4O$ for the product.

The formation of **8** can easily be rationalized by the reaction of the alcoholate of **2a** with DPPCl to give the corresponding alkyl diphenyl phosphate **9** (see, *e.g.*, [9]), followed by an S_N2 reaction with the azide ion.

In the next experiment, **2a** was treated with *ca.* 2.2 equiv. of LDA, followed by *ca.* 1.1 equiv. of DPPCl. Surprisingly, a new, rather unpolar product was formed (TLC), which, after chromatographic workup, was obtained as a colorless, crystalline material. On the basis of the spectroscopic and analytical data, the structure was determined as 1,*N*-dimethyl-*N*-phenylcyclopropanecarboxamide (**10**; *Scheme 2*). Finally, this structure was established by X-ray crystallography (*Fig.*).

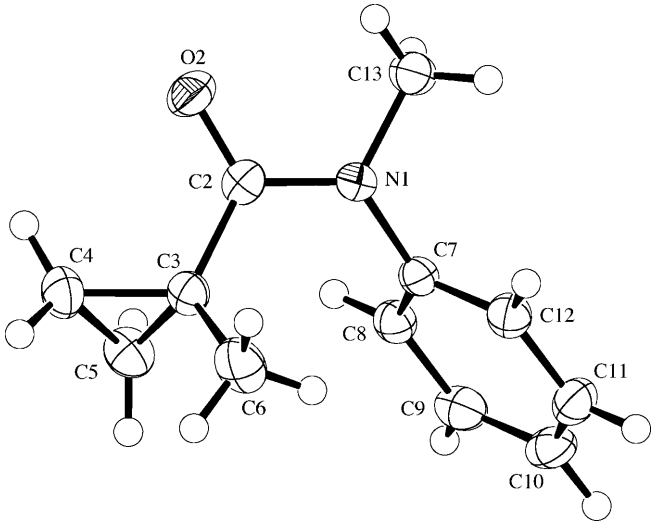


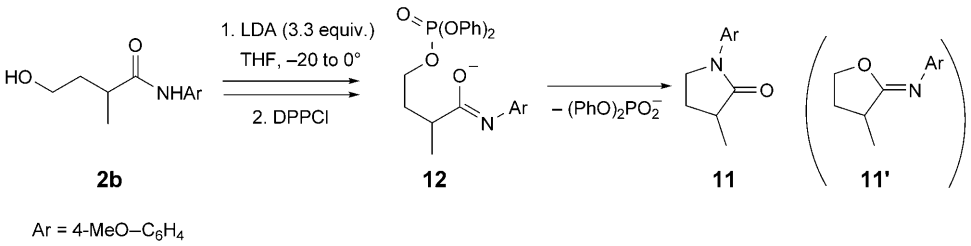
Figure. *ORTEP Plot* [10] *of the molecular structure of* **10** (50% probability ellipsoids, arbitrary atom numbering)

A likely intermediate in the formation of **10** is the anion of **9**, which undergoes cyclization to give the cyclopropane by elimination of diphenyl phosphate (*cf.* [11]).

The analogous reaction of the *N*-monosubstituted amide **2b**, which had been prepared by the reaction of **7** with 4-methoxyaniline, with *ca.* 3.3 equiv. of LDA gave, after chromatographic workup, a product with a base peak in the CI-MS at *m*/*z* 206 ($[M+1]^+$), corresponding to a molecular formula of $C_{12}H_{15}NO_2$, *i.e.*, the product of the dehydration. The ^{1}H- and ^{13}C-NMR data clearly indicated that the product was not the expected cyclopropanecarboxamide: the NMR spectra showed signals of two different CH_2 groups (*e.g.*, δ(C) 46.8 and 27.0 ppm) and of a CH group (37.9 ppm). Whereas the IR absorption at 1685 cm^{-1} was in agreement with the structure of lactam **11** [12] as well as with the iminolactone **11′** [13], the NMR data clearly indicated that **11** was formed (*Scheme 3*). The CH_2 signals at 46.8 (^{13}C) and 3.77–3.72 (^{1}H) ppm are characteristic

for the CH_2N group [14], whereas the CH_2O signals of **11′** would be expected at *ca.* 62 and 4.2 ppm, respectively [15][16]. The formation of **11** may be rationalized by the cyclization of intermediate **12**. Although ring closure *via* nucleophilic attack of the O- or the N-atom of the amide group is possible, it has been shown that, in the case of 4-bromobutyranilide, under very basic conditions, *i.e.*, in the cyclization of the corresponding anion, the formation of the lactam is strongly preferred [17].

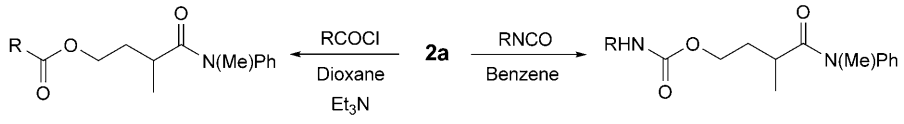
Scheme 3



Ar = 4-MeO–C_6H_4

Finally, the transformations of the OH group of **2a** to an ester moiety in **13** and to a urethane moiety in **14** were achieved *via* the reactions with acid chlorides and isocyanates, respectively, under standard conditions (*Scheme 4*).

Scheme 4



13a R = Me
13b R = Cl_2CH
13c R = Cyclopropyl
13d R = Ph
13e R = 4-NO_2–C_6H_4

14a R = *t*-Bu
14b R = Cyclohexyl
14c R = Ph

Conclusions. – The reaction of the *N*,*N*-disubstitued 4-hydroxybutanamide **2a** with 2 equiv. of LDA and DPPCl led to the cyclopropanecarboxamide **10**, whereas the analogous *N*-monosubstituted amide **2b** under similar conditions yielded the lactam **11**. The formation of **10** *via* the base-catalyzed cyclization of **2a** offers a new access to the important class of cyclopropanecarboxamides[4]), which are known as partial structures of physiologically active compounds (*e.g.*, DPP-IV inhibitors [19a], melanocortin receptor agonists [19b], antidepressants [19c], HCV NS5B inhibitors [19d][19e], etc.). The described results show that, for the attempted synthesis of a 2*H*-azirin-3-amine **1** with an OH group in R^1, a starting material **2** with a suitably protected OH group should be used.

---

[4]) For recent syntheses of cyclopropanecarboxamides, see [18].

We thank the analytical units of our institute for spectra and analyses. Financial support of the work by the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, is gratefully acknowledged.

Experimental Part

1. *General.* Solvents were purified by standard procedures. TLC: aluminium sheets, silica gel *60* F_{254} (*Merck*). Prep. TLC: glass plates, silica gel *60* F_{254} (2 mm; *Merck*). Column chromatography (CC): silica gel *C-560* (0.04–0.063 mm; *Uetikon-Chemie*). Medium-pressure liquid chromatography (MPLC): *LiChroprep Si 60*, 15–25 μm (*Merck*); column: *Kron-Lab 4/98-Pro*, 480 × 30 mm or *Labomatic*, 380 × 20 mm. M.p.: *Mettler-FP-5* or *Büchi 510* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 781* or *Perkin-Elmer 1600* FT-IR spectrophotometer; in KBr unless otherwise stated. ^{1}H- and ^{13}C-NMR Spectra: *Bruker ARX-300* instrument (300 and 75.5 MHz, resp.), in $CDCl_3$; multiplicities of C-atoms from DEPT spectra. MS: *Finnigan MAT-90*, *Finnigan SSQ-700* (CI with NH_3), or *Finnigan TSQ-700* instrument (ESI). Elemental analyses were performed by the Mikroanalytisches Laboratorium des Organisch-chemischen Instituts der Universität Zürich (*Elementar Vario EL* instrument).

2. *Starting Materials.* The preparation of *4-hydroxy-2,*N-*dimethyl*-N-*phenylbutanamide* (**2a**) was carried out according to [8] and has been previously described in [7a]. All other reagents were commercially available.

3. *Reactions with 4-Hydroxy-2,*N-*dimethyl*-N-*phenylbutanamide* (**2a**). 3.1. *4-Azido-2,*N-*dimethyl*-N-*phenylbutanamide* (**8**). To a stirred soln. of ^{i}Pr_2NH (0.47 ml, 3.32 mmol) in THF (10 ml) at −20°, BuLi (2M soln. in pentane, 1.60 ml, 3.20 mmol) was added under Ar, and the mixture was allowed to warm to 0°. A soln. of **2a** (600 mg, 2.89 mmol) in THF (5 ml) was added dropwise, and the mixture was stirred at 0° for 1 h. Then, diphenyl phorphorochloridate (DPPCl; 0.62 ml, 2.98 mmol) was added dropwise. After 30 min, the ice bath was removed, and the mixture was stirred at r.t. for 24 h. The formed precipitate was filtered off under Ar, the THF soln. was dropped into a suspension of NaN_3 (0.565 mg, 8.69 mmol) in dry DMF (1.5 ml), and the mixture was stirred at r.t. for 4 d. Then, Et_2O was added, and the mixture was filtered over a *Celite* pad, the solvent was evaporated, and the residue was dissolved in Et_2O. The soln. was washed with 5% aq. $NaHCO_3$ (2×), the aq. layer was washed with Et_2O, the combined org. layers were dried ($MgSO_4$), the solvent was evaporated under reduced pressure, and the crude product was purified by bulb-to-bulb distillation and CC (Et_2O/hexane 2:5): 322 mg (48%) of **8**. Yellow oil. IR (film): 3061*w*, 2971*m*, 2934*m*, 2875*m*, 2096*s*, 1654*s*, 1595*s*, 1496*s*, 1462*s*, 1426*s*, 1390*s*, 1328*m*, 1266*s*, 1173*w*, 1116*s*, 1074*m*, 1037*m*, 1001*w*, 916*w*, 775*m*, 750*w*, 701*s*. ^{1}H-NMR: 7.50–7.36, 7.23–7.19 (2*m*, 5 arom. H); 3.32–3.14 (*m*, CH_2N_3); 3.28 (*s*, MeN), 2.64–2.49 (*m*, CH); 2.09–1.93, 1.60–1.47 (2*m*, CH_2); 1.05 (*d*, *J* = 6.8, Me). ^{13}C-NMR: 175.6 (*s*, CO); 143.7 (*s*, 1 arom. C); 129.7, 127.9, 127.2 (3*d*, 5 arom. CH); 49.3, 32.9 (2*t*, 2 CH_2); 37.4 (*q*, MeN); 33.8 (*d*, CH); 18.0 (*q*, Me). CI-MS: 234 (14), 233 (100, $[M+1]^+$), 205 (13), 190 (11), 107 (9).

3.2. *1,*N-*Dimethyl*-N-*phenylcyclopropanecarboxamide* (**10**). To a stirred soln. of ^{i}Pr_2NH (0.94 ml, 6.65 mmol) in THF (10 ml) at −20°, BuLi (2M soln. in pentane; 3.19 ml, 6.38 mmol) was added under Ar, and the mixture was allowed to warm to 0°. A soln. of **2a** (600 mg, 2.89 mmol) in THF (5 ml) was added dropwise, and the mixture was stirred at 0° for 1 h. Then, DPPCl (1.23 ml, 5.96 mmol) was added dropwise. After 30 min, the ice bath was removed, and the mixture was stirred at r.t. for 24 h. The formed precipitate was filtered off under Ar, the solvent was evaporated, and Et_2O was added. The mixture was filtered over a *Celite* pad, the solvent was evaporated, and the residue was dissolved in Et_2O. The soln. was washed with 5% aq. $NaHCO_3$ (2×), the aq. layer was washed with Et_2O, the combined org. layers were dried ($MgSO_4$), the solvent was evaporated under reduced pressure, and the crude product was purified by CC (Et_2O/hexane 1:5): 412 mg (75%) of **10**. Crystallization from hexane gave colorless prisms. M.p. 77.5–78.5°. IR: 3089*w*, 3046*w*, 2969*m*, 2951*m*, 2924*m*, 2867*w*, 1637*s*, 1594*s*, 1496*s*, 1469*m*, 1434*m*, 1413*s*, 1383*s*, 1370*s*, 1311*m*, 1284*w*, 1246*s*, 1158*w*, 1118*s*, 1076*w*, 948*w*, 910*w*, 859*w*, 811*w*, 198*w*, 779*m*, 750*m*, 706*s*. ^{1}H-NMR: 7.45–7.35, 7.31–7.20 (2*m*, 5 arom. H); 3.29 (*s*, MeN); 1.12–1.05, 0.44–0.37 (2*m*, 2 CH_2); 0.92 (*s*, Me). ^{13}C-NMR: 174.5 (*s*, CO); 144.5 (*s*, 1 arom. C); 129.1, 127.1, 126.8 (3*d*, 5 arom. CH); 39.0 (*q*, MeN); 21.9 (*q*, Me); 20.8 (*s*, C(1)); 15.5 (*t*, 2 CH_2). CI-MS: 191 (12), 190 (100, $[M+1]^+$). Anal. calc. for $C_{12}H_{15}NO$ (189.25): C 76.16, H 7.99, N 7.40; found: C 76.14, H 7.85, N 7.44.

Crystals suitable for the X-ray crystal-structure determination were grown from hexane by slow evaporation of the solvent.

4. *Reaction with 4-Hydroxy*-N-*(4-methoxyphenyl)-2-methylbutanamide* (**2b**). 4.1. *Preparation of* **2b**. In analogy to [8], a soln. of 4-methoxyaniline (1.54 g, 12.51 mmol) in 1,2-dichloroethane (4.5 ml) was added to a stirred suspension of $AlCl_3$ (0.87 g, 6.50 mmol) in 1,2-dichloroethane (2.5 ml) at 15–25°. Then, *α-methyl-γ-butyrolactone* (**7**; 0.5 ml, 5.28 mmol) was added, and the mixture was stirred at r.t. for 4 h. After quenching the reaction with ice/H_2O (5 ml), the mixture was stirred for an additional 0.5 h, the resulting suspension was filtered over *Celite*, and the org. phase was separated. The aq. phase was extracted with CH_2Cl_2, and the combined org. phase was washed with H_2O and brine, and dried (Na_2SO_4). Evaporation of the solvent and CC (CH_2Cl_2/MeOH 100:1) yielded 575 mg (52%) of **2b**. Pale rosa powder. M.p. 95.2–95.7°. IR: 3443*m*, 3283*s*, 3193*m*, 3133*m*, 3071*w*, 2974*m*, 2953*m*, 2934*m*, 2837*m*, 1652*s*, 1603*s*, 1549*s*, 1514*s*, 1459*m*, 1444*m*, 1415*m*, 1380*m*, 1348*m*, 1298*s*, 1239*s*, 1185*m*, 1170*m*, 1134*w*, 1098*m*, 1053*s*, 1035*s*, 1000*m*, 944*w*, 828*s*, 807*w*, 762*w*, 716*m*. ^{1}H-NMR: 7.88 (br. *s*, NH); 7.37, 6.79 (*AA′BB′*, 4 arom. H); 3.75 (*s*, MeO); 3.71–3.64 (*m*, CH_2O); 2.87 (br. *s*, OH); 2.68–2.54 (*m*, CH); 1.97–1.84, 1.76–1.62 (2*m*, CH_2); 1.22 (*d*, J = 6.9, Me). ^{13}C-NMR: 175.0 (*s*, CO); 156.3, 130.9 (2*s*, 2 arom. C); 121.9, 114.0 (2*d*, 4 arom. CH); 60.1, 36.5 (2*t*, 2 CH_2); 55.4 (*q*, MeO); 38.5 (*d*, CH); 17.6 (*q*, Me). CI-MS: 225 (12), 224 (100, $[M+1]^+$), 207 (9), 206 (77). Anal. calc. for $C_{12}H_{17}NO_3$ (223.27): C 64.55, H 7.67, N 6.27; found: C 64.53, H 7.85, N 6.15.

4.2. *1-(4-Methoxyphenyl)-3-methylpyrrolidin-2-one* (**11**). To a stirred soln. of ^{i}Pr$_2$NH (0.66 ml, 4.66 mmol) in THF (20 ml) at −20°, BuLi (2M soln. in pentane; 2.20 ml, 4.44 mmol) was added under Ar, and the mixture was allowed to warm to 0°. A soln. of **2b** (300 mg, 1.34 mmol) in THF (5 ml) was added dropwise, and the mixture was stirred at 0° for 1 h. Then, DPPCl (0.86 ml, 4.13 mmol) was added dropwise. After 30 min, the ice bath was removed, and the mixture was stirred at r.t. for 24 h. The mixture was worked up as described in *Sect. 3.2*, and the crude product was purified by CC (Et_2O/hexane 1:2): 240 mg (87%) of **11**. Colorless crystals. M.p. 83.1–84.8°. IR: 2952*m*, 2836*w*, 1685*s*, 1515*s*, 1482*m*, 1442*m*, 1397*s*, 1324*m*, 1290*m*, 1252*s*, 1226*s*, 1180*m*, 1121*m*, 1098*m*, 1050*m*, 1030*s*, 918*w*, 884*w*, 830*s*, 790*w*, 720*w*, 704*w*. ^{1}H-NMR: 7.53, 6.90 (*AA′BB′*, 4 arom. H); 3.81 (*s*, MeO); 3.77–3.72 (*m*, CH_2O); 2.73–2.59 (*m*, CH); 2.43–2.30, 1.83–1.70 (2*m*, CH_2); 1.30 (*d*, J = 6.7, Me). ^{13}C-NMR: 176.2 (*s*, O–C=N); 156.3, 132.9 (2*s*, 2 arom. C); 121.4, 113.9 (2*d*, 4 arom. CH); 55.4 (*q*, MeO); 46.8, 27.0 (2*t*, 2 CH_2); 37.9 (*d*, CH); 16.2 (*q*, Me). CI-MS: 411 (9, $[2M+1]^+$), 223 (8, $[M+NH_4]^+$), 207 (13), 206 (100, $[M+1]^+$). Anal. calc. for $C_{12}H_{15}NO_2$ (205.25): C 70.22, H 7.37, N 6.82; found: C 70.10, H 7.65, N 6.92.

5. *Reaction of* **2a** *with Acid Chlorides. General Procedure 1* (*GP 1*). To a soln. of **2a** in dioxane, the corresponding acid chloride and Et_3N were added, and the mixture was heated to reflux for 2 h. The solvent was evaporated, and CH_2Cl_2 was added, the org. phase was washed with 10% aq. HCl, sat. aq. $NaHCO_3$, and brine, and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure, and pure product was obtained after CC.

5.1. *3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Acetate* (**13a**). According to *GP 1*, with **2a** (100 mg, 0.48 mmol), dioxane (5 ml), AcCl (0.04 ml, 0.56 mmol), and Et_3N (0.05 ml, 0.36 mmol). Yield: 108 mg (90%) of **13a**. Colorless, viscous oil, which solidified on cooling. IR: 3062*w*, 3039*w*, 2970*m*, 2937*m*, 2878*m*, 1745*s*, 1650*s*, 1596*s*, 1497*s*, 1463*m*, 1429*s*, 1391*s*, 1365*m*, 1329*m*, 1244*s*, 1118*s*, 1074*m*, 1039*s*, 776*s*, 703*s*. ^{1}H-NMR: 7.38–7.22, 7.13–7.07 (2*m*, 5 arom. H); 3.89 (*t*, J = 6.2, CH_2O); 3.18 (*s*, MeN); 2.53–2.40, 2.02–1.89, 1.55–1.42 (3*m*, CH, CH_2); 1.83 (*s*, MeCO); 0.98 (*d*, J = 6.8, Me). ^{13}C-NMR: 174.8 (*s*, O–C=O); 169.8 (*s*, CO); 143.0 (*s*, 1 arom. C); 128.8, 126.8, 126.4 (3*d*, 5 arom. CH); 61.5 (*t*, CH_2O) 36.4 (*q*, MeN); 32.3 (*d*, CH); 32.1 (*t*, CH_2); 19.8 (*q*, *Me*CO); 17.1 (*q*, Me). CI-MS: 516 (54, $[2M+NH_4]^+$), 499 (21, $[2M+1]^+$), 267 (33, $[M+NH_4]^+$), 251 (15), 250 (100, $[M+1]^+$), 249 (13, M^+), 190 (24).

5.2. *3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Dichloroacetate* (**13b**). According to *GP 1*, with **2a** (150 mg, 0.72 mmol), dioxane (10 ml), dichloroacetyl chloride (0.11 ml, 1.14 mmol), and Et_3N (0.1 ml, 0.72 mmol). Yield: 200 mg (87%) of **13b**. Yellowish, viscous oil. ^{1}H-NMR: 7.39–7.25, 7.16–7.09 (2*m*, 5 arom. H); 5.73 (*s*, $CHCl_2$); 4.20–4.03 (*m*, CH_2O); 3.19 (*s*, MeN); 2.58–2.45, 2.11–1.98, 1.64–1.50 (3*m*, CH, CH_2); 0.98 (*d*, J = 6.8, Me). ^{13}C-NMR: 175.2 (*s*, O–C=O); 164.2 (*s*, CO); 143.7 (*s*, 1 arom. C); 129.8, 127.8, 127.2 (3*d*, 5 arom. CH); 65.6 (*t*, CH_2O); 64.1 (*s*, $CHCl_2$); 37.4 (*q*, MeN); 33.0 (*d*, CH); 32.5 (*t*, CH_2); 18.0 (*q*, Me). CI-MS: 335 (17, $[M+NH_4]^+$), 318 (100, $[M+1]^+$), 284 (19), 228 (21), 226 (64). Anal. calc. for $C_{14}H_{17}Cl_2NO_3$ (318.20): C 52.84, H 5.39, N 4.40, Cl 22.28; found: C 53.10, H 5.32, N 4.42, Cl 21.94.

5.3. *3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Cyclopropanecarboxylate* (**13c**). According to *GP 1*, with **2a** (100 mg, 0.48 mmol), dioxane (10 ml), cyclopropanecarbonyl chloride (0.04 ml, 0.44 mmol), and Et_3N (0.07 ml, 0.50 mmol). Yield: 127 mg (95%) of **13c**. Pale yellow oil. IR (film): 3061*w*, 3014*w*, 2968*m*, 2935*m*, 1719*s*, 1654*s*, 1595*s*, 1496*s*, 1454*s*, 1390*s*, 1366*s*, 1328*m*, 1270*s*, 1199*s*, 1178*s*, 1117*s*, 1074*m*, 1034*m*, 1000*w*, 938*w*, 913*w*, 853*w*, 824*w*, 775*m*, 747*w*, 702*s*. ^{1}H-NMR: 7.38–7.21, 7.11–7.07 (2*m*, 5 arom. H); 3.88 (*t*, $J = 6.2$, CH_2O); 3.17 (*s*, MeN); 2.53–2.40, 2.02–1.90, 1.54–1.42, 1.41–1.32 (4*m*, 2 CH, CH_2); 0.98 (*d*, $J = 6.8$, Me); 0.89–0.79, 0.78–0.69 (2*m*, 2 CH_2). ^{13}C-NMR: 175.7 (*s*, O–C=O); 174.5 (*s*, CO); 143.9 (*s*, 1 arom. C); 129.6, 127.7, 127.2 (3*d*, 5 arom. CH); 62.5 (*t*, CH_2O); 37.3 (*q*, MeN); 33.2 (*d*, CH); 33.1 (*t*, CH_2); 12.7 (*d*, CH); 8.2, 8.1 (2*t*, 2 CH_2). CI-MS: 277 (16), 276 (100, $[M+1]^+$), 190 (11).

5.4. *3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Benzoate* (**13d**). According to *GP 1*, with **2a** (300 mg, 1.45 mmol), dioxane (20 ml), BzCl (0.17 ml, 1.45 mmol), and Et_3N (0.2 ml, 1.43 mmol). Yield: 370 mg (82%) of **13d**. Colorless, viscous oil, which solidified in h.v. IR (film): 3062*w*, 2970*m*, 1716*s*, 1654*s*, 1596*s*, 1496*s*, 1452*s*, 1428*m*, 1391*s*, 1315*m*, 1274*s*, 1176*m*, 1117*s*, 1071*m*, 1028*m*, 1001*w*, 950*w*, 846*w*, 775*m*, 749*w*, 713*s*. ^{1}H-NMR: 7.85–7.80, 7.50–7.45, 7.35–7.30, 7.10–7.00 (4*m*, 10 arom. H); 4.18 (br. *s*, CH_2O); 3.18 (br. *s*, MeN); 2.65–2.60, 2.20–2.10, 1.70–1.60 (3*m*, CH, CH_2); 1.04 (br. *s*, Me). ^{13}C-NMR: 175.6 (*s*, O–C=O); 166.2 (*s*, CO); 143.8, 135.5 (2*s*, 2 arom. C); 132.7, 129.6, 129.4, 128.1, 127.5, 127.1 (6*d*, 10 arom. CH); 62.9 (*t*, CH_2O) 37.2 (*q*, MeN); 33.3 (*d*, CH); 33.1 (*t*, CH_2); 18.1 (*q*, Me). CI-MS: 329 (7, $[M+NH_4]^+$), 313 (18), 312 (100, $[M+1]^+$), 190 (5), 178 (19). Anal. calc. for $C_{19}H_{21}NO_3$ (311.37): C 73.29, H 6.80, N 4.50; found: C 73.04, H 6.69, N 4.50.

5.5. *3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl 4-Nitrobenzoate* (**13e**). According to *GP 1*, with **2a** (150 mg, 0.72 mmol), dioxane (10 ml), 4-nitrobenzoyl chloride (134 mg, 0.72 mmol), and Et_3N (0.1 ml, 0.72 mmol). Yield: 128 mg (50%) of **13e**. Pale yellow solid. M.p. 98.5–99.0°. IR: 3115*w*, 2970*w*, 2934*w*, 1724*s*, 1651*s*, 1610*m*, 1594*m*, 1527*s*, 1516*s*, 1496*m*, 1458*m*, 1427*m*, 1394*m*, 1350*m*, 1324*m*, 1280*s*, 1154*w*, 1122*s*, 1106*m*, 1080*w*, 1021*m*, 948*w*, 874*w*, 848*w*, 819*w*, 777*w*, 746*w*, 719*s*, 705*m*. ^{1}H-NMR: 8.17, 7.97 (*AA'BB'*, 4 arom. H); 7.27–7.13, 7.10–7.04 (2*m*, 5 arom. H); 4.22 (*t*-like, CH_2O); 3.18 (*s*, MeN); 2.68–2.53, 2.25–2.08, 1.73–1.61 (3*m*, CH, CH_2); 1.05 (*d*, $J = 6.8$, Me). ^{13}C-NMR: 175.5 (*s*, O–C=O); 164.3 (*s*, CO); 150.4, 143.9, 135.4 (3*s*, 3 arom. C); 130.6, 129.7, 127.7, 127.1, 123.3 (5*d*, 9 arom. CH); 64.0 (*t*, CH_2O) 37.4 (*q*, MeN); 33.4 (*d*, CH); 32.9 (*t*, CH_2); 18.1 (*q*, Me). CI-MS: 358 (19), 357 (100, $[M+1]^+$), 328 (7), 327 (37), 240 (17), 223 (43). Anal. calc. for $C_{19}H_{20}N_2O_5$ (356.38): C 64.04, H 5.66, N 7.86; found: C 63.88, H 5.76, N 7.93.

6. *Reaction of* **2a** *with Isocyanates. General Procedure 2* (*GP 2*). To a soln. of **2a** in dry benzene, the corresponding isocyanate was added, and the mixture was heated to reflux for 4 h. The solvent was evaporated, and the crude product was purified by CC.

6.1. *3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl (*tert*-Butyl)carbamate* (**14a**). According to *GP 2*, with **2a** (100 mg, 0.48 mmol), benzene (10 ml), *t*-BuNCO (0.06 ml, 0.51 mmol). Yield: 100 mg (68%) of **14a**. Colorless, viscous oil. IR ($CHCl_3$): 3441*w*, 3007*m*, 2970*m*, 2874*w*, 1719*s*, 1641*s*, 1596*m*, 1508*s*, 1498*s*, 1457*m*, 1431*m*, 1092*m*, 1038*w*, 1001*w*, 921*w*, 839*w*. ^{1}H-NMR: 7.69–7.54, 7.44–7.38 (2*m*, 5 arom. H); 4.70 (br. *s*, NH); 4.22–4.05 (*m*, CH_2O); 3.49 (*s*, MeN); 2.82–2.69, 2.32–2.17, 1.85–1.70 (3*m*, CH, CH_2); 1.52 (*s*, 3 Me); 1.29 (*d*, $J = 6.8$, Me). ^{13}C-NMR: 175.8 (*s*, CO); 154.7 (*s*, O–C(O)–N); 144.0 (*s*, 1 arom. C); 129.6, 127.6, 127.3 (3*d*, 5 arom. CH); 62.1 (*t*, CH_2O); 50.0 (*s*, Me_3C); 37.3 (*q*, MeN); 33.4 (*t*, CH_2); 33.3 (*d*, CH); 28.8 (*q*, Me_3C); 18.0 (*q*, Me). ESI-MS: 329 (27, $[M+Na]^+$), 307 (85, $[M+1]^+$), 208 (47), 190 (100).

6.2. *3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Cyclohexylcarbamate* (**14b**). According to *GP 2*, with **2a** (150 mg, 0.72 mmol), benzene (20 ml), cyclohexyl isocyanate (0.095 ml, 0.75 mmol). Yield: 175 mg (73%) of **14b**. Colorless, viscous oil. IR ($CHCl_3$): 3445*w*, 3023*s*, 2977*s*, 2896*m*, 1709*s*, 1642*m*, 1590*m*, 1521*s*, 1477*m*, 1424*s*, 1047*s*, 929*s*, 877*m*, 850*s*. ^{1}H-NMR: 7.48–7.32, 7.25–7.17 (2*m*, 5 arom. H); 4.49 (br. *d*, NH); 4.03–3.88 (*m*, CH_2O); 3.27 (*s*, MeN); 2.62–2.45 (*m*, CH); 2.08–1.10 (*m*, CH_2, 11 H of cyclohexyl); 1.05 (*d*, $J = 6.8$, Me). ^{13}C-NMR: 175.8 (*s*, CO); 155.5 (*s*, O–C(O)–N); 144.0 (*s*, 1 arom. C); 129.6, 127.6, 127.3 (3*d*, 5 arom. CH); 62.6 (*t*, CH_2O); 49.6 (*d*, CH of cyclohexyl); 37.3 (*q*, MeN); 33.4 (*t*, CH_2); 33.2 (*d*, CH); 33.3, 25.3, 24.6 (3*t*, 5 CH_2 of cyclohexyl); 18.0 (*q*, Me). ESI-MS: 371 (9, $[M+K]^+$), 356 (13), 355 (100, $[M+Na]^+$), 333 (10, $[M+1]^+$), 190 (11), 156 (8).

6.3. *3-Methyl-4-[methyl(phenyl)amino]-4-oxobutyl Phenylcarbamate* (**14c**). According to *GP 2*, with **2a** (150 mg, 0.72 mmol), benzene (20 ml), PhNCO (0.08 ml, 0.72 mmol). Yield: 161 mg (68%) of **14c**. Colorless, viscous oil. IR ($CHCl_3$): 3436*w*, 3023*s*, 2977*s*, 2896*m*, 1732*s*, 1642*m*, 1597*m*, 1521*s*, 1477*m*, 1424*s*,

1047*s*, 929*s*, 877*m*, 850*s*. ^{1}H-NMR: 7.52–7.30, 7.27–7.20, 7.17–7.08 (3*m*, 10 arom. H); 5.20 (br. *s*, NH); 4.20–4.02 (*m*, CH_2O); 3.30 (*s*, MeN); 2.70–2.56, 2.22–2.07, 1.72–1.59 (3*m*, CH, CH_2); 1.13 (*d*, $J = 6.8$, Me). ^{13}C-NMR: 175.8 (*s*, CO); 153.4 (*s*, O–C(O)–N); 143.8, 138.1 (2*s*, 2 arom. C); 129.7, 128.8, 127.7, 127.2, 123.1, 118.4 (6*d*, 10 arom. CH); 63.1 (*t*, CH_2O); 37.3 (*q*, MeN); 33.4 (*t*, CH_2); 33.2 (*d*, CH); 18.1 (*q*, Me). CI-MS: 328 (20), 327 (100, $[M+1]^+$), 208 (11), 191 (10), 190 (81).

7. *X-Ray Crystal-Structure Determination of* **10** (*Table* and *Fig.*)[5]). All measurements were performed on a *Rigaku AFC5R* diffractometer using graphite-monochromated MoK_α radiation (λ 0.71069 Å) and a 12-kW rotating anode generator. The data collection and refinement parameters are given in the *Table*, and a view of the molecule is shown in the *Figure*. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. The structure was solved by direct methods using SHELXS97 [20], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions (d(C–H) = 0.95 Å), and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent

Table. *Crystallographic Data for Compound* **10**

Crystallized from	hexane
Empirical formula	$C_{12}H_{15}NO$
Formula weight	189.26
Crystal color, habit	colorless, prism
Crystal dimensions [mm]	0.28 × 0.48 × 0.48
Temp. [K]	173(1)
Crystal system	orthorhombic
Space group	*Pbca*
Z	8
Reflections for cell determination	25
2θ Range for cell determination [°]	34–40
Unit cell parameters	
a [Å]	20.820(2)
b [Å]	14.230(3)
c [Å]	7.055(2)
V [Å^3]	2090.2(6)
D_x [g cm^{-3}]	1.203
μ(MoK_α) [mm^{-1}]	0.0763
Scan type	$\omega/2\theta$
$2\theta_{(max)}$ [°]	55
Total reflections measured	3338
Symmetry independent reflections	2391
Reflections used [$I > 2\sigma(I)$]	1671
Parameters refined	128
Final R	0.0445
wR	0.0403
Weights: p in $w = [\sigma^2(F_o) + (pF_o)^2]^{-1}$	0.005
Goodness of fit	1.879
Secondary extinction coefficient	$2.0(1) \times 10^{-6}$
Final Δ_{max}/σ	0.0003
$\Delta\rho$ (max; min) [e Å^{-3}]	0.24; −0.19

[5]) CCDC-794912 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

C-atom. Refinement of the structure was carried out on *F* using 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 [21a], and the scattering factors for H-atoms were taken from [22]. Anomalous dispersion effects were included in F_c [23]; the values for f' and f'' were those of [21b]. The values of the mass attenuation coefficients are those of [21c]. All calculations were performed using the teXsan [24] crystallographic software package.

REFERENCES

[1] H. Heimgartner, *Angew. Chem., Int. Ed.* **1991**, *30*, 238; H. Heimgartner, *Isr. J. Chem.* **1986**, *27*, 3; H. Heimgartner, *Wiss. Z. Karl-Marx Univ. Leipzig, Math.-Naturwiss. R.* **1983**, *32*, 365; H. Heimgartner, *Isr. J. Chem.* **1981**, *21*, 151.

[2] J. M. Villalgordo, H. Heimgartner, *Helv. Chim. Acta* **1993**, *76*, 2830.

[3] A. Rahm, A. Linden, B. R. Vincent, H. Heimgartner, M. Mühlstädt, B. Schulze, *Helv. Chim. Acta* **1991**, *74*, 1002.

[4] a) M. K. G. Mekhael, S. Bienz, A. Linden, H. Heimgartner, *Helv. Chim. Acta* **2004**, *87*, 2385; b) M. K. G. Mekhael, R. J. Smith, S. Bienz, A. Linden, H. Heimgartner, *Z. Naturforsch. B* **2002**, *57*, 444.

[5] M. K. G. Mekhael, H. Heimgartner, *Helv. Chim. Acta* **2003**, *86*, 2805.

[6] M. K. G. Mekhael, Ph.D. Thesis, University of Zürich, 2003.

[7] a) K. A. Brun, H. Heimgartner, *Helv. Chim. Acta* **2005**, *88*, 2951; b) F. M. Hilty, K. A. Brun, H. Heimgartner, *Helv. Chim. Acta* **2004**, *87*, 2539.

[8] P. Lesimple, D. C. H. Bigg, *Synthesis* **1991**, 306.

[9] C. Airoldi, S. Merlo, F. Nicotra, *J. Carbohydr. Chem.* **2010**, *29*, 30; B. E. Maryanoff, A. B. Reitz, G. F. Tutwiler, S. J. Benkovic, P. A. Benkovic, S. J. Pilkis, *J. Am. Chem. Soc.* **1984**, *106*, 7851; A. W. Frank, H. Goldwhite, *Crit. Rev. Biochem. Mol. Biol.* **1984**, *16*, 51; L. T. Sniegoski, E. White, *J. Labelled Compd*. **1983**, *20*, 303; T. Ukita, H. Hayatsu, *J. Am. Chem. Soc.* **1962**, *84*, 1879; D. A. Brown, T. Malkin, G. K. Maliphant, *J. Chem. Soc.* **1955**, 1584.

[10] C. K. Johnson, 'ORTEP II', Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.

[11] H. Quast, T. Dietz, *Synthesis* **1995**, 1300.

[12] K. Hatada, Y. Ono, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2517.

[13] H. Saitô, K. Nukada, *Tetrahedron* **1966**, *22*, 3313.

[14] C. Wang, L. Liu, W. Wang, D.-S. Ma, H. Zhang, *Molecules* **2010**, *15*, 1154.

[15] A. Wilk, M. C. Chmielewski, A. Grajkowski, L. R. Phillips, S. L. Beaucage, *J. Org. Chem.* **2002**, *67*, 6430.

[16] B. A. Cunningham, G. L. Schmir, *J. Am. Chem. Soc.* **1966**, *88*, 551.

[17] B. A. Cunningham, G. L. Schmir, *J. Org. Chem.* **1966**, *31*, 3751.

[18] J. M. Concellón, H. Rodríguez-Solla, E. G. Blanco, M. A. Villa-García, N. Alvaredo, S. García-Granda, M. R. Díaz, *Adv. Synth. Catal.* **2009**, *351*, 2185; S. Lauru, N. S. Simpkins, D. Gethin, C. Wilson, *Chem. Commun.* **2008**, 5390; J. M. Concellón, H. Rodríguez-Solla, C. Méjica, E. G. Blanco, *Org. Lett.* **2007**, *9*, 2981; J. M. Concellón, H. Rodríguez-Solla, C. Gómez, *Angew. Chem., Int. Ed.* **2002**, *41*, 1917; P. E. Eaton, K. A. Lukin, *J. Am. Chem. Soc.* **1993**, *115*, 11370.

[19] a) D. K. Baeschlin, G. Fenton, K. Namoto, N. Ostermann, R. Sedrani, F. Sirokin, PCT Int. Appl. 2007, 115821 (*Chem. Abstr.* **2007**, *147*, 448757); b) K. Lee, H.-S. Park, I.-A. Ahn, H.-J. Yoo, J.-Y. Kim, D.-Y. Choi, H.-J. Yim, K.-H. Chung, D.-S. Shim, S.-K. Lee, Y. Kondoh, R. Hirabayashi, S. Honda, H. Kaku, J. Shishikura, H. Ito, T. Kurama, PCT Int. Appl. 2005, 047251 (*Chem. Abstr.* **2005**, *143*, 7980); c) A. Nakagawa, N. Watanabe, I. M. Omori, C. Barbui, A. Cipriani, H. McGuire, R. Churchill, T. A. Furukawa, *CNS Drugs* **2008**, *22*, 587; B. Bonnaud, H. Cousse, G. Mouzin, M. Briley, A. Stenger, F. Fauran, J.-P. Couzinier, *J. Med. Chem.* **1987**, *30*, 318; d) J. A. Bender, M. Ding, R. G. Gentles, P. Hewawasam, US Pat. Appl. Publ. 2008, 146537 (*Chem. Abstr.* **2008**, *149*, 79502); e) P. Hewawasam, Y. Tu, J. A. Bender, Z. Yang, US Pat. Appl. Publ. 2009, 130057 (*Chem. Abstr.* **2009**, *150*, 563866).

[20] G. M. Sheldrick, SHELXS97, Program for the Solution of Crystal Structures, University of Göttingen, Germany, 1997.
[21] a) E. N. Maslen, A. G. Fox, M. A. O'Keefe, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic, Dordrecht, 1992, Vol. C, Table 6.1.1.1, p. 477; b) D. C. Creagh, W. J. McAuley, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic, Dordrecht, 1992, Vol. C, Table 4.2.6.8, p. 219; c) D. C. Creagh, J. H. Hubbell, in 'International Tables for Crystallography', Ed. A. J. C. Wilson, Kluwer Academic, Dordrecht, 1992, Vol. C, Table 4.2.4.3, p. 200.
[22] R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175.
[23] J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781.
[24] teXsan: Single Crystal Structure Analysis Software, Version 1.10, *Molecular Structure Corporation*, The Woodlands, Texas, 1999.

Received September 30, 2010