144. Synthesis of Benzazepine Analogues of Noscapine

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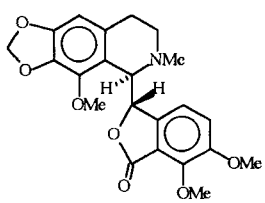
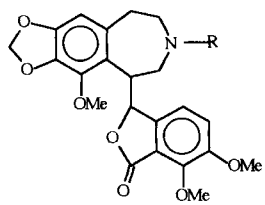
The synthesis of benzazepine analogues of the opium alkaloid noscapine (**1**) is described. The benzazepines **2** and **3** were prepared starting from nornarceine ethyl ester (**4**; readily available from **1**) in several steps. X-Ray analysis of compound **2** revealed that it is not a diastereoisomer mixture but a racemate of the *threo*-form and thus has the same configuration as **1**.

Introduction. – The opium alkaloid noscapine (**1**) is widely used as cough depressant. Its antitussive effect is similar to that of codeine, while it does not show respiratory depression, constipation, and dependence liability. Recently, high-affinity binding sites were found for **1** in guinea-pig brain. These binding sites are supposedly different from those previously described for antitussives such as codeine, other opioids, or dextromethorphan [1]. Since it was also demonstrated that **1** shows efficacy against liver failure in rats, it could be effective in the treatment of hepatopathy [2].



Noscapine (**1**)



2 R = Me

3 R = H

In view of the pharmacological properties of the isoquinoline alkaloid noscapine (**1**), it was of interest to prepare its 3-benzazepine analogues, *e.g.* **2** and **3**, and to evaluate these derivatives pharmacologically.

Chemistry. – Since treatment of nornarceine ethyl ester hydrochloride (**4** · HCl; readily available from noscapine (**1**) [3]) with formalin in EtOH did not afford the *Mannich* product **5** but the *Pictet-Spengler* product **6** (*Scheme 1*), position 7 of the benzodioxole ring had to be blocked reversibly.

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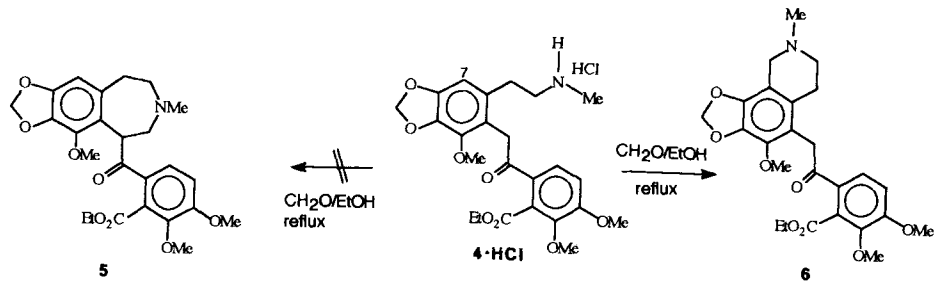
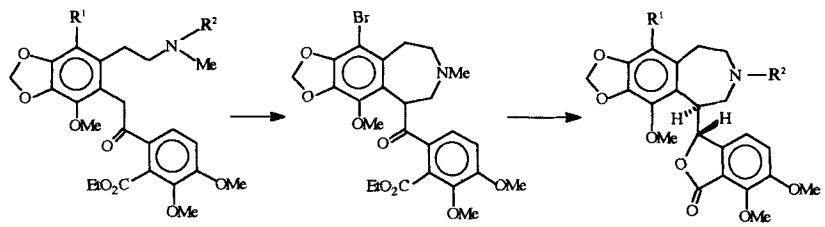
Scheme 1



As 7-protecting group of **4**, we chose the Br-substituent. Prior to bromination, the N-atom of **4** had to be protected. This was accomplished with 2,2,2-trichloroethyl chloroformate [4] yielding carbamate **7**. Bromination was then carried out with Br_2 in $CCl_4/CHCl_3$ and $NaHCO_3$ at 0° (→**8**) and deprotection at the N-atom performed reductively with Zn in AcOH to give 7-brominated nornaceine ethyl ester **9** (*Scheme 2*). Later, the synthesis of **9** was substantially improved. *N*-Benzylnornarceine ethyl ester (**10**; the precursor in the synthesis of **4** [3]) was debenzylated with vinyl chloroformate [5] (→carbamate **11**), and bromination with Br_2 in $CCl_4/CHCl_3$ and $NaHCO_3$ yielded tribrominated carbamate **12**. The latter was cleaved by refluxing in EtOH to give **9** (*Scheme 2*).

Scheme 2



4 $R^1 = R^2 = H$
7 $R^1 = H$, $R^2 = CO_2CH_2CCl_3$
8 $R^1 = Br$, $R^2 = CO_2CH_2CCl_3$
9 $R^1 = Br$, $R^2 = H$
10 $R^1 = H$, $R^2 = PhCH_2$
11 $R^1 = H$, $R^2 = CO_2CH{=}CH_2$
12 $R^1 = Br$, $R^2 = CO_2CHBrCH_2Br$

14 $R^1 = Br$, $R^2 = Me$
2 $R^1 = H$, $R^2 = Me$
15 $R^1 = H$, $R^2 = CO_2CH{=}CH_2$
16 $R^1 = H$, $R^2 = CO_2CHClCH_3$
3 $R^1 = R^2 = H$

Benzazepine **13** was then obtained by *Mannich* reaction of **9**. Subsequent reduction with $NaBH_4$ yielded phthalide **14** and catalytic hydrogenation over Pd/C the desired benzazepine **2** (*Scheme 2*). Since neither TLC nor ^{1}H-NMR showed any sign of a diastereoisomer mixture for **14** and **2**, an X-ray analysis of **2** was performed. This analysis revealed that **2** does not consist of a diastereoisomer mixture but represents the racemate of the *threo*-form and thus has the same configuration as noscapine (**1**; see *Fig.*). Thus, reduction of **13** with $NaBH_4$ was completely stereospecific.

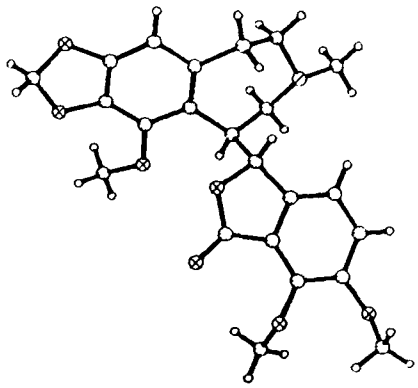


Figure. *X-Ray diffraction structure of* **2**

Benzazepine **2** was *N*-demethylated with vinyl chloroformate [5] to give vinyl carbamate **15**. The latter underwent HCl addition in CH_2Cl_2 to afford 1-chloroethyl carbamate **16**. After refluxing **16** in MeOH, benzazepine **3** was isolated (*Scheme 2*).

Compounds **2** and **3** are presently being evaluated pharmacologically for antitussive activity. The results of this study will be published elsewhere.

Experimental Part

General. See [6]. TLC: *Polygram-Sil-G/UV254* plates (4 × 8 cm); mobile phase $CHCl_3$/MeOH/conc. NH_4OH soln. 90:9:1 unless otherwise stated; visualization by UV light and I_2 stain. ^{1}H-NMR Spectra: *Jeol-JNM-PMX*-60 (60 MHz), *Varian-Gemini-200* (200 MHz), *Bruker-AC-250* (250 MHz), or *Bruker-AM-400* (400 MHz) spectrometer; δ in ppm, Me_4Si as internal reference, J in Hz. Electron-ionization (EI) MS: *Finnigan-MAT-44-S* mass spectrometer. Elemental analyses were performed at the Analytical Department of *F. Hoffmann-La Roche Ltd.*, Basel, Switzerland.

Ethyl 2,3-Dimethoxy-6-{[6-methoxy-2-methyl-7,8-(methylenedioxy)isoquinolin-5-yl]acetyl}benzoate Hydrochloride (**6**·HCl). A soln. of **4**·HCl (6.0 g, 12.1 mmol) and 37% formalin (3.5 ml, 43.6 mmol) in EtOH (18 ml) was refluxed for 3 h. Crude **6**·HCl (5.4 g) was obtained after cooling the mixture in the refrigerator overnight. Recrystallization from H_2O afforded 3.31 g (54%) of pure **6**·HCl. M.p. 224–226°. IR (KBr): 3440 (NH^+), 1720 (ester), 1670 (CO). ^{1}H-NMR (60 MHz, (D_6)DMSO): 8.02 (*d*, J = 8, 1 arom. H); 7.18 (*d*, J = 8, 1 arom. H); 6.03 (*s*, OCH_2O); 3.90, 3.72, 3.66 (3 *s*, 3 MeO); 2.84 (*s*, MeN^+); 1.18 (*t*, J = 7, Me). EI-MS: 471 (M^+).

The salt **6**·HCl was converted into the free base **6** in the usual way. M.p. 157–158°. Anal. calc. for $C_{25}H_{29}NO_8$: C 63.68, H 6.20, N 2.97; found: C 63.33, H 6.29, N 2.95.

N-*(2,2,2-Trichloroethoxycarbonyl)nornarceine Ethyl Ester* (= *Ethyl 2,3-Dimethoxy-6-{{4-methoxy-6-{2-[*N*-methyl-*N*-(2,2,2-trichloroethoxycarbonyl)amino]ethyl}-1,3-benzodioxol-5-yl}acetyl}benzoate;* **7**). A mixture of **4**·HCl (10.0 g, 20.2 mmol), $KHCO_3$ (6.0 g, 59.9 mmol), 2,2,2-trichloroethyl chloroformate (3.4 ml, 24.1 mmol), and EtOH-free $CHCl_3$ (120 ml) was stirred under reflux for 5 h. The inorg. material was filtered off and the filtrate washed subsequently with 1N HCl, H_2O, and brine, dried, and evaporated to give 12.4 g of a yellowish oil which was crystallized from $(i\text{-}Pr)_2O$: 10.4 g (81%) of **7**. An anal sample was obtained by recrystallization from EtOH. M.p. 108–110°. IR (KBr): 1720 (ester, carbamate), 1675 (CO). ^{1}H-NMR (400 MHz, $CDCl_3$; 2 rotamers): 7.89, 7.83 (2 *d*, J = 8.6, 8.6, 1 arom. H); 6.99, 6.98 (2 *d*, J = 8.6, 8.6, 1 arom. H); 6.44, 6.43 (2 *s*, 1 arom. H); 5.89 (*s*, OCH_2O); 4.71, 4.70 (2 *s*, CH_2CCl_3); 4.37 (*q*, J = 7.0, $MeCH_2O$); 4.30, 4.22 (2 *s*, CH_2CO); 3.96 (*s*, MeO); 3.86 (*s*, 2 MeO); 2.91, 2.87 (2 *s*, MeN); 1.31 (*t*, J = 7, $MeCH_2O$). EI-MS: 634 (M^+). Anal. calc. for $C_{27}H_{30}Cl_3NO_{10}$ (634.90): C 51.08, H 4.76, Cl 16.75, N 2.21; found: C 51.4, H 4.90, Cl 16.79, N 2.14.

*Ethyl 6-{{7-Bromo-4-methoxy-6-{2-[*N*-methyl-*N*-(2,2,2-trichloroethoxycarbonyl)amino]ethyl}-1,3-benzodioxol-5-yl}acetyl}-2,3-dimethoxybenzoate* (**8**). To a cooled (−10°) and stirred mixture of **7** (8.4 g, 13.2 mmol),

$NaHCO_3$ (30.0 g, 357.1 mmol), and EtOH-free $CHCl_3$ (400 ml) was added slowly 0.1M Br_2 in CCl_4 (133 ml, 13.3 mmol) while the temp. was kept below 0°. The inorg. material was filtered off 15 min after the addition of the Br_2 soln. was completed. The filtrate was evaporated and the resulting yellowish oily residue crystallized from EtOH: 8.85 g (94%) of **8**. A small sample was recrystallized from EtOH for analysis. M.p. 141–144°. IR (KBr): 1720 (ester, carbamate), 1675 (CO). ^{1}H-NMR (200 MHz, $CDCl_3$; 2 rotamers): 7.96, 7.80 (2 *d*, *J* = 8.6, 8.6, 1 arom. H); 7.00, 6.98 (2 *d*, *J* = 8.6, 8.6, 1 arom. H); 5.99 (*s*, OCH_2O); 4.70, 4.66 (2 *s*, CH_2CCl_3); 4.42, 4.27 (2 *s*, CH_2CO); 4.36 (*q*, *J* = 7.1, MeCH_2O); 3.97 (*s*, MeO); 3.87 (*s*, MeO); 3.85 (*s*, MeO); 3.00, 2.97 (2 *s*, MeN); 1.30 (*t*, *J* = 7.1, *Me*CH_2O). EI-MS: 713 (M^+). Anal. calc. for $C_{27}H_{29}BrCl_3NO_{10}$: C 45.43, H 4.10, Br 11.19, Cl 14.90, N 1.96; found: C 45.83, H 4.21, Br 11.08, Cl 14.75, N 1.99.

Ethyl 6-{{7-Bromo-4-methoxy-6-[2-(methylamino)ethyl]-1,3-benzodioxol-5-yl}acetyl}-2,3-dimethoxybenzoate (**9**·HBr). a) *From* **8**. To a cooled (ice/H_2O) and stirred soln. of **8** (8.4 g, 11.8 mmol) in glacial AcOH (100 ml) and H_2O (25 ml) was added activated Zn powder (14.0 g, 214 mmol) in several portions while the temp. was maintained below 10°. After 5 h stirring at 0–5°, the mixture was filtered, the filtrate cooled, alkalinized with conc. NH_4OH soln., and extracted with $CHCl_3$. The org. layer was dried and evaporated to give 6.7 g of a brown oil which was converted into the HBr salt in the usual way: 5.9 g (81%) of **9**·HBr. Recrystallization of a small portion of this material from EtOH/Et_2O afforded an anal. sample. M.p. 225–227°. IR (KBr): 3420 (NH_2^+), 1725 (ester), 1675 (CO). ^{1}H-NMR (60 MHz, $CDCl_3$): 8.80 (br. *s*, NH_2^+); 7.95 (*d*, *J* = 8, 1 arom. H); 6.96 (*d*, *J* = 8, 1 arom. H); 5.92 (*s*, OCH_2O); 3.91 (*s*, MeO); 3.76 (*s*, 2 MeO); 2.60, 2.40 (2 *s*, MeN^+); 1.28 (*t*, *J* = 7, *Me*CH_2OCO). Anal. calc. for $C_{24}H_{28}BrNO_8$·HBr: C 46.55, H 4.72, Br 25.80, N 2.26; found: C 46.34, H 4.81, Br 26.01, N 2.21.

b) From **11**. A mixture of **11** (7.0 g, 13.3 mmol), $NaHCO_3$ (30 g, 357.1 mmol) and EtOH-free $CHCl_3$ (40 ml) was cooled to −10° while stirring. Then 0.1M Br_2 in CCl_4 (266 ml, 26.6 mmol) was added dropwise while the temp. was kept below 0°. After the Br_2 addition was completed, the mixture was stirred at 0° for 20 min and then filtered, the filtrate evaporated, and the yellow oil (10.15 g) subjected to column chromatography (neutral alumina, grade II, CH_2Cl_2): 7.2 g of TLC-pure **12** as a slightly yellow foam which was not further characterized. A soln. of this foam in EtOH (40 ml) was refluxed for 3 h, then concentrated to *ca.* ¼ of the volume. After addition of Et_2O, 6.6 g (80%) of **9**·HBr (m.p. 215–220°) were isolated. A small sample was recrystallized from EtOH/Et_2O to afford pure **9**·HBr, identical by mixed m.p., IR, and ^{1}H-NMR with the compound prepared from **8**. M.p. 224–227°.

N-(Vinyloxycarbonyl)nornarceine Ethyl Ester (= *Ethyl 2,3-Dimethoxy-6-{{4-methoxy-6-{2-[N-methyl-N-(vinyloxycarbonyl)amino]ethyl}-1,3-benzodioxol-5-yl}acetyl}benzoate*; **11**). A mixture of **10** [3] (10 g, 18.1 mmol) $KHCO_3$ (5.4 g, 54.5 mmol), vinyl chloroformate (2.11 g, 19.8 mmol), and $ClCH_2CH_2Cl$ (80 ml) was stirred at 60–65° (bath temp.) for 4 h. The inorg. material was filtered off, the filtrate evaporated, washed with H_2O (2 × 50 ml), dried, and evaporated to give 10.1 g of a yellow oil which was crystallized from MeOH: 6.7 g (70%) of **11**. A small sample was recrystallized from MeOH for analysis. M.p. 119–120°. IR (KBr): 1720 and 1700 (ester, carbamate); 1670 (CO). ^{1}H-NMR (200 MHz, $CDCl_3$; 2 rotamers): 7.91, 7.83 (2 *d*, *J* = 8.6, 8.6, 1 arom. H); 7.18 (*m*, 1 olef. H); 6.98 (2 *d*, *J* = 8.6, 8.6, 1 arom. H); 6.45, 6.41 (2 *s*, 1 arom. H); 5.90 (*s*, OCH_2O); 4.71 (*m*, 2 olef. H); 4.36 (*q*, *J* = 7.1, MeCH_2O); 4.28, 4.21 (2 *s*, CH_2CO); 3.96 (*s*, MeO); 3.86 (*s*, 2 MeO); 2.87 (*s*, MeN); 1.30 (*t*, *J* = 7.1, *Me*CH_2O). Anal. calc. for $C_{27}H_{31}NO_{10}$: C 61.24, H 5.90, N 2.65; found: C 61.21, H 6.09, N 2.57.

*Ethyl 6-{[10-Bromo-6,7,8,9-tetrahydro-4-methoxy-7-methyl-5*H*-1,3-dioxolo[4,5-h][3]benzazepin-5-yl]carbonyl}-2,3-dimethoxybenzoate Hydrobromide* (**13**·HBr). A soln. of **9**·HBr (7.75 g, 12.51 mmol) and 37% formalin (15 ml, 187 mmol) in EtOH (110 ml) was refluxed for 18 h. The soln. was concentrated *in vacuo* to *ca.* 50 ml, treated with Et_2O, and kept overnight in the refrigerator: 5.5 g (69%) of **13**·HBr as colorless crystals. For analysis, a small sample was recrystallized from EtOH. M.p. 170–174°. IR (KBr): 3400 (NH^+), 1725 (ester), 1675 (CO). ^{1}H-NMR (60 MHz, $CDCl_3$): 7.48 (*d*, *J* = 8, 1 arom. H); 6.73 (*d*, *J* = 8, 1 arom. H); 5.93 (*s*, OCH_2O); 4.40 (*q*, *J* = 7, MeCH_2O); 3.82, 3.75, 3.66 (3 *s*, 3 MeO); 2.88 (*s*, MeN); 1.36 (*t*, *J* = 7, *Me*CH_2O). Anal. calc. for $C_{25}H_{28}BrNO_8$·HBr·0.5 EtOH: C 47.72, H 4.93, Br 24.42, N 2.14; found: C 47.50, H 5.08, Br 24.41, N 2.20.

*3-(10-Bromo-6,7,8,9-tetrahydro-4-methoxy-7-methyl-5*H*-1,3-dioxolo[4,5-h][3]benzazepin-5-yl)-6,7-dimethoxyisobenzofuran-1(3*H*)-one* (**14**). $NaBH_4$ (750 mg, 19.8 mmol) was added in several small portions to a cooled (ice/H_2O) and stirred soln. of **13**·HBr (1.35 g, 2.13 mmol) in EtOH (20 ml). Then the ice-bath was removed, the mixture stirred at r.t. for 1 h and excess $NaBH_4$ destroyed with 30% AcOH soln. After alkalinization with conc. NH_4OH soln. and extraction with $CHCl_3$, the org. layer was dried and evaporated to give 1.3 g of a colorless foam which was crystallized from EtOH: 905 mg (83%) of **14**. An anal. sample was obtained by recrystallization from acetone. M.p. 201–203°. IR (KBr): 1765 (lactone). ^{1}H-NMR (60 MHz, $CDCl_3$): 7.30 (*d*, *J* = 8, 1 arom. H); 7.15 (*d*, *J* = 8, 1 arom. H); 6.02 (*s*, OCH_2O); 3.90 (*s*, 2 MeO); 3.78 (*s*, MeO); 2.35 (*s*, MeN). Anal. calc. for $C_{23}H_{24}BrNO_7$: C 54.56, H 4.78, Br 15.78, N 2.77; found: C 54.35, H 4.80, Br 15.75, N 2.64.

*6,7-Dimethoxy-3-(6,7,8,9-tetrahydro-4-methoxy-7-methyl-5*H*-1,3-dioxolo[4,5-h][3]benzazepin-5-yl)isobenzofuran-1(3*H*)-one* (**2**). A mixture of **14** (2.15 g, 4.25 mmol), 10% Pd/C (370 mg), and glacial AcOH (60 ml) was

hydrogenated at 40 psi for 72 h. Then the catalyst was filtered off and the filtrate alkalinized with conc. NH_4OH soln. while cooling. After extraction with $CHCl_3$, the org. layer was dried and evaporated to give 1.74 g of a colorless foam which was crystallized from EtOH: 1.44 g (80%) of **2**. A small portion was recrystallized from MeCN for analysis. M.p. 176–178°. IR (KBr): 1760 (lactone). ^{1}H-NMR (250 MHz, $CDCl_3$): 7.24 (*s*, 2 arom. H); 6.37 (*s*, 1 arom. H); 5.96 (*d*, J = 10.3, CHOCO); 5.92 (*d*, J = 1.5, OCH_2O); 4.11, 3.95, 3.93 (3 *s*, 3 MeO); 2.40 (*s*, MeN). Anal. calc. for $C_{23}H_{25}NO_7$: C 64.63, H 5.90, N 3.28; found: C 64.52, H 5.92, N 3.32.

6,7-Dimethoxy-3-(6,7,8,9-tetrahydro-4-methoxy-5 H-*1,3-dioxolo[4,5-*h*][3]benzazepin-5-yl)isobenzofuran-1(3*H*)-one Hydrochloride* (**3**·HCl). A mixture of **2** (1.1 g, 2.57 mmol), vinyl chloroformate (1.36 g, 12.78 mmol), $KHCO_3$ (770 mg, 7.71 mmol), and $ClCH_2CH_2Cl$ (12 ml) was stirred at 60–65° (bath temp.) for 3 h. The inorg. material was filtered off and the filtrate washed with H_2O, dried, and evaporated: 1.2 g of **15**. Colorless foam (pure by TLC). IR (KBr): 1755 (lactone), 1710 (carbamate). ^{1}H-NMR (60 MHz, $CDCl_3$): 7.20–6.95 (*m*, 2 arom. H, 1 vinyl H); 6.31 (*s*, 1 arom. H); 5.88 (*s*, OCH_2O); 4.45 (*m*, 1 vinyl H); 4.02 (*s*, MeO); 3.86 (*s*, 2 MeO).

Through a soln. of **15** (1.0 g, 2.07 mmol) in anh. CH_2Cl_2 (30 ml), HCl-gas was bubbled for 60 min. The soln. was kept at r.t. overnight and then evaporated to give **16** as a colorless foam (pure by TLC) which was used for the next step without further purification and characterization. A soln. of this foam in MeOH (25 ml) was refluxed for 2 h and then evaporated to give 900 mg of colorless foam which was crystallized from anh. MeOH/anh. Et_2O: 770 mg of **3**·HCl. An anal. sample was obtained by recrystallization from MeOH. M.p. 177–178°. IR (KBr): 3400 (NH_2^+), 1750 (lactone). ^{1}H-NMR (60 MHz, (D_6)DMSO): 9.60 (br. *s*, NH_2^+); 7.42 (*d*, J = 8, 1 arom. H); 7.08 (*d*, J = 8, 1 arom. H); 6.82 (*s*, 1 arom. H); 5.93 (*s*, OCH_2O); 3.84 (*s*, 2 MeO); 3.70 (*s*, MeO). Anal. calc. for $C_{22}H_{23}NO_7 \cdot HCl$: C 56.47, H 5.60, Cl 7.58, N 2.99; found: C 56.88, H 5.54, Cl 7.62, N 3.05.

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REFERENCES

[1] M. O. Karlsson, B. Dahlstroem, A. Neil, *Eur. J. Pharmacol.* **1988,** *145,* 195.
[2] *Mitsubishi Chemical Industries Co. Ltd.*, Jpn. Kokai 59,161,315, 1984 (*CA:* **1985,** *102,* 576s).
[3] W. Klötzer, S. Teitel, A. Brossi, *Monatsh. Chem.* **1972,** *103,* 1210.
[4] T. A. Montzka, J. D. Matiskella, R. A. Partyka, *Tetrahedron Lett.* **1974,** 1325.
[5] R. A. Olofson, R. C. Schnur, L. Bunes, J. P. Pepe, *Tetrahedron Lett.* **1977,** 1567.
[6] H. Schmidhammer, D. Obendorf, G.-F. Pirkner, T. Sams, *J. Org. Chem.* **1991,** *56,* 3457.