which underwent fairly rapid decomposition.

Kinetic Procedures. Each run was carried out by the removal at appropriate time intervals of 5-mL portions from 50 mL of a solution initially ca. 5×10^{-3} M in freshly prepared substrate. Infinity titers (V_∞) were taken after 10 half-lives. For runs in 97 and 80% TFE, the time to V_∞ was reduced by addition of a 5-mL portion to 10 or 5 mL of ethanol and allowing the solution to stand for 4 days before addition of acetone and titration in the usual manner. The titration procedures for runs in acetic and formic acids and the calculation of the first-order solvolytic rate coefficients were as previously described.[5] For experiments in other solvents, the 5-mL portions were added to 15 mL of cooled acetone (solid CO_2), containing Lacmoid (resorcinol blue) as indicator, and titration was against a standardized solution of NaOMe in MeOH.

Acknowledgment. N.HJ.I. thanks the Institut Teknologi MARA (Selangor, Malaysia) for financial support during the conduct of this research. D.N.K. thanks Prof. R. Gompper (Institut für Organische Chemie, Universität München) for hospitality while this manuscript was being prepared.

3,4-Benzodiazocine Derivatives from *N*-Aminonoscapinium Chloride

Helmut Schmidhammer,* Dieter Obendorf, Gerhard-Franz Pirkner, and Tatjana Sams

Institute of Organic and Pharmaceutical Chemistry, University of Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

Received March 8, 1990

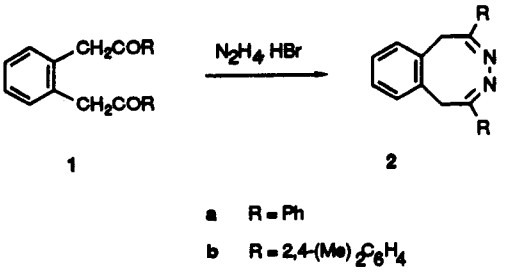
Only a few 3,4-benzodiazocines have been reported in the literature so far.[1] Allinger and Youngdale[2] prepared the first 3,4-benzodiazocine derivatives (1,6-dihydro-3,4-benzodiazocines **2a** and **2b**, respectively) from the corresponding *o*-phenylenediacyl compounds **1a** and **1b**, respectively, by treatment with hydrazine hydrobromide (Scheme I).

Heine et al.[3] treated *o*-phenylenediacetyl chloride (**3**) with 3,3-pentamethylenediaziridine to obtain diaziridine **4**. Isomerization and rearrangement of **4** gave the 3,4-benzodiazocine-2,5-dione **5** (Scheme II).

Reported here is a simple, efficient, and direct route to 3,4-benzodiazocine derivatives from *N*-aminonoscapinium chloride (**7**). N-Amination of noscapine (**6**) with chloramine has been described by Grace.[4] We prepared *N*-aminonoscapinium chloride from noscapine by using either *O*-(2,4-dinitrophenyl)hydroxylamine (DNPH)[5,6] or *O*-(diphenylphosphinyl)hydroxylamine (DPH)[7,8] as N-amination reagent. Hofmann degradation of **7** with diluted NaOH yielded *N*-aminonornarceine (**8**). Heating compound **8** to 140–150 °C gave the yellow lactam **9**, while treatment of **8** with absolute EtOH/HCl afforded the isomeric red enone **10** (Scheme III).

Since both compounds (**9** and **10**) were available only in low yields by the methods described, we sought for a more efficient route for the synthesis of such 3,4-benzodiazocine structures. Instead of amphoteric **8**, we wanted to prepare first the *N*-aminonornarceine ethyl ester (**11**) analogously to the formation of *N*-benzylnornarceine ethyl ester from *N*-benzylnoscapinium bromide with EtOH/Et_3N.[9] Refluxing **7** in EtOH/Et_3N afforded the desired

Scheme I

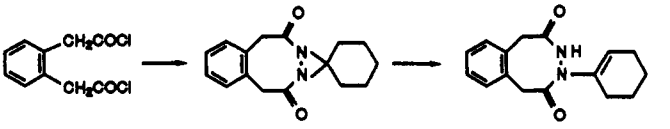


1 2

a R = Ph

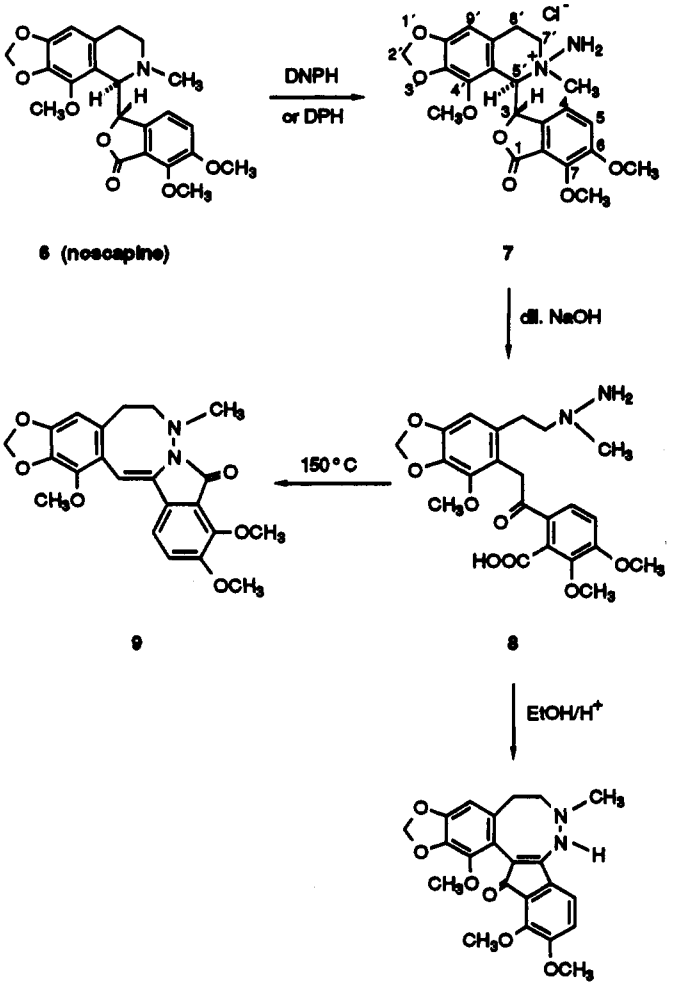
b R = 2,4-(Me)$_2$C$_6$H$_3$

Scheme II



3 4 5

Scheme III



(1) Katoh, A.; Nishio, T.; Kashima, C. *Heterocycles* **1987**, *26*, 2223.
(2) Allinger, N. L.; Youngdale, G. A. *J. Org. Chem.* **1960**, *25*, 1509.
(3) Heine, H. W.; Baclawski, L. M.; Bonser, S. M.; Wachob, G. D. *J. Org. Chem.* **1976**, *41*, 3229.
(4) W. R. Grace & Co., Brit. Pat. 883,741 (1961); *Chem. Abstr.* **1962**, *57*, 3448 f.
(5) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.
(6) Sheradsky, T. *J. Heterocycl. Chem.* **1967**, *4*, 413.
(7) Harger, M. J. P. *J. Chem. Soc., Chem. Commun.* **1979**, 768.
(8) Klötzer, W.; Baldinger, H.; Karpitschka, E. M.; Knoflach, J. *Synthesis* **1982**, 592.
(9) Klötzer, W.; Teitel, S.; Brossi, A. *Monatsh. Chem.* **1972**, *103*, 1210.
(10) A diastereomeric mixture was obtained: TLC (AcOEt/EtOH 3:2): R_f 0.2 and 0.1, respectively; ^{1}H NMR showed two sets of signals: intensity I/II 2:1 (Table I).

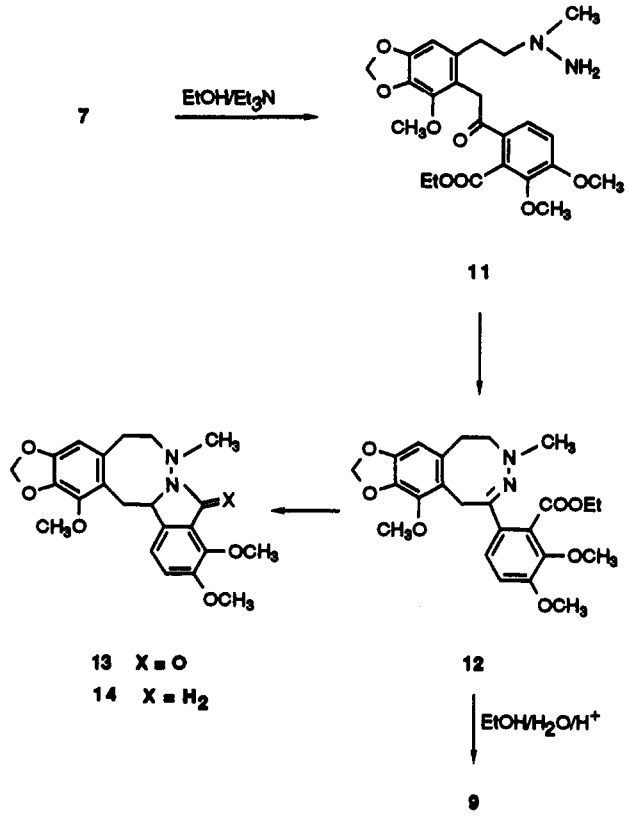
0022-3263/91/1956-3457$02.50/0

Table I. ^{1}H NMR Chemical Shifts (300 MHz, Me_2SO-d_6; δ) for Compound 7[a]

I	II	
7.64 d (J = 8 Hz)	7.97 d (J = 8 Hz)	2 arom H (C-4 H, C-5 H)
7.32 s	6.25 s	2 H (NH_2)
6.76 s	6.42 s	1 H (C-3 H)
6.61 s	6.58 s	1 arom H (C-9′ H)
5.93 d (J = 0.8 Hz)	5.90 d (J = 0.8 Hz)	1 H (C-2′ H)
5.91 d (J = 0.8 Hz)	5.87 d (J = 0.8 Hz)	1 H (C-2′ H)
5.85 s	5.56 s	1 H (C-5′ H)
3.88 s	3.89 s	3 H (CH_3O)
3.78 s	3.76 s	3 H (CH_3O)
3.39 s	3.98 s	3 H (CH_3N^+)
3.21[b] s	3.15[b] s	3 H (C-4′ CH_3O)

[a] The signals of the comparable protons of the two diastereoisomers (I, II) show by integration a ratio of 2:1 (I:II). [b] Upfield shift due to shielding of the C-4′ CH_3O group by the aromatic ring in the favoured conformation of quarternary 1-benzyltetrahydroisoquinolinium salts.[13]

Scheme IV



benzodiazocine **12** directly in 72% yield, while compound **11** could not be isolated. Hydrolysis of **12** in EtOH/dilute HCl at room temperature yielded lactam **9**, whereas isomeric enone **10** was detected in the reaction mixture only in traces (TLC).

The 2,3-double bond of **12** was saturated by catalytic hydrogenation over Pt/C in EtOH to give lactam **13** in 60% yield. LAH reduction of the lactam function in Et_2O afforded isoindole **14** in 88% yield. No IR lactam carbonyl absorption was observed with compound **14**, whereas lactam **13** exhibited IR carbonyl lactam absorption at 1680 cm^{-1}.

Since the isoindoles **13** and **14** have similar structural features in comparison to a series of indolo[2,1-*a*]isoquinolines, which were found to possess cytostatic effects,[11] these compounds were tested for cytostatic effects on MDA-MB 231 mammary tumor cells. Up to concentrations of 10^{-5} M no cytostatic effect was observed.[12]

Experimental Section

Melting points were determined on a Kofler melting point microscope and are uncorrected. IR spectra (in cm^{-1}) were obtained with a Beckman Accu Lab 2 apparatus. ^{1}H NMR spectra were recorded on a Bruker AM 300 (300 MHz) or a JEOL JNM-PMX 60 (60 MHz) spectrometer (δ in ppm, tetramethylsilane as internal reference). Electron-ionization (EI-MS) and chemical-ionization (CI-MS) mass spectra were recorded on a Finnigan MAT 44 S mass spectrometer. Thin-layer chromatography (TLC) was performed on Polygram Sil G/UV254 plates (4 × 8 cm) with visualization by UV light and iodine stain (mobile phase CH_2Cl_2/MeOH/concentrated NH_4OH 90/9/0.5 unless otherwise stated). Elemental analyses were performed at the Analytical Department of Hoffmann-La Roche, Inc., Basle, Switzerland.

***N*-Aminonoscapinium Chloride (7).[4] Method A.** DNPH (9.0 g, 45 mmol) was added to a cooled (ca. 10 °C) solution of **6** (18.0 g, 43.5 mmol) in 40 mL of $CHCl_3$ in three portions while stirring. The resulting solution was kept at room temperature for 3 h, the solvent was then evaporated, and the residue was partitioned between 180 mL of 2 N HCl and 80 mL of AcOEt. The organic layer was extracted with H_2O (3 × 10 mL), and the combined aqueous phases were washed with AcOEt (2 × 20 mL) and evaporated. The residue was dissolved in 50 mL of EtOH and evaporated (this operation was repeated twice). The resulting colorless foam (20.3 g) was crystallized from EtOH/Et_2O to give 17.5 g (87%; mp 222–229 °C) of **7**.[10] For analysis, a small sample was recrystallized from EtOH/Et_2O:[10] mp 227–230 °C (lit.[4] mp 230 °C). IR (KBr): 3400 (NH_2), 1750 (CO). Anal. Calcd for $C_{22}H_{25}N_2O_7Cl$: C, 56.84; H, 5.42; N, 6.03; Cl, 7.63. Found: C, 56.50; H, 5.30 N, 5.94; Cl, 7.57.

Method B. DPH (2.37 g, 10.2 mmol) was added to a cooled (0–5 °C) solution of **6** (4.13 g, 10 mmol) in 80 mL of $CHCl_3$ in five portions while stirring. The resulting mixture was stirred at 0–5 °C for 3 h and then at room temperature for an additional hour during which dissolution took place. After evaporation, the crystalline residue was dissolved in 100 mL of H_2O, and then 2.5 mL of 4 N HCl was added. The colorless precipitate (diphenylphosphonic acid) was filtered off, and filtrate was evaporated to give an amorphous residue, which was dried in an exsiccator over KOH for 20 h. The dried residue was recrystallized from anhydrous EtOH/anhydrous Et_2O to yield 3.59 g (77%) of **7** (mp 227–230 °C). This material was identical with material obtained by method A by TLC, mixed melting point, IR, and ^{1}H NMR.

***N*-Aminonornarceine (8).** NaOH (2 N, 4.8 mL) was added dropwise to a stirred solution of **7** (1.5 g, 3.19 mmol) in 15 mL of H_2O within 5 min at room temperature. The now yellowish solution was stirred for another 45 min at room temperature, and then the pH was adjusted to ca. 4 with glacial AcOH. After cooling, the brownish precipitate was collected, washed with H_2O, and dried to give 1.22 g (86%) of **8** (mp 138–145 °C). A portion of this material was recrystallized from EtOH/H_2O for analysis: mp 142–145 °C. IR (KBr): 3320 (OH, NH_2), 1675 (CO), 1570 (CO_2H). ^{1}H NMR (60 MHz, Me_2SO-d_6): δ 7.51 (d, 1 arom H, J = 8 Hz), 7.02 (d, 1 arom H, J = 8 Hz), 6.48 (s, 1 arom H), 5.97 (s, 2 H, OCH_2O), 3.96, 3.92, and 3.83 (3 s, 9 H, 3 CH_3O), 3.52 (s, 2 H, $ArCH_2O$), 2.85 (m, 4 H), 2.65 (s, 3 H, CH_3N). Anal. Calcd for $C_{22}H_{26}N_2O_8 \cdot 1.2H_2O$: C, 56.45; H, 6.12; N, 5.99. Found: C, 56.13; H, 6.38; N, 6.17.

6,7,8,9-Tetrahydro-3,4,14-trimethoxy-7-methyl-[1,3]dioxolo[4′,5′:4,5][3,4]benzodiazocino[2,3-*a*]isoindol-5-one (9). A mixture of **8** (220 mg, 0.43 mmol) and 3 mL of liquid paraffin was kept at 140–150 °C (bath temperature) until gas evolution ceased (ca. 30 min). After cooling, liquid paraffin was removed with petroleum ether (bp 40–60 °C), and the yellow-brown residue

(11) Ambros, R.; Schneider, M. R.; von Angerer, S. *J. Med. Chem.* **1990**, *33*, 153.

(12) The tests on cytostatic effects were performed by Prof. Dr. E. von Angerer, Institute of Pharmacy, University of Regensburg, Federal Republic of Germany.

(13) Schmidhammer, H.; Eigenmann, R.; Klötzer, W. *Eur. J. Med. Chem.-Chim. Ther.* **1980**, *15*, 151.

was treated with boiling EtOH (5 mL) to yield 96 mg (55%) of raw **9** (mp 230–238 °C dec). Pure **9** (yellow) was obtained by recrystallization from glacial AcOH: mp 238–241 °C dec. IR (KBr): 1690 (CO). ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 7.75 (d, 1 arom H, J = 8 Hz), 7.28 (d, 1 arom H, J = 8 Hz), 6.60 (s, 1 arom H), 6.45 (s, 1 olef H), 6.00 (s, 2 H, OCH_2O), 3.99, 3.91, and 3.87 (3 s, 9 H, 3 CH_3O), 2.81 (s, 3 H, CH_3N) 2.60 (m, 4 H). Anal. Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.06; H, 5.37; N, 6.72.

Compound **9** was also obtained from **12**: A solution of **12** (200 mg, 0.44 mmol), 6 mL of EtOH, and 2 mL of 2 N HCl was kept at room temperature for 72 h, and then it was poured on ice-cooled dilute NH_4OH (20 mL). After extractions with CH_2Cl_2 (2 × 10 mL), the combined organic layers were washed with H_2O (2 × 10 mL), dried, and evaporated to give 172 mg of a red-brown oil which was crystallized from MeOH to yield 117 mg (65%; mp 233–237 °C dec). This material was identical with material obtained by the procedure described above by TLC, mixed melting point, IR, and ^{1}H NMR.

5,6,7,8-Tetrahydro-1,2,13-trimethoxy-6-methyl-[1,3]dioxolo[4′,5′:4,5]benzo[*f*]indeno[1,2-*c*]-1,2-diazocin-14-one (10). A solution of **8** (1.0 g, 2.15 mmol) in 20 mL of anhydrous EtOH/HCl was refluxed for 4 h and then poured on 100 mL of ice-cooled saturated $NaHCO_3$ solution. The red precipitate was collected and recrystallized from EtOH to give 137 mg (16%) of pure **10**: mp 277–279 °C dec. IR (KBr): 1645 (CO). ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 8.60 (br s, 1 H, NH), 7.31 (d, 1 arom H, J = 8 Hz), 6.93 (d, 1 arom H, J = 8 Hz), 6.49 (s, 1 arom H), 5.96 (s, 2 H, OCH_2O), 3.87, 3.83, and 3.80 (3 s, 9 H, 3 CH_3O), 2.73 (m, 4 H), 2.57 (s, 3 H, CH_3N). Anal. Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.05; H, 5.51; N, 6.81.

2,3-Dimethoxy-6-[1,4,5,6-tetrahydro-11-methoxy-4-methyl-[1,3]dioxolo[4′,5′:4,5][3,4]benzodiazocin-2-yl]benzoic Acid Ethyl Ester (12). A solution of **7** (17.5 g, 42.3 mmol) in 80 mL of EtOH and 10.5 mL of triethylamine was refluxed for 17 h. Then the volume of the resulting red solution was reduced in vacuo by ca. two-thirds. During this operation, crystallization took place. After cooling, 12.3 g (73%; mp 140–146 °C) of **12** was obtained. For analysis, a small sample was recrystallized from EtOH: mp 147–150 °C. IR (KBr): 1720 (ester), 1685 (C=N). ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.25 (d, 1 arom H. J = 8 Hz), 6.86 (d, 1 arom H, J = 8 Hz), 6.21 (s, 1 arom H), 5.78 (s, 2 H, OCH_2O), 4.18 (q, 2 H, CH_2CH_3, J = 7 Hz), 4.02 (s, 2 H, $ArCH_2$), 3.84 (s, 6 H, 2 CH_3O), 3.58 (s, 3 H, CH_3O), 2.93 (s, 4 H), 2.78 (s, 3 H, CH_3N), 1.26 (t, 3 H, CH_3CH_2, J = 7 Hz). CI-MS: m/z 457 (M^+ + 1). Anal. Calcd for $C_{24}H_{28}N_2O_7$: C, 63.15; H, 6.18; N, 6.14. Found: C, 62.92; H, 6.32; N, 6.17.

6,7,8,9,15,15a-Hexahydro-3,4,14-trimethoxy-7-methyl-[1,3]dioxolo[4′,5′:4,5][3,4]benzodiazocino[2,3-*a*]isoindol-5-one (13). A mixture of **12** (3.0 g, 6.57 mmol), 900 mg of 10% Pt/C, and 150 mL of EtOH was hydrogenated at 40 °C and 50 psi for 24 h. The catalyst was filtered off, the filtrate was evaporated, and the residue (colorless foam) was crystallized from EtOH (yield 1.6 g; 59%). An analytical sample was obtained by recrystallization from EtOH: mp 165 °C. IR (KBr): 1680 (CO). ^{1}H NMR (60 MHz, $CDCl_3$): δ 7.02 (dd, 2 arom H, J = 8, 8 Hz), 6.25 (s, 1 arom H), 5.76 (s, 2 H, OCH_2O), 4.28 (m, 1 H, ArCH), 3.92 (s, 3 H, CH_3O), 3.83 (s, 6 H, 2 CH_3O), 3.27 (m, 2 H), 2.91 (s, 3 H, CH_3N), 2.65 (m, 4 H). CI-MS: m/z 413 (M^+ + 1). Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.07; H, 5.98; N, 6.78.

6,7,8,9,15,15a-Hexahydro-3,4,14-trimethoxy-7-methyl-[1,3]dioxolo[4′,5′:4,5][3,4]benzodiazocino [2,3-*a*]isoindole (14). Compound **13** (500 mg; 1.22 mmol) was transferred with anhydrous Et_2O from a Soxhlet apparatus to a stirred and refluxing mixture of 100 mg of LAH and 15 mL of Et_2O under N_2 within 4 h. The mixture was stirred under reflux for an additional hour, and then excess LAH was destroyed with 30 mL of saturated Na_2SO_4 solution. The Et_2O phase was separated after addition of 10 mL of H_2O, the aqueous layer was extracted with Et_2O (2 × 10 mL), and the combined organic layers were dried and evaporated. The resulting slightly brown foam was crystallized from EtOH to yield 425 mg (88%) of **14** (mp 148–152 °C). A small sample was recrystallized from EtOH: mp 152–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00 (d, 1 arom H, J = 8 Hz), 6.82 (d, 1 arom H, J = 8 Hz), 6.42 (s, 1 arom H), 5.88 and 5.86 (2 d, 2 H, OCH_2O, J = 0.8 Hz), 4.22 (m, 1 H, ArCH), 4.16 (s, 2 H, $ArCH_2N$), 3.86 (s, 3 H, CH_3O), 3.80 (s, 6 H, 2 CH_3O), 2.28 (s, 3 H, CH_3N). EI-MS: m/z 398 (M^+). Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 6.11; H, 6.58; N, 6.94.

Acknowledgment. In grateful remembrance we are mindful of the initiation of this work by the late Prof. Dr. W. Klötzer. We are indebted to Prof. Dr. E. von Angerer (Institute of Pharmacy, University of Regensburg, Federal Republic of Germany) for evaluation of the cytostatic effects. We want to thank Prof. Dr. K.-H. Ongania for performing the mass spectra and Mag. H.-P. Kählig for recording the 300-MHz spectra (both from the Institute of Organic and Pharmaceutivcal Chemistry, University of Innsbruck). We further thank the Analytical Department of Hoffmann-La Roche & Co., Inc., Basle, Switzerland, for elemental analyses.

Registry No. **6**, 128-62-1; **7**, 103937-31-1; **8**, 129917-22-2; **9**, 129917-23-3; **10**, 129917-24-4; **11**, 129942-14-9; **12**, 129917-25-5; **13**, 129917-26-6; **14**, 129917-27-7; DNPH, 17508-17-7; DPH, 72804-96-7.

Mechanistic Implications of Pyrophosphate Formation in the Oxidation of *O*,*S*-Dimethyl Phosphoramidothioate

D. Ralph Leslie*

Materials Research Laboratory, DSTO, P.O. Box 50, Ascot Vale, Vic. 3032, Australia

William T. Beaudry, Linda L. Szafraniec, and Dennis K. Rohrbaugh

U.S. Army Chemical Research, Development and Engineering Center, Aberdeen Proving Ground, Maryland 21010-5423

Received October 1, 1990

The chemical oxidation of phosphorothiolates **1** has been the subject of a number of studies that have emphasized the identification of intermediates in the reaction sequence.[1-6] Interest in the process was initiated by the desire to identify the potent in vivo phosphorylating species that are proposed to form via oxidative bioactivation of thiophosphorus insecticides. Chemical oxidation (Scheme I) is believed to involve the initial formation of a reactive *S*-oxide (**2**), which rearranges to a phosphinyloxy sulfenate (**3**), possibly via a phosphoranoxide.[2,3] Subsequent oxidation of **3** ultimately produces the phosphinyloxy sulfonate **4**, which is stable in the absence of nucleophilic species.

When the oxidation is performed in the absence of an added nucleophilic species, in addition to **4**, a significant fraction of the symmetrical pyrophosphate **5** is observed.[3,6] Formation of **5** is assumed to result from the reaction of one of the species **2**–**4** with the free acid **6** (eq 1), in turn formed by hydrolysis of **2**, **3**, or **4** by adventitious water in nominally dry solvents.[7] While investigating the oxi-

(1) Bellet, E. M.; Casida, J. E. *J. Agric. Food Chem.* **1974**, *22*, 207–211.
(2) Segall, Y.; Casida, J. E. In *Phosphorus Chemistry*; Quin, L. D., Verkade, J., Eds.; ACS Symposium Series 171, American Chemical Society: Washington D.C., 1981; pp 337–340.
(3) Segall, Y.; Casida, J. E. *Tetrahedron Lett.* **1982**, *23*, 139–142.
(4) Segall, Y.; Casida, J. E. *Phosphorus Sulfur* **1983**, *18*, 209–212.
(5) Thompson, C. M.; Castellino, S.; Fukuto, T. R. *J. Org. Chem.* **1984**, *49*, 1696–1699.
(6) Bielawski, J.; Casida, J. E. *J. Agric. Food Chem.* **1988**, *36*, 610–615.
(7) Mixed anhydride **4** has been described as an exclusively sulfonating agent (refs 2 and 4) which could not therefore form **5** by reaction with **6**, or as both a phosphorylating and sulfonating agent (ref 6). In dry methanol, **4** is exclusively phosphorylating (Dabkowski, W.; Michalski, J.; Radziejewski, C.; Skrzypczynski, Z. *Chem. Ber.* **1982**, *115*, 1636–1643).

0022-3263/91/1956-3459$02.50/0