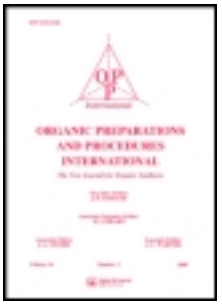


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

SYNTHESIS OF N-(4-CHLOROBUTYL)BUTANAMIDE, A CHLORINATED AMIDE ISOLATED FROM ALOE SABAEA

Matthias D'hooghe [a], Zsolt Szakonyi [a], Ferenc Fülöp [a] & Norbert De Kimpe [a]

[a] Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000, Ghent, BELGIUM Phone: +0032 92645951 Fax: +0032 92645951 E-mail:

[b] Institute of Pharmceutical Chemistry, University of Szeged, POB 121, H-6701, Szeged, HUNGARY

Published online: 11 Feb 2009.

To cite this article: Matthias D'hooghe , Zsolt Szakonyi , Ferenc Flp & Norbert De Kimpe (2003) SYNTHESIS OF N-(4-CHLOROBUTYL)BUTANAMIDE, A CHLORINATED AMIDE ISOLATED FROM ALOE SABAEA , Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 35:5, 501-507, DOI: 10.1080/00304940309355861

To link to this article: http://dx.doi.org/10.1080/00304940309355861

ORGANIC PREPARATIONS AND PROCEDURES INT., 35 (5), 501-507 (2003)

SYNTHESIS OF *N*-(4-CHLOROBUTYL)BUTANAMIDE, A CHLORINATED AMIDE ISOLATED FROM *ALOE SABAEA*

Matthias D'hooghe,[†] Zsolt Szakonyi,[††] Ferenc Fülöp[††] and Norbert De Kimpe*,[†]

[†]*Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University Coupure Links 653, B-9000 Ghent, BELGIUM*

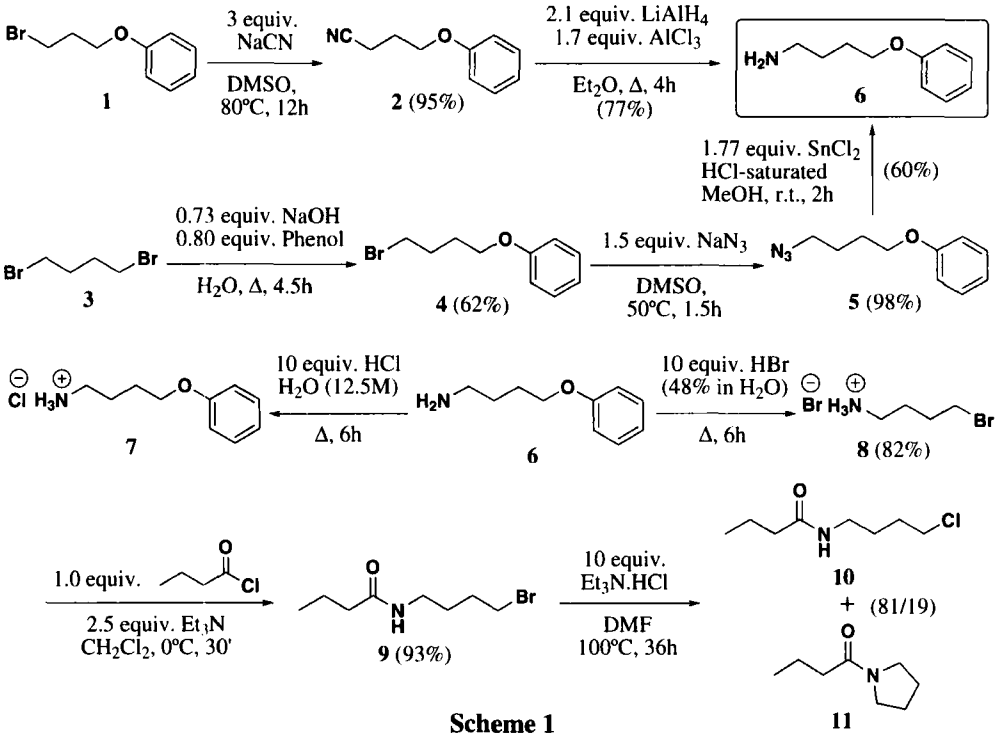
**Tel: +0032 92645951, fax: +0032 92646243, e-mail: norbert.dekimpe@UGent.be*

[††]*Institute of Pharmaceutical Chemistry, University of Szeged H-6701 Szeged, POB 121, HUNGARY*

Aloe species, native to Africa and Arabia, have been used traditionally by local inhabitants as medicinal plants, as well as a source of arrow poison.[1,2] Phytochemical investigation of *Aloe sabaea*, a representative of the Aloeaceae family, has revealed the presence of a chlorinated amide, namely *N*-(4-chlorobutyl)butanamide (**10**).[3] This was the first report of the occurrence of a chlorinated compound in this family. Despite the simple structure of this natural product, no synthesis has been reported. Since halogenated compounds occur in marine organisms, algae, lichens and even in higher plants, the preparation of such types of compounds is of current scientific interest.[4] Therefore, the present report describes a short and efficient synthesis of *N*-(4-chlorobutyl)butanamide (**10**).

Two possible strategies can be suggested, the first consisting in the alkylation of butanamide with a ω,ω'-chlorohalobutane and the second in the condensation of butyryl chloride and 4-chlorobutylamine. Several attempts to alkylate butanamide with 1-bromo-4-chlorobutane using a variety of bases such as sodium hydride, lithium diisopropylamide and *n*-butyllithium in tetrahydrofuran at room temperature or reflux, sometimes in the presence of HMPA, were unsuccessful and the starting materials were recovered. The major difficulty of the second approach is the use of a 4-halobutylamine, since the free amine can undergo cyclization to pyrrolidine or can give rise to cross-linked products. Since an efficient procedure for the synthesis of 4-bromobutylamine hydrobromide (**8**) had been described,[5] two different routes were thus evaluated for the synthesis of the adequate precursor of **8**, namely 4-phenoxybutylamine (**6**) (*Scheme 1*). In the first procedure, 1,4-dibromobutane (**3**) was converted into 1-bromo-4-phenoxybutane (**4**) by reaction with sodium phenoxide in water. Treatment of **4** with sodium azide in DMSO at 50°C afforded 4-phenoxybutyl azide (**5**) in quantitative yield. Reduction of **5** with $SnCl_2$ in HCl-satu-

rated methanol gave the corresponding amine **6**.[6] In the second route, which was based on a similar reaction of 2-(4-bromobutoxy)biphenyl in the literature,[7] the commercially available 1-bromo-3-phenoxypropane (**1**) was treated with NaCN in DMSO, resulting in the corresponding



Scheme 1

nitrile **2** in 95% yield. Reduction of the cyano group of **2** with $LiAlH_4$ in the presence of $AlCl_3$ afforded 4-phenoxybutylamine (**6**) in an overall yield of 73%. The desired 4-bromobutylamine hydrobromide (**8**) was then prepared by reaction of 4-phenoxybutylamine (**6**) with 48% aqueous HBr solution at reflux for 6 hrs. This modified procedure, adapted from Brown and van Gulick,[5] constitutes an improvement of both the experimental handling as well as the yield. When a similar procedure was applied using concentrated HCl instead of HBr, only the hydrochloride salt of 4-phenoxybutylamine (**7**) was formed. This implied that a bromide/chloride exchange would be necessary in a final stage, since the chlorinated analogue of amine **8** could not be prepared this way.

The synthesis of *N*-(4-bromobutyl)butanamide (**9**) was performed by coupling of butyryl chloride with 4-bromobutylamine hydrobromide (**8**) in the presence of Et_3N (*Scheme 1*). To accomplish the natural product synthesis, triethylamine hydrochloride was used for the necessary bromide/chloride substitution, resulting in *N*-(4-chlorobutyl)butanamide (**10**) and 1-butyrylpyrrolidine (**11**) as a side-product. This substituted pyrrolidine **11** has been reported as a major compound identified from pyrolyzed proline Amadori and proline/glucose mixtures,[8,9] and

as a compound in the volatile oil of *Rhododendron* from Sichuan Liangshan.[10] It was observed that the amount of 1-butyrylpyrrolidine (**11**) increased upon prolonged reaction times. After 36 hrs, a ratio of 81/19 (**10/11**) was found, whereas a ratio of 75/25 was found after 60 hrs heating, as determined by GC-MS analysis. Purification of *N*-(4-chlorobutyl)butanamide (**10**) was performed by means of flash chromatography. Based on the spectral data of the synthesized compound and that of the natural product isolated from *Aloe sabaea*,[3] both compounds were judged to be chemically identical, apart from some minor shifts in ppm values due to the use of different deuterated solvents.

In conclusion, the first synthesis of the naturally occurring *N*-(4-chlorobutyl)butanamide (**10**), isolated from *Aloe sabaea*, was developed in an overall yield of 45%.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded at 60 MHz (JEOL PMX 60SI) or at 270 MHz (JEOL JNM-EX 270) with $CDCl_3$ as solvent and tetramethylsilane as internal standard, or D_2O as a solvent and CH_3CN as reference. ^{13}C NMR spectra were recorded at 67.8 MHz (JEOL JNM-EX 270) with $CDCl_3$ or D_2O as solvent. Mass spectra were obtained with a mass spectrometer (VARIAN MAT 112, 70 eV) using a GC-MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas) or a Hewlett-Packard 6890 GC Plus coupled with a HP 5973 mass selective detector (MSD, quadrupole type, 70 eV), equipped with a CIS-4 programmed temperature vaporization (PTV) injector (Gerstel), and a HP5-MS capillary column (30 x 0.25 mm i.d., coating thickness: 0.25µm). Compound purity was assessed by this method. IR spectra were measured with a Perkin Elmer 210 spectrophotometer or a Spectrum One FT-IR. Dichloromethane was dried over calcium hydride. Methanol was dried by distillation over magnesium, while diethyl ether was dried by distillation over sodium benzophenone ketyl. Other solvents were used as received from the supplier.

4-Phenoxybutyl Azide (5).- Although two references dealing with 4-phenoxybutyl azide (**5**) could be found,[11,12] no spectral data have been published. To a solution of commercially available 1-bromo-4-phenoxybutane (**4**) (11.45 g, 50 mmol), prepared from 1,4-dibromobutane (**3**) and aqueous sodium phenoxide in DMSO (100 mL), was added NaN_3 (4.88 g, 1.50 equiv.) in small portions. The suspension was heated at 50°C for 1.5 hrs behind a safety screen. The reaction mixture was then poured into ice-water and extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with water (1 x 25 mL) and dried ($MgSO_4$). After removal of the drying agent and evaporation of the solvent (in tap-water cooled water bath), 4-phenoxybutyl azide (**5**) (9.31 g, 98%) was isolated as a yellow liquid. The crude product was used as such in the next step (purity > 95% as determined by GC).

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.60-1.90 (m, 4H, $CH_2(C\underline{H}_2)_2CH_2$), 3.33 (t, J = 6.4 Hz, 2H, CH_2N_3), 3.96 (t, J = 6.4 Hz, 2H, $C\underline{H}_2OC_6H_5$), 6.80-7.50 (m, 5H, OC_6H_5). **^{13}C NMR** (67.8 MHz, $CDCl_3$): δ 25.8 and 26.5 ($CH_2(\underline{C}H_2)_2CH_2$), 51.2 ($CH_2N_3$), 67.0 ($\underline{C}H_2OC_6H_5$), 114.5 (2 x HC_{ortho}), 120.7 (HC_{para}), 129.5 (2 x HC_{meta}), 158.9 (C-O). **IR** (NaCl, cm^{-1}): ν = 2090 (N_3).

4-Phenoxybutylamine (6). *Procedure 1.*- To a solution of stannous chloride (43.92 g, 1.77 equiv.) in HCl-saturated MeOH (400 mL), was added dropwise at 0°C a solution of 4-phenoxybutyl azide (**5**) (29.50 g, 155 mmol) in MeOH (100 mL). After stirring for 2 hrs at room temperature, the reaction mixture was evaporated and aqueous NaOH (300 mL, 2.5M) was added to the solid residue. Extraction with CH_2Cl_2 (4 x 200 mL), drying ($MgSO_4$), filtration and evaporation of the solvent *in vacuo* yielded 4-phenoxybutylamine (**6**) (15.41 g, 60%) as a yellow liquid.[6]

Procedure 2.- To a suspension of $LiAlH_4$ (1.36 g, 2.10 equiv.) and dry Et_2O (40 mL) was added dropwise at room temperature a solution of $AlCl_3$ (3.87 g, 1.70 equiv.) in dry Et_2O (40 mL). After 5 minutes, a mixture of 4-phenoxybutanenitrile (**2**)[13-15] (2.75 g, 17 mmol), prepared from 1-bromo-3-phenoxypropane (**1**), in dry Et_2O (10 mL) was added. This mixture was heated for 4 hrs under reflux, cooled to 0°C, and neutralized with a solution of 20 mL of 20% NaOH and 30 mL benzene. The solid material was filtered off and washed with benzene (5 x 25 mL). The filtrate was extracted with HCl (30 mL, 6M in H_2O). The aqueous phase was made alkaline with NH_4OH (25% in water) and extracted with benzene (3 x 25 mL) (the extraction was performed in a well-ventilated hood). The combined organic extracts were dried ($MgSO_4$), and after filtration and removal of the solvent *in vacuo*, 4-phenoxybutylamine (**6**) (2.17 g, 77%) was isolated as a yellow liquid. The product appears to be unstable in contact with air, and was therefore used as such in the next step (purity > 95% as determined by GC). Although compound **6** is known in literature,[16-19] no spectral characterization has been reported.

^{1}H NMR (270 MHz, $CDCl_3$): δ 1.33 (br s, 2H, NH_2), 1.55-1.66 and 1.76-1.86 (2 x m, 4H, $CH_2(C\underline{H}_2)_2CH_2$), 2.75 (t, J = 6.93 Hz, 2H, $C\underline{H}_2NH_2$), 3.96 (t, J = 6.44 Hz, 2H, $C\underline{H}_2OC_6H_5$), 6.87-6.95 (m, 3H, 2 x HC_{ortho} and HC_{para}), 7.24-7.35 (m, 2H, 2 x HC_{meta}). **^{13}C NMR** (67.8 MHz, $CDCl_3$): δ 26.68 and 30.35 ($CH_2(\underline{C}H_2)_2CH_2$), 41.94 ($CH_2NH_2$), 67.56 ($\underline{C}H_2OC_6H_5$), 114.45 (2 x HC_{ortho}), 120.54 (HC_{para}), 129.41 (2 x HC_{meta}), 158.97 (CO). **IR** (NaCl, cm^{-1}): ν = 3372 (NH_2). **MS** (70 eV): m/z (%): 165 (M^+, 1), 94 (32), 86 (16), 84 (23), 77 (16), 72 (100), 65 (12), 55 (10), 43 (10).

4-Bromobutylamine Hydrobromide (8).[5]- 4-Phenoxybutylamine (**6**) (29.00 g, 176 mmol) was dissolved in 48% aqueous HBr solution (200 mL, 10 equiv.) and refluxed for 6 hrs. Water was removed from the cooled reaction mixture at 11 mmHg, and the residue was finally dried at high vacuum (0.01 mmHg). The orange crystals were dissolved in hot acetone and precipitated by EtOAc. Filtration of the solid material, washing with diethyl ether and removal of the residual solvent *in vacuo* (0.01 mmHg) yielded 4-bromobutylamine hydrobromide (**8**) (33.61 g, 82%) as light orange crystals. Although this compound is known in the literature,[5,20-26] no spectral data had been reported.

^{1}H NMR (60 MHz, D_2O): δ 1.76-1.79 (m, 2H, $C\underline{H}_2CH_2NH_2$), 1.85-1.88 (m, 2H, $C\underline{H}_2CH_2Br$), 2.98 (br s, 2H, $C\underline{H}_2NH_2$), 3.40-3.50 (m, 2H, CH_2Br). **^{13}C NMR** (67.8 MHz, D_2O): δ 25.8 ($\underline{C}H_2CH_2NH_2$), 29.2 ($\underline{C}H_2CH_2Br$), 34.0 (CH_2NH_2), 39.1 (CH_2Br). **IR** (NaCl, $CDCl_3$, cm^{-1}): ν = 3435 (NH_3^+).

***N*-(4-Bromobutyl)butanamide (9)**.- To an ice cooled solution of butyryl chloride (5.33 g, 50 mmol) and 4-bromobutylamine hydrobromide (**8**) (11.65 g, 1.00 equiv.) in CH_2Cl_2 (50 mL) was added Et_3N (12.65 g, 2.5 equiv.) dropwise and the solution was stirred for 30 minutes at 0°C. The reaction mixture was poured into water and extracted with CH_2Cl_2 (3 x 25 mL). Drying ($MgSO_4$), followed by filtration and evaporation of the solvent *in vacuo* afforded *N*-(4-bromobutyl)butanamide (**9**) which was purified by column chromatography (hexane/EtOAc 1/1), resulting in the pure compound as a light yellow oil (10.33 g, 93%).

^{1}H NMR (270 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.43 Hz, 3H, CH_3), 1.59-1.75 (m, 4H, $C\underline{H}_2CH_2NH$ and $CH_3C\underline{H}_2$), 1.84-1.95 (m, 2H, $C\underline{H}_2CH_2Br$), 2.16 (t, *J* = 7.43 Hz, 2H, CH_2CO), 3.29 (q, *J* = 6.71 Hz, 2H, $C\underline{H}_2NH$), 3.44 (t, *J* = 6.60 Hz, 2H, CH_2Br), 5.75 (br s, 1H, NH). **^{13}C NMR** (67.8 MHz, $CDCl_3$): δ 13.78 (CH_3), 19.35 ($CH_3\underline{C}H_2$), 28.18 ($\underline{C}H_2CH_2NH$), 30.08 ($\underline{C}H_2CH_2Br$), 33.42 (CH_2Br), 38.38 and 38.45 ($\underline{C}H_2CO$ and CH_2NH), 173.96 (CO). **IR** (NaCl, cm^{-1}): ν = 3392 (NH), 1644 and 1551 (CONH). **MS** (70 eV): m/z (%): 221/3 (M^+, 13), 206/8 (14), 193/5 (100), 142 (70), 135/7 (16), 128 (33), 114 (37), 100 (43), 72 (19), 71 (51), 55 (31), 43 (45). Light yellow oil, TLC Rf 0.24 (hexane/EtOAc 1/1).

Anal. Calcd for $C_8H_{16}BrNO$: C 43.26; H 7.26; N 6.31. Found: C 43.29; H 7.30; N 6.28

***N*-(4-Chlorobutyl)butanamide (10)**.- A mixture of *N*-(4-bromobutyl)butanamide (**9**) (5.55 g, 25 mmol) and $Et_3N{\bullet}HCl$ (34.42 g, 10.00 equiv.), dissolved in DMF (100 mL), was heated at 100°C for 36 hrs. The reaction mixture was poured into water, extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic extracts were washed with water (3 x 50 mL). After drying ($MgSO_4$), removal of the drying agent and the solvent, a mixture of *N*-(4-chlorobutyl)butanamide (**10**)[3] (81%) and 1-butyrylpyrrolidine (**11**) (19%) was obtained. The percentage of these compounds in the mixture was determined by GC-MS. Separation and purification was performed by means of column chromatography (hexane/EtOAc 1/1), resulting in the pure *N*-(4-chlorobutyl)butanamide (**10**) as a light yellow oil (3.27 g, 91%) and in 1-butyrylpyrrolidine (**11**) as a light yellow oil (0.57 g, 85%).

^{1}H NMR (270 MHz, $CDCl_3$):[3] δ 0.95 (t, *J* = 7.26 Hz, 3H, CH_3), 1.59-1.73 (m, 4H, $C\underline{H}_2CH_2NH$ and $CH_3C\underline{H}_2$), 1.76-1.86 (m, 2H, $C\underline{H}_2CH_2Cl$), 2.16 (t, *J* = 7.43 Hz, 2H, CH_2CO), 3.29 (q, *J* = 6.49 Hz, 2H, $C\underline{H}_2NH$), 3.56 (t, *J* = 6.27 Hz, 2H, CH_2Cl), 5.85 (br s, 1H, NH). **^{13}C NMR** (67.8 MHz, $CDCl_3$): δ 13.78 (CH_3), 19.34 ($CH_3\underline{C}H_2$), 27.01 ($\underline{C}H_2CH_2NH$), 29.94 ($\underline{C}H_2CH_2Cl$), 38.47 and 38.58 ($\underline{C}H_2CO$ and CH_2NH), 44.69 (CH_2Cl), 173.78 (CO). **IR** (NaCl, cm^{-1}): ν = 3398 (NH), 1644 and 1552 (CONH). **MS** (70 eV): m/z (%): 177/9 (M^+, 13), 162/4 (17), 149/51 (75), 142 (68), 128 (63), 114 (63), 100 (75), 91/3 (27), 87 (22), 72 (27), 71 (100), 58 (18), 55 (59), 43 (88), 41 (41). Light yellow oil, TLC Rf 0.21 (hexane/EtOAc 1/1).

1-Butyrylpyrrolidine (11): **^{1}H NMR** (270 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.09 Hz, 3H, CH_3), 1.57-1.72 and 1.90-1.98 (2 x m, 4H and 2H, $CH_2(C\underline{H}_2)_2CH_2N$ and $CH_3C\underline{H}_2$), 2.24 (t, *J* = 7.59 Hz, CH_2CO), 3.39-3.49 (m, 4H, 2 x CH_2N). **^{13}C NMR** (67.8 MHz, $CDCl_3$): δ 14.05 (CH_3), 18.38 ($CH_3\underline{C}H_2$), 24.44 and 26.15 ($CH_2\underline{C}H_2\underline{C}H_2CH_2N$), 36.75 ($\underline{C}H_2CO$), 45.62 and 46.70 (2 x CH_2N),

171.82 (CO). **IR** (NaCl, cm^{-1}): ν = 1630 (CONH). **MS** (70 eV): m/z (%): 141 (M^+, 64), 126 (23), 113 (85), 112 (22), 98 (38), 85 (30), 71 (44), 70 (100), 56 (22), 55 (34), 43 (61). Light yellow oil, TLC Rf 0.13 (hexane/EtOAc 1/1).

Acknowledgments.- The authors are indebted to the Fund for Scientific Research-Flanders (FWO-Vlaanderen) and to Ghent University for financial support.

REFERENCES

1. R. H. Cheney, *Quart. J. Crude Drug Res.*, **10**, 1523 (1970).

2. H. D. Neuwinger, *"Afrikanische Arzneipflanzen und Jagdgifte: Chemie, Pharmakologie, Toxikologie. Aloeaceae"* p. 1-7, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1998.

3. T. Blitzke, A. Porzel, M. Masaoud and J. Schmidt, *Phytochemistry*, **55**, 979 (2000).

4. G. W. Gribble, *Progress in the Chemistry of Organic Natural Products*, **68**, 1 (1996).

5. R. F. Brown and N. M. van Gulick, *J. Am. Chem. Soc.*, **77**, 1079 (1955).

6. S. N. Maiti, M. P. Singh and R. G. Micetich, *Tetrahedron Lett.*, **27**, 1423 (1986).

7. I. Cervená, J. Holubek, E. Svátek, J. Metys and M. Protiva, *Collect. Czech. Chem. Commun.*, **54**, 1966 (1989).

8. A. Huyghues-Despointes, V. A. Yaylayan and A. Keyhani, *Agr. Food Chem.*, **42**, 2519 (1994).

9. L. Debrauwer, G. Vernin, J. Metzger, A. M. Siouffi and J. L. Larice, *Bull. Soc. Chim. Fr.*, 244 (1991).

10. H. Li, X. Dong, M. Ding and W. Wang, *Yaowu Fenxi Zazhi*, **20,** 78 (2000); *Chem. Abstr.* **133**, 168481 (2000).

11. S. Kim, K. M. Yeon and K. S. Yoon, *Tetrahedron Lett.*, **38,** 3919 (1997).

12. M. P. Doyle, J. L. Whitefleet and R. J. Bosch, *J. Org. Chem.*, **44**, 2923 (1979).

13. J. Schuur and J. Gasteiger, *Anal. Chem.*, **69**, 2398 (1997).

14. J. A. Young, J. G. Grasselli and W. M. Ritchey, *J. Magn. Resonance*, **14**, 194 (1974).

15. J. A. Young, J. G. Grasselli and W. M. Ritchey, *Anal. Chem.*, **45**, 1410 (1973).

16. K. Takeuchi, T. J. Kohn, T. A. True, D. E. Mais, J. H. Wikel, B. G. Utterback, V. L. Wyss and J. A. Jakubowski, *J. Med. Chem.*, **41**, 5362 (1998).

17. C. C. Van de Sande, F. Van Gaever, L. Dhaenens and R. Myngheer, *Org. Mass Spectrom.*, **14**, 191 (1979).

18. A. Gaiffe and C. Launay, *Comptes Rendus des Séances de l'Academie des Sciences, Série C: Sciences Chimiques*, **264**, 1496 (1967).

19. D. G. Doherty, R. Shapira and W. T. Jr. Burnett, *J. Am. Chem. Soc.*, **79**, 5667 (1957).

20. M. E. Hedrera and I. A. Perillo, *J. Heterocycl. Chem.*, **37**, 1431 (2000).

21. W. Wei, T. Tomohiro, M. Kodaka and H. Okuno, *J. Org. Chem.*, **65**, 8979 (2000).

22. F. Ramiandrasoa, M. L. Milat, G. Kunesch and S. Chuilon, *Tetrahedron Lett.*, **30**, 1365 (1989).

23. Y. Hashimoto, H. Iijima, Y. Nozaki and K. Shudo, *Biochemistry*, **25**, 5103 (1986).

24. G. Kunesch, *Tetrahedron Lett.*, **24**, 5211 (1983).

25. D. F. DeTar and N. P. Luthra, *J. Am. Chem. Soc.*, **102**, 4505 (1980).

26. D. L. Klayman, M. M. Grenan and D. P. Jacobus, *J. Med. Chem.*, **12**, 510 (1969).

(Received March 13, 2003; in final form June 19, 2003)

****