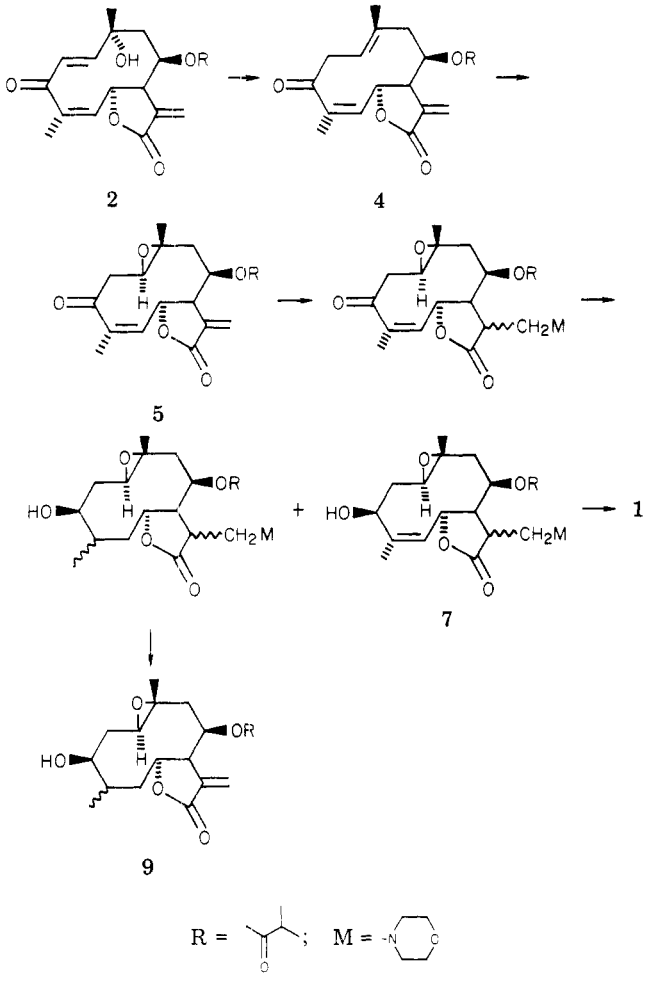
Scheme I



indicated that the starting material had been consumed, and the solution was diluted with water and extracted with $CHCl_3$. Evaporation of the washed and dried extract gave a residue which showed two spots on TLC. These were separated by preparative TLC (ethyl acetate–benzene, 3:1). The major product, **7**, was recrystallized from petroleum ether (bp 60–80 °C): yield 14 mg; mp 170 °C; IR 3500, 1725, 1110, 850 cm^{-1}; NMR 6.60 (dd, J = 12, 2 Hz, H-6), 5.2–5.45 (c, H-5 and H-8), 4.40 (br, H-3), 1.80 (d, J = 1.5 Hz, H-15), 1.25 (H-14), 1.15 (d, J = 7 Hz, H-3′ and H-4′); mass spectrum m/e 437 (M^+), 350, 349, 332, 262, 100, 87, 71 (base peak).

Anal. Calcd for $C_{23}H_{35}O_7N$: mol wt 437.241 14. Found: mol wt 437.241 06.

The minor product (**8**, yield 8 mg) was a gum: IR 3500, 1765, 1730, 1125 cm^{-1}; mass spectrum m/e 439 (M^+), 352, 351, 264, 228. Because **8** had a tendency to decompose, it was immediately mixed with CH_3I,[9] kept overnight at room temperature, diluted with $CHCl_3$, washed with three 50-mL portions of 10% aqueous $NaHCO_3$ and water, dried, and evaporated. The residue (**9**, 6 mg) was a gum: IR 3500, 1765, 1730, 1100 cm^{-1}; NMR 6.25 and 5.70 (2 d, J = 2.5 Hz, H-13), 5.2–5.5 (C, H-5 and H-8), 3.65 (br, H-3), 1.25 (H-14), 1.15 (d, J = 7 Hz, H-3′ and H-4′), 1.05 (d, J = 7 Hz, H-15); mass spectrum m/e 352 (M^+), 337, 264, 246, 71.

Treatment of 12 mg of **7** with CH_3I and workup in the manner described in the previous paragraph gave on evaporation of $CHCl_3$ 10 mg of **1**: mp 210 °C, after recrystallization from $CHCl_3$–hexane; mixture melting point with authentic tagitinin E (mp 210 °C) undepressed; identical on TLC (ethyl acetate–benzene, 1:9); IR, NMR, and mass spectra superimposable.

Acknowledgment. We thank Dr. R. P. Rastogi for a sample of authentic tagitinin E.

Registry No. **1**, 59979-58-7; **2**, 59979-56-5; **4**, 72301-72-5; **5**, 72301-73-6; **6**, 72301-74-7; **7**, 72301-75-8; **8**, 72301-76-9; **9**, 72301-77-0; morpholine, 110-91-8.

Synthesis and Characterization of a Cyclic Acylammonium Chloride

Norton P. Peet* and Shyam Sunder

Pharmaceutical Research and Development–Medicinal Chemistry, The Dow Chemical Company, Indianapolis, Indiana 46268

Received February 6, 1979

We were recently interested in the preparation of (2-chloroethyl)ureas for use as alkylating agents in the preparation of compounds for pharmacological evaluation. Specifically, we attempted first to synthesize (chloroethyl)urea **4**. *N*-Ethyl-*N*-(2-hydroxyethyl)-4-morpholinecarboxamide (**3**) was prepared in straightforward fashion from morpholinecarbonyl chloride (**1**) and 2-(ethylamino)ethanol (**2**) as shown in Scheme I. However, treatment of a chloroform solution of **3** with thionyl chloride or phosgene did not yield **4**, but rather a hygroscopic salt [ν(C=O) 1800 cm^{-1}] which has been identified as **5**.

Treatment of **5** with sodium methoxide yielded a single product, which we assigned as carbamate **6** (Scheme II). An authentic sample of **6** was produced by treating methyl *N*-(2-chloroethyl)-*N*-ethylcarbamate (**10**) with morpholine. [(Chloroethyl)carbamate **10**, in turn, was prepared from the (hydroxyethyl)carbamate **8** and thionyl chloride. The main product of this reaction was 3-ethyl-2-oxazolidinone (**9**).] Interestingly, inner salt **5** could also be quantitatively prepared from **1** and *N*-ethylaziridine.

Treatment of **3** with 4-oxo-4*H*-1-benzopyran-2-carbonyl chloride (**11**) afforded the expected ester **12** (Scheme III) as a white solid (96% yield). However, when the piperidinyl analogues of **3** (**13a–d**) were treated with **11**, oils (**14a–d**) resulted which converted, upon standing for several days, to their corresponding acylammonium carboxylate salts (**15a–d**). These transformations were monitored by infrared and NMR spectroscopy. The liquid physical states of **14a–d** may be responsible for their conversions to **15a–d**, possibly via chloride catalysis. Another explanation for the stability of **12** and the instability of **14a–d** is that morpholine (pK_a = 8.33)[1] is less basic than piperidine (pK_a = 11.123)[1] or the methylpiperidines and is therefore less nucleophilic and less prone to initiate carboxylate displacement.

Acylammonium salts have been isolated or implicated as intermediates in other instances. For example, a series of (alkoxycarbonyl)trialkylammonium fluoroborates has been synthesized and used in peptide synthesis.[2] The use of 2,2,2-trichloroethyl chloroformate in the demethylation of tertiary amines[3] is a classic example of the intermediacy of acylammonium salts. In addition, perchlorate[4] and antimony pentachloride[5] salts of heterocycles having positive charge on nitrogen atoms which are adjacent to carbonyl groups have been reported.

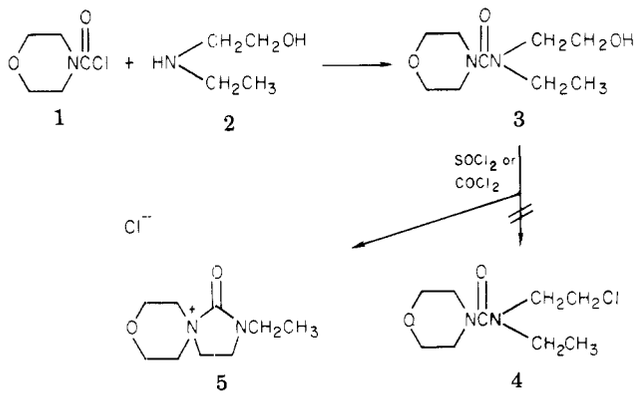
Experimental Section[6]

***N*-Ethyl-*N*-(2-hydroxyethyl)-4-morpholinecarboxamide (3).** A 29.9-g (0.200 mol) quantity of 4-morpholinecarbonyl

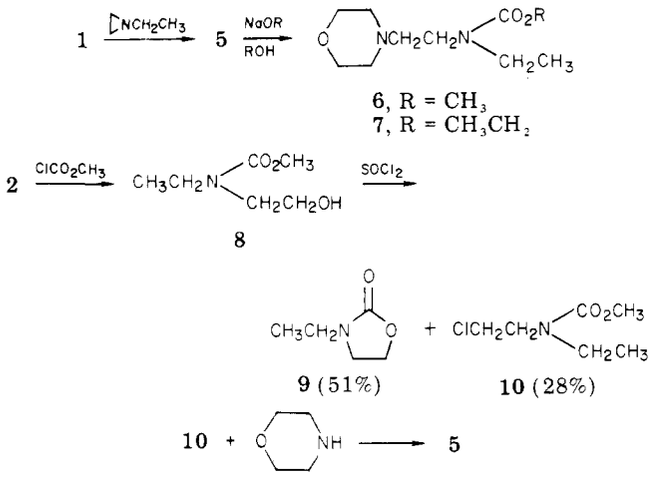
(1) "Handbook of Chemistry and Physics", 55th ed., R. C. Weast, Ed., CRC Press, Cleveland, OH, 1974, p D-127.
(2) J. V. Paukstelis and M. Kim, *J. Org. Chem.*, **39**, 1499 (1974).
(3) (a) T. A. Montzka, J. D. Matiskella, and R. A. Partyka, *Tetrahedron Lett.*, 1325 (1974); (b) M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", Vol. 5, Wiley, New York, 1975, pp 686–7.
(4) G. N. Dorofeenko, Y. I. Ryabukhin, and V. V. Mezheritskii, *Zh. Org. Khim.*, **10**, 2233 (1974).
(5) W. Flitsch and K. Gurke, *Angew. Chem.*, **87**, 38 (1975).

0022-3263/80/1945-0536$01.00/0

Scheme I



Scheme II



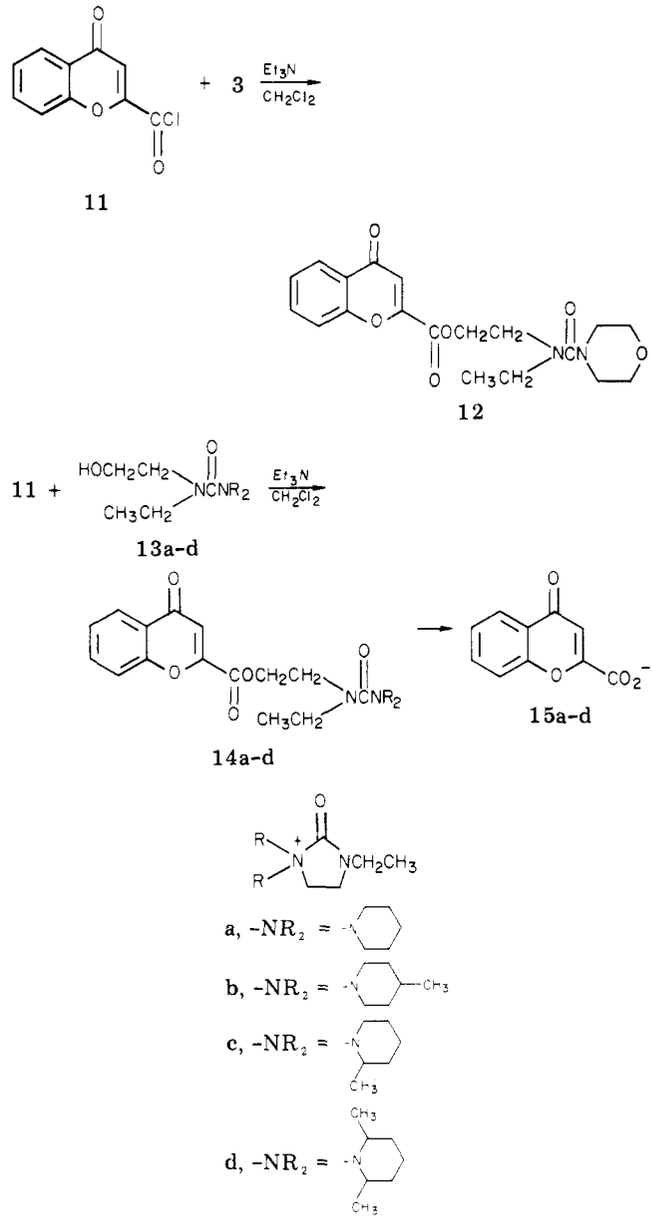
chloride (1)[7] was added (exothermic) over a 15-min period to a solution of 35.7 g (0.400 mol) of 2-(ethylamino)ethanol (2) in 100 mL of benzene. After 30 min the amine hydrochloride was removed by filtration, and the filtrate was concentrated to leave 40.4 g (100%) of 3 as a clear oil: IR 3420 (broad OH), 1620 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 5.22 (s, 1, OH, D_2O exchangeable), 3.95–3.58 (m, 6, three OCH_2 groups), 3.58–3.05 (m, 8, four NCH_2 groups), 1.17 (t, J = 7.2 Hz, 3, CH_3); mass spectrum (70 eV, electron impact), m/e 202 (molecular ion). Distillation of 3 (2 mm) resulted in partial decomposition. One of the decomposition products was identified as 9.

Preparation of 3-Ethyl-2-oxospiro(imidazolidine-1,4′-morpholinium) Chloride (5). A. From 3 and Thionyl Chloride. To 35.0 g (0.173 mol) of 3 in 100 mL of chloroform was added, slowly with ice-bath cooling, 22.7 g (0.190 mol) of thionyl chloride (redistilled). After standing overnight, the solution was concentrated to leave 38.2 g (100%) of 5 as a clear glass, which crystallized on standing. A sample could be recrystallized from ethyl acetate–benzene to give hygroscopic white prisms, mp 60–65 °C; IR 1800 (C=O) cm^{-1}; NMR (D_2O) δ 4.60–3.10 (m, 14, seven CH_2 groups), 1.23 (t, J = 7.2 Hz, 3, CH_3).

B. From 3 and Phosgene. To a solution of 10.1 g (50.0 mmol) of 3 in 75 mL of ethyl acetate was added 50 mL of phosgene. The addition was exothermic. After 15 min, the solution became cloudy, and an oil separated. The mixture was thoroughly concentrated to yield 11.0 g (100%) of 5, which was identical in all respects with the material prepared as in part A.

C. From 1 and *N*-Ethylaziridine. To a solution of 7.48 g (50.0 mmol) of 1 in 50 mL of chloroform was added 5 mL of

Scheme III



N-ethylaziridine.[8] Several minutes after the addition, an exotherm occurred. After 30 min, an aliquot was concentrated, and IR indicated completeness of the reaction. The solution was concentrated, and the resulting white solid was washed with ether to yield 11.0 g (100%) of 5, which was identical in all respects with the material prepared as in part A.

Methyl *N*-Ethyl-*N*-(2-hydroxyethyl)carbamate (8). To a solution of 89.1 g (1.00 mol) of 2-(ethylamino)ethanol (2) in 300 mL of benzene was added, with ice-bath cooling over a 30-min period, 47.2 g (0.500 mol) of methyl chloroformate. After 15 min of stirring, the white solid was removed by filtration, and the filtrate was washed with water, dried (Na_2SO_4), and concentrated to yield 23.2 g of 8. Concentration of the water wash gave an additional 40.0 g of 8. The total yield of 8 was 63.2 g (86%): bp 145–147 °C (27 mm); IR 3425 (broad OH), 1695 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 4.97–3.10 (m, 10, $HOCH_2CH_2NCH_2$ and OCH_3, with OCH_3 s at 3.63), 1.10 (t, J = 7 Hz, 3, NCH_2CH_3); VPC (5 ft × $^1/_8$ in. 5% SE-30, 150 °C) showed a single component.

Anal. Calcd for $C_6H_{13}NO_3$: C, 48.96; H, 8.90; N, 9.52. Found: C, 48.69; H, 8.63; N, 9.71.

Treatment of 8 with Thionyl Chloride. To a solution of 44.2 g (0.300 mol) of 8 in 200 mL of $CHCl_3$ was added 39.3 g (0.330 mol) of thionyl chloride over a 25-min period (gas evolution). The solution was heated at reflux for 5 min and allowed to stand for

(6) Melting points were recorded with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded as Nujol mulls or liquid films with a Perkin-Elmer 727B instrument, NMR spectra with Varian T-60 and Perkin-Elmer R32 (90 MHz) spectrometers, and mass spectra with a Hitachi RMU-6D mass spectrometer. Combustion analyses were performed by Dow Analytical Laboratories, Midland, MI.

(7) A. Sekera, I. Jakubec, J. Kral and C. Urba, *Chem. Listy*, **46**, 762 (1952); *Chem. Abstr.*, **47**, 12302*f* (1953).

(8) This material should be handled with extreme caution.

72 h. Concentration left 33.1 g of light oil, which, by VPC (5 ft × 1/8 in. 5% SE-30, 150 °C), was a mixture of two components (1.7 and 3.6 min). The oil was distilled at reduced pressure in six fractions. Fractions 1–3 yielded 13.8 g (28%) of pure methyl *N*-(2-chloroethyl)-*N*-ethylcarbamate (**10**): bp 125 °C (33 mm); IR 1705 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.70 (s, 3, OCH_3), 3.70–3.54 (m, 4, CH_2CH_2), 3.40 (q, J = 7 Hz, 2, CH_2CH_3), 1.13 (t, J = 7 Hz, 3, CH_2CH_3).

Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.62; H, 7.28; N, 8.50.

Fractions 5 and 6 contained 17.7 g (51%) of pure 3-ethyl-2-oxazolidinone (**9**): bp 148 °C (25 mm) [lit.[9] bp 92 °C (1 mm)]; IR 1750 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 4.50–4.13 (m, 2, OCH_2), 3.80–3.39 (m, 2, NCH_2CH_2), 3.30 (q, J = 7 Hz, 2, CH_2CH_3), 1.15 (t, J = 7 Hz, 3, CH_3).

Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.20; H, 7.70; N, 12.02.

Preparation of Methyl *N*-Ethyl-*N*-[2-(4-morpholinyl)-ethyl]carbamate (6). A. From 5. To a solution of 11.0 g (50.0 mmol) of **5** (prepared as in part A or C) in 50 mL of methanol was added 15 mL of 25% methanolic sodium methoxide. A white precipitate formed immediately. The mixture was concentrated and partitioned between water and methylene chloride, and the organic phase was dried (Na_2SO_4) and concentrated to leave 10.7 g (99%) of **6**: bp 111 °C (0.7 mm); IR (neat) 1705 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 3.64–3.48 (m, 7, both carbamate NCH_2 groups and OCH_3, with OCH_3 s at 3.57), 3.22 (q, J = 7 Hz, 4, CH_2OCH_2), 2.60–2.27 (m, 6, three CH_2 groups adjacent to morpholino N), 1.10 (t, J = 7 Hz, 3, CH_2CH_3); mass spectrum (70 eV), m/e 216 (molecular ion).

Anal. Calcd for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32; N, 12.95. Found: C, 55.48; H, 9.32; N, 13.09.

B. From 10 and Morpholine. A solution of 7.42 g (44.8 mmol) of **10** and 15.7 g (180 mmol) of morpholine in 50 mL of benzene was heated at reflux for 100 h. The mixture was cooled, washed with water, dried (Na_2SO_4), and concentrated. Distillation at reduced pressure gave 8.54 g (88%) of **6**, which was identical in all respects with the material prepared as in part A.

Ethyl *N*-Ethyl-*N*-[2-(4-morpholinyl)ethyl]carbamate (7). Carbamate **7** was prepared from **5** and ethanolic sodium ethoxide, by using the procedure described for **6**: 82% yield; bp 122 °C (1.7 mm); IR 1700 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 4.07 (q, J = 7 Hz, 2, OCH_2CH_3), 3.77–3.48 (m, 4, both carbamate NCH_2 groups), 3.27 (q, J = 7 Hz, 4, CH_2OCH_2), 2.60–2.27 (m, 6, three CH_2 groups adjacent to morpholino N), 1.22 (t, J = 7 Hz, 3, OCH_2CH_3), and 1.09 (t, J = 7 Hz, 3, NCH_2CH_3); mass spectrum (70 eV) m/e 230 (molecular ion).

Anal. Calcd for $C_{11}H_{22}N_2O_3$: C, 57.36; H, 9.63; N, 12.17. Found: C, 57.58; H, 9.75; N, 12.38.

4-Oxo-4*H*-1-benzopyran-2-carbonyl Chloride (11). To a slurry of 19.0 g (0.100 mol) of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid[10] in 250 mL of cyclohexane was added 23.0 g (0.110 mol) of phosphorus pentachloride. After 45 min at reflux, a clear solution resulted. The solution was kept cold for 15 h, and the resulting needles were collected to yield 18.6 g (89%) of **11**: mp 104–108 °C (lit.[12] mp 108–109 °C); IR 1750 (acid chloride C=O), 1645 (ketone C=O), 1610 (C=C) cm^{-1}.

2-[*N*-Ethyl-*N*-(4-morpholinylcarbonyl)amino]ethyl 4-Oxo-4*H*-1-benzopyran-2-carboxylate (12). To a solution of 10.5 g (50.3 mmol) of **11** in 50 mL of methylene chloride was added 10.1 g (50.3 mmol) of **3**. After being stirred for 15 min the solution was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated to yield 18.1 g (96%) of **12** as a viscous oil. Trituration with ether produced a white solid: mp 118–119 °C (ethanol); IR 1740 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 8.34–8.10 (m, 1, aromatic), 7.95–7.30 (m, 3, aromatic), 7.07 (s, 1, H at the 3-position of benzopyranone), 4.57 (t, J = 5.5 Hz, 2, CO_2CH_2), 3.87–3.04 (m, 12, morpholinyl plus CH_2NCH_2), 1.22 (t, J = 7 Hz, 3, CH_3).

Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 60.77; H, 5.91; N, 7.42.

Compounds 13a–d, 14a–d, and 15a–d. Ureas **13a–d** were made in the same fashion as **3**. Treatment of these ureas with **11** in methylene chloride followed by workup produced, initially, the respective esters **14a–d** as oils. The gradual conversion of these oils to their corresponding acylammonium carboxylate salts **15a–d** was monitored spectrally. In the infrared spectra, the ester carbonyl bands at 1740 cm^{-1} diminished as the carbonyl bands of the inner salts at 1800 cm^{-1} intensified. When monitored by NMR, the conversions were clearly observed at δ 7.1, where one sharp signal (due to the proton at the 3-position of the benzopyranone moiety) replaced another.

Registry No. **1**, 15159-40-7; **2**, 110-73-6; **3**, 72275-32-2; **5**, 72275-33-3; **6**, 72275-34-4; **7**, 72275-35-5; **8**, 72275-36-6; **9**, 5261-18-7; **10**, 72275-37-7; **11**, 5112-47-0; **12**, 72275-38-8; **13a**, 72275-39-9; **13b**, 72275-40-2; **13c**, 72275-41-3; **13d**, 72275-42-4; **14a**, 72275-43-5; **14b**, 72275-44-6; **14c**, 72275-45-7; **14d**, 72275-46-8; **15a**, 72275-49-1; **15b**, 72275-51-5; **15c**, 72275-53-7; **15d**, 72275-55-9; *N*-ethylaziridine, 1072-45-3; methyl chloroformate, 79-22-1; morpholine, 110-91-8; 4-oxo-4*H*-1-benzopyran-2-carboxylic acid, 4940-39-0.

(9) A. H. Homeyer, U.S. Patent 2 399 118, Apr 23, 1946; *Chem. Abstr.*, **40**, 4085[3] (1946).
(10) This acid was prepared using the procedure of B. Barker and G. P. Ellis, *J. Chem. Soc. C*, 2609 (1970): mp 251–252 °C (lit.[11] mp 250 °C).
(11) V. A. Zagorevskii and D. A. Zykov, *Zh. Obshch. Khim.*, **33**, 2469 (1963); *Chem. Abstr.*, **59**, 15214*b* (1963).
(12) P. Tronche, J. Couquelet, and P. Jolland, *Ann. Pharm. Fr.*, **23**, 573 (1965); *Chem. Abstr.*, **64**, 12632*f* (1966).

Preparation and Determination of Configurationally Pure *trans*-(2*S*,3*S*)-2,3-Epoxybutane

Volker Schurig,* Bernhard Koppenhoefer, and Waldemar Buerkle

Institut für Organische Chemie, Universität Tübingen, D 74 Tübingen, Federal Republic of Germany

Received August 23, 1979

The unambiguous determination of enantiomeric compositions and absolute configurations of chiral oxiranes and related synthons is highly warranted in view of their importance for the preparation of optically active natural, pharmaceutical, and synthetic products.[1] Unfortunately, the former effort has until now lagged behind the synthetic approach. The traditional determination of "optical" purities in resorting to polarimetry is not always a reliable measure for enantiomeric compositions,[2] and, in addition, it requires the knowledge of the specific rotation ($[\alpha]_{max}$) of the pure enantiomer, usually not known with certainty. The characterization of enantiomeric compositions of oxiranes by NMR analysis in chiral solvents[3] or in the presence of chiral shift reagents[4] may be complicated by insufficient enantiomeric resolution and/or by spectral complexity, limiting its application for the accurate determination of the smallest amounts of enantiomeric impurities. We[5] and others[6] have recently shown that "complexation" gas chromatography may offer a high promise for the direct determination of enantiomeric compositions of volatile oxiranes and related substrates

(1) D. Seebach and H. O. Kalinowski, *Nachr. Chem. Tech.*, **24**, 415 (1976).
(2) A. Horeau, *Tetrahedron Lett.*, 3121 (1969).
(3) Pirkle's method; see: I. Moretti, F. Taddei, G. Torre, and N. Spassky, *J. Chem. Soc., Chem. Commun.*, 25 (1973).
(4) Whitesides' method; see: R. R. Fraser, M. A. Petit, and J. K. Saunders, *J. Chem. Soc., Chem. Commun.*, 1450 (1971); M. Kainosho, K. Ajisaka, W. H. Pirkle, and S. D. Beare, *J. Am. Chem. Soc.*, **94**, 5924 (1972); J. Gombos, E. Haslinger, and U. Schmidt, *Chem. Ber.*, **109**, 2645 (1976); B. Seuring and D. Seebach, *Helv. Chim. Acta*, **60**, 1175 (1977); J. J. Baldwin, A. W. Raab, K. Mensler, B. H. Arison, and D. E. McClure, *J. Org. Chem.*, **43**, 4876 (1978).
(5) V. Schurig, *Angew. Chem., Int. Ed. Engl.*, **16**, 110 (1977); V. Schurig and W. Bürkle, *ibid.*, **17**, 132 (1978).
(6) B. T. Golding, P. J. Sellars, and A. K. Wong, *J. Chem. Soc., Chem. Commun.*, 570 (1977).

0022-3263/80/1945-0538$01.00/0