3-[(Phenylseleno)methyl]-6-(phenylseleno)-2-oxabicyclo-[2.2.2]octane (8a) and 4-(Phenylseleno)-7-[(phenylseleno)-methyl]-6-oxabicyclo[3.2.1]octane (8b). The reaction and workup procedures were analogous to those described above (4-vinylcyclohexene, 0.109 g, 1 mmol; reflux 8 h). Liquid chromatographic analysis [hexane–chloroform (9:1) as eluent, benzophenone as internal standard] showed the presence of **8a** (0.415 mmol, 42%) and **8b** (0.018 mmol, 2%). A mixture of **8a** and **8b** was isolated in a same way as described above: yellow oil; IR (film) 3060, 2950, 1589, 1475, 1435, 1210, 1070, 1025, 980, 890, 740, 690 cm^{-1}; ^1H NMR δ 1.3–2.4 (m, 7 H), 2.6–3.3 (m, 2 H), 3.3–3.9 (m, 1 H), 3.9–4.6 (m, 2 H), 7.1–7.7 (m, 10 H); ^{13}C NMR δ 25.5 (t), 26.8 (t), 31.9 (t), 32.5 (t), 38.7 (t), 44.7 (d), 68.9 (d),[24] 79.0 (d), 81.0 (d), phenyl signals. Anal. Calcd for $C_{20}H_{22}OSe_2$: C, 55.06; H, 5.08. Found: C, 55.27; H, 5.11.

Acid-Catalyzed Isomerization of 1b to 1a. To a solution of **1b** (0.436 g, 1 mmol) and phenyl selenocyanate (0.364 g, 2 mmol) in methanol (20 mL) containing hydrogen chloride (36.5% aqueous HCl, 0.1 mL; 1 mmol as HCl) was added copper(II) chloride (0.314 g, 1 mmol), and the resulting mixture was stirred under reflux for 5 h. Water (50 mL) was added, and the products were extracted with chloroform (3 × 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to leave a yellow oil. After removal of phenyl selenocyanate by column chromatography [silica gel; hexane–chloroform (3:1) and chloroform as eluents], ^1H NMR measurement revealed that the product contained more than 90% of **1b** and less than 10% of **1a** by integration of signals due to methine protons.

Acid-Catalyzed Isomerization of 4b to 4a. To a solution of **4b** (0.141 g, 0.5 mmol) in methanol (2 mL) was added hydrogen chloride (36.5% aqueous HCl, 0.05 mL; 0.5 mmol as HCl), and the resulting solution was stirred under reflux for 5 h. After the workup procedure as described above, the yellow oil obtained was purified by column chromatography [silica gel; hexane–ethyl acetate (20:1) as eluent] to give **4** (0.111 g, 0.39 mmol, 79%). The **4a**/**4b** isomer ratio was estimated to be 80:20 by integration of the signals due to the methine protons in ^1H NMR spectrum. The same reaction of **4b** in methanol containing phenyl selenocyanate (2 molar equiv) and copper(II) chloride (1 molar equiv) as well as hydrogen chloride gave the same result, indicating that hydrogen chloride worked as a catalyst in this isomerization reaction.

(24) Attributed to minor component.

Registry No. **1a**, 75494-81-4; **1b**, 70187-90-5; **2a**, 72695-46-6; **2b**, 72695-47-7; **3a**, 32160-45-5; **3b**, 4277-34-3; **4a**, 77552-07-9; **4b**, 77552-08-0; *cis*-**5a**, 72991-21-0; *trans*-**5a**, 72991-22-1; **5b**, 72991-23-2; *cis*-**6**, 72991-24-3; *trans*-**6**, 72991-25-4; *cis*-**7**, 72991-26-5; *trans*-**7**, 72991-27-6; **8a**, 72991-28-7; **8b**, 72991-29-8; (*Z*,*Z*)-1,5-cyclooctadiene, 1552-12-1; phenyl selenocyanate, 2179-79-5; copper(II) chloride, 7447-39-4; 9-oxabicyclo[3.3.1]nonane, 281-05-0; 9-oxabicyclo[4.2.1]-nonane, 284-20-8; 1,5-hexadiene, 592-42-7; diallyl ether, 557-40-4; diallyl sulfide, 592-88-1; 4-vinylcyclohexene, 100-40-3.

Rearrangements of Penicillin Sulfoxides. 2.[1] Spectral Data and X-ray Crystallography of the Novel Imidazo[5,1-*c*][1,4]thiazine Ring System

Abraham Nudelman*

Chemistry Department, Bar-Ilan University, Ramat-Gan, Israel

Tali E. Haran and Zippora Shakked*

Department of Structural Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Received December 30, 1980

The novel imidazo[5,1-*c*][1,4]thiazine ring system has been obtained by rearrangement of penicillin sulfoxide esters upon treatment with ethoxycarbonyl isocyanate. The unexpected structure of the rearrangement product **4b** was established by X-ray analysis. A mechanism involving C_5–S cleavage and the formation of an episulfonium ion, D, is postulated.

Penicillin sulfoxides undergo numerous rearrangements to a variety of ring systems.[2] A number of publications[3] have described the attempted synthesis of the elusive penicillin sulfilimines. In the course of our investigation we treated penicillin sulfoxide esters **1**[4] with ethoxycarbonyl isocyanate[5] with the aim of preparing the corresponding sulfilimines.[6] This paper describes the physical, spectroscopic, and X-ray data, which establish the structure of the novel products produced in the course of the investigation.

The reaction took place (Scheme I) when a tetrahydrofuran solution of a penicillin sulfoxide ester, **1**,[4] was heated with 2 mol of ethoxycarbonyl isocyanate **2**[5] for 17 h. A major product was isolated in yields of 54% (**1a** → **3a**), 31% (**1b** → **3b**) and 40% (**1c** → **3c**).[7]

Elemental analysis of the products **3a–c** indicated that the elements of carbon and nitrogen had been incorporated and that one hydrogen had been lost from the empirical formula of the respective starting materials. High-reso-

(1) A. Nudelman and R. J. McCaully, *J. Org. Chem.*, **42**, 2887 (1977).
(2) For recent reviews see: (a) E. H. Flynn, Ed., "Cephalosporins and Penicillins, Chemistry and Biology", Academic Press, New York, 1972; (b) D. H. R. Barton, *Pure Appl. Chem.*, **33**, 1 (1973); (c) R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Acc. Chem. Res.*, **6**, 32 (1973); (d) A. Nudelman, *Int. J. Sulfur Chem., Part B*, **7**, 1 (1972); (e) A. Nudelman, *Phosphorus Sulfur*, **2**, 51 (1976); (f) A. Nudelman, *ibid.*, **9**, 1 (1980).
(3) (a) M. Numata, Y. Imashiro, I. Minamida, and M. Yamaoka, *Tetrahedron Lett.*, 5097 (1972); (b) J. E. G. Kemp, D. Ellis, and M. D. Cloiser, *ibid.*, 3781 (1979).
(4) D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc. C*, 3540 (1971).
(5) R. W. Lamon, *J. Heterocycl. Chem.* **6**, 261 (1969).
(6) (a) C. King, *J. Org. Chem.*, **25**, 352 (1960); (b) R. Neidlein and E. Heukelbach, *Arch. Pharm. (Weinheim, Ger.)*, **199**, 64 (1966); (c) R. Appel and H. Rittersbacher, *Chem. Ber.*, **97**, 852 (1964).
(7) R. L. Lewis and D. Walker, British Patent Appl., 2017705; *Chem. Abstr.*, **93**, 95265 (1980). These authors claim that the expected penams and cephams are obtained upon treatment of **1a** with acyl and sulfonyl isocyanates.

0022-3263/81/1946-3026$01.25/0

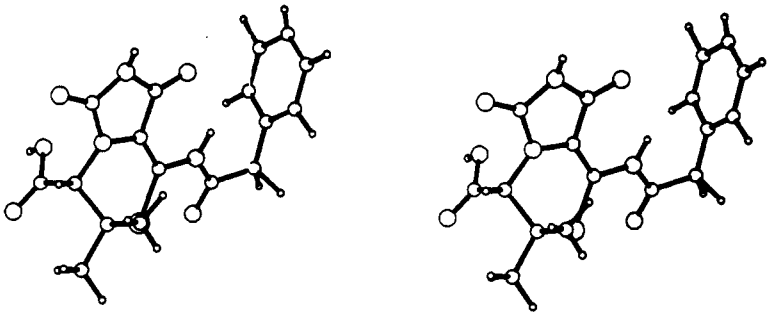
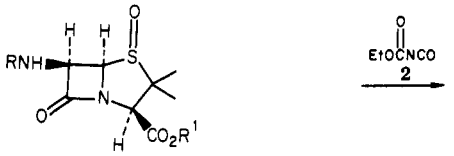
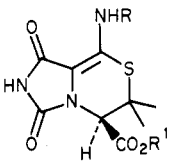


Figure 1. Penicillin rearrangement product **4b**.

Scheme I



1a, R = $C_6H_5OCH_2C{=}O$; $R^1 = CH_2C_6H_4$-*p*-NO_2
b, R = $C_6H_5CH_2C{=}O$; $R^1 = CH_2C_6H_4$-*p*-NO_2
c, R = $C_6H_5OCH_2C{=}O$; $R^1 = CH_2C_6H_4$-*p*-CH_3



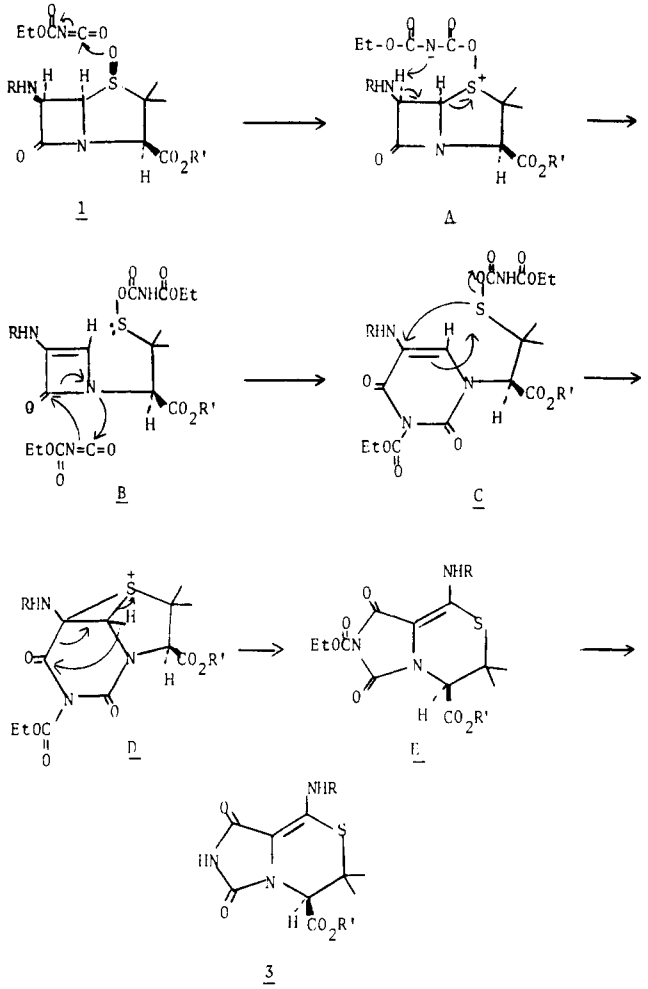
3a, R = $C_6H_5OCH_2C{=}O$; $R^1 = CH_2C_6H_4$-*p*-NO_2
b, R = $C_6H_5CH_2C{=}O$; $R^1 = CH_2C_6H_4$-*p*-NO_2
c, R = $C_6H_5OCH_2C{=}O$; $R^1 = CH_2C_6H_4$-*p*-CH_3
4a, R = $C_6H_5OCH_2C{=}O$; R^1 = H
b, R = $C_6H_5CH_2C{=}O$; R^1 = H
5a, R = H; $R^1 = CH_2C_6H_4$-*p*-NO_2
b, R = H; $R^1 = CH_2C_6H_4$-*p*-CH_3
6, R = H; R^1 = H

lution mass spectrometry in the case of **3b** (M^+ measured *m/e* 510.1205, calcd *m/e* 510.1208) confirmed the elemental analysis (see the table in the supplementary material). The characteristic β-lactam absorption was absent in the infrared spectra, and a carbonyl absorption attributable to O=C—N—C=O was observed at 5.78 μm. Stepwise fragmentation of the ester and amide groups of **3b** in the mass spectrum further confirmed their presence in the rearrangement product. In addition to proton signals due to these ester and amide, the NMR spectrum exhibited geminal methyl singlets, a singlet for the proton in the α-position to the carboxylic group, and two singlets for N–H exchange protons.

When **3a–c** were treated with methanol–hydrogen chloride, whereby the R amido group was solvolyzed, the resulting products, **5a–c**, showed extremely low basicity and could not be extracted into aqueous acid. Furthermore, they could not be converted into hydrochlorides for solid-state infrared spectra by Hofmann's method.[8] Hydrogenolysis of the ester group of **5** over 5% palladium on alumina or charcoal gave acid **6**. The same acid was also obtained from **3** by a similar hydrogenolysis of the benzylic ester to give the acid **4** followed by cleavage with methanolic hydrogen chloride. The weakly basic nature of the amido, imido, and vinylogous amido nitrogens of compound **6** was evident by the absence of any primary zwitterionic salt bands in the 3.5- and 5.0-μm regions in the infrared spectrum.

(8) B. R. Hofmann and G. H. Ellis, *Anal. Chem.*, **39**, 406 (1967).

Scheme II



The definitive and unexpected structure of the rearrangement product was obtained from X-ray analysis of the acid **4b**, which is shown in Figure 1.

Compound **4b** was crystallized from acetone–ether as white needles. The unit cell of the acid **4b** (molecular formula $C_{17}H_{17}N_3O_5S$), as determined by X-ray diffraction analysis, contained two molecules with the following cell dimensions and symmetry: a = 7.3317 (0.0009) Å, b = 14.6098 (0.0008) Å, c = 8.3713 (0.0020) Å, β = 107.97 (0.0148)°, space group $P2_1$, d_c = 1.41 g/cm^3. Intensities were measured on a Nonius CAD-4 diffractometer using graphite-monochromated Cu Kα radiation. Data reduction yielded 1756 unique reflections corrected for Lorentz and polarization effects. The structure was solved by direct methods (MULTAN), followed by least-squares refinement with anisotropic temperature factors for all heavy atoms and isotropic temperature factors for hydrogen atoms. The final R value was 0.038 for 1728 observed reflections.

In view of these results, the rearrangement mechanism shown in Scheme II is proposed.[9] Initial acylation of the sulfoxide 1 gives A, which upon removal of the proton in position 6 followed by S–C_5 bond cleavage results in the formation of the reactive unsaturated β-lactam B. This intermediate readily reacts with a second molecule of isocyanate to form C. Ring closure of C to the episulfonium ion D is followed by a proton loss with concomitant bond rearrangement to E, which readily undergoes a loss of EtOC=O to give the final product 3. Analogous S–C_5 bond cleavage and episulfonium ion formation have been recently proposed by Chou and coworkers.[9a]

Experimental Section

(4-Methylphenyl)methyl 3,3-Dimethyl-7,*S*-dioxo-6-[(phenoxyacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1c). The title compound was prepared by the literature procedure[4] used in the preparation of the corresponding *p*-nitrobenzyl ester (**1b**). This compound had the following: mp 105–106 °C; $[\alpha]^{24}_{546}$ +165.74° (*c* 0.989, acetone); NMR ($CDCl_3$) δ 1.04 (s, 3), 1.63 (s, 3), 2.33 (s, 3, *p*-Me), 4.51 (s, 2, OCH_2C=O), 4.70 (s, 1, 3-H), 5.02 (d, 1, 5-H), 5.25 (s, 2, CO_2CH_2), 6.1 (dd, 1, 6-H), 6.8–7.6 (m, 9), 8.3 (d, 1, NH).

Anal. Calcd for $C_{24}H_{26}N_2O_6S$: C, 61.26; H, 5.57; N, 5.95. Found: C, 61.17; H, 5.61; N, 5.82.

(4-Nitrophenyl)methyl 2,3,5,6-Tetrahydro-6,6-dimethyl-1,3-dioxo-8-[(phenoxyacetyl)amino]-1*H*-imidazo[5,1-*c*][1,4]thiazine-5-carboxylate (3a). A solution of *p*-nitrobenzyl 1-oxo-6-(2-phenoxyacetamido)penicillanate (**1a**;[4] 25.5 g, 0.05 mol) and ethoxycarbonyl isocyanate (13.2 g, 0.11 mol) in 400 mL of anhydrous tetrahydrofuran was refluxed for 17 h. The solution was cooled, mixed with charcoal, filtered, and flash evaporated. The residual oil was dissolved in dichloromethane and was washed several times with water. The organic phase was dried and evaporated to an oil which was crystallized from isopropyl alcohol to give a total of 14.4 g (54% yield) of **3a**, which melted with decomposition over a wide range but gave a single spot on silica gel TLC with ether as eluent: $[\alpha]^{24}_{546}$ −249.5° (*c* 1.056, acetone); NMR ($CDCl_3$) δ 1.53 (s, 3), 1.60 (s, 3), 4.66 (s, 2, OCH_2C=O), 4.76 (s, 1, 5-H), 5.32 (s, 2, CO_2CH_2), 6.9–7.5 (m, 5), 7.88 (q, 4, J_{AB} = 8 Hz), 9.35 (br s, 1, NH), 11.5 (s, 1, NH).

Anal. Calcd for $C_{24}H_{22}N_4O_8S{\cdot}0.25H_2O$: C, 54.29; H, 4.27; N, 10.55. Found: C, 54.19; H, 4.26; N, 10.23.

(4-Nitrophenyl)methyl 2,3,5,6-Tetrahydro-6,6-dimethyl-1,3-dioxo-8-[(phenylacetyl)amino]-1*H*-imidazo[5,1-*c*][1,4]thiazine-5-carboxylate (3b). A solution of **1b** (4.85 g, 0.01 mol) and ethoxycarbonyl isocyanate[5] (2.6 g, 0.022 mol) in 100 mL of anhydrous tetrahydrofuran was refluxed for 17 h. The solvent was flash evaporated, and the residue was chromatographed on 1000 g of silica gel by elution with 3:2 ether–pentane. A total of 1000 mL of eluent was collected per fraction. The title compound (1.6 g, 31% yield) was obtained from the combined residues of fractions 5–12. It was crystallized from acetone: mp 189–191 °C; $[\alpha]^{24}_{546}$ −315.8° (*c* 1.064, acetone); NMR ($CDCl_3$) δ 1.44 (s, 3), 1.53 (s, 3), 3.73 (s, 2, CH_2C=O), 4.67 (s, 1, 5-H), 5.24 (q, 2, CO_2CH_2), 7.35 (s, 5, Ph), 7.81 (q, 4, J_{AB} = 9 Hz), 8.93 (s, 1 NH), 10.28 (s, 1, NH).

Anal. Calcd for $C_{24}H_{22}N_4O_7S{\cdot}0.5H_2O$: C, 55.38; H, 4.65; N, 10.76; S, 6.16. Found: C, 54.98; H, 4.91; N, 10.74;, S, 6.37.

(4-Methylphenyl)methyl 2,3,5,6-Tetrahydro-6,6-dimethyl-1,3-dioxo-8-[(phenoxyacetyl)amino]-1*H*-imidazo[5,1-*c*][1,4]thiazine-5-carboxylate (3c). The procedure for the preparation of **3c** was the same as that described for the *p*-nitrobenzyl ester (**3b**). The product **3c** was obtained in 40% yield; it did not melt but slowly decomposed above 80 °C: $[\alpha]^{26}_{546}$ −315.63° (*c* 1.017, acetone); NMR ($CDCl_3$) δ 1.46 (s, 3), 1.51 (s, 3), 2.31 (s, 3, *p*-Me), 4.60 (s, 2, CO_2CH_2), 4.71 (s, 1, 5-H), 5.18 (s, 2, OCH_2C=O), 6.9–7.6 (m, 9), 9.70 (s, 1, NH), 11.50 (s, 1, NH).

Anal. Calcd for $C_{25}H_{25}N_3O_6S$: C, 60.59; H, 5.09; N, 8.48, S, 6.47. Found: C, 60.04; H, 4.99; N, 8.28; S, 6.50.

2,3,5,6-Tetrahydro-6,6-dimethyl-1,3-dioxo-8-[(phenoxyacetyl)amino]-1*H*-imidazo[5,1-*c*][1,4]thiazine-5-carboxylic Acid (4a). To a solution of **3a** (8.7 g, 16.5 mmol) in 200 mL of 3:2 ethanol–methanol was added 9 g of 5% palladium on alumina catalyst, and the mixture was hydrogenolyzed at room temperature. Within 2 h the theoretical amount of hydrogen was absorbed. The catalyst was filtered, and the filtrate was flash evaporated to an oil which was dissolved in ethyl acetate. The solution was extracted with saturated sodium bicarbonate; the aqueous phase was filtered, covered with fresh ethyl acetate, and acidified to pH 1.7 with concentrated hydrochloric acid. The organic phase was separated, mixed with charcoal, dried over magnesium sulfate, filtered, and evaporated to a foam which was crystallized from acetone/ether/pentane to give 4.7 g (71% yield) of **4a**: mp 207–210 °C; $[\alpha]^{24}_{546}$ −389.6° (*c* 0.988, acetone), NMR (Me_2SO) δ 1.40 (s, 3), 1.55 (s, 3), 4.62 (s, 1, 5-H), 4.70 (s, 2, OCH_2C=O), 6.8–7.6 (m, 5), 11.25 (s, 1, NH), 11.5 (br s, 1 NH).

Anal. Calcd for $C_{17}H_{17}N_3O_6S{\cdot}0.5H_2O$: C, 50.99; H, 4.53; N, 10.49; S, 8.01. Found: C, 51.13; H, 4.42; N, 10.33; S, 8.26.

2,3,5,6-Tetrahydro-6,6-dimethyl-1,3-dioxo-8-[(phenylacetyl)amino]-1*H*-imidazo[5,1-*c*][1,4]thiazine-5-carboxylic Acid (4b). Compound **4b** was prepared by a procedure similar to that described for **4a** by hydrogenolysis of **3b** (1.02 g, 2 mmol) on 1 g catalyst. The product obtained (400 mg, 54% yield) decomposed above 205 °C: $[\alpha]^{24}_{546}$ −457.06° (*c* 1.048, acetone); NMR (Me_2SO) δ 1.35 (s, 3), 1.51 (s, 3), 3.75 (s, 2, CH_2C=O), 4.60 (s, 1, 5-H), 5.3–6 (br band, CO_2H), 7.33 (s, 5, Ph), 10.3 (s, 1, NH), 11.4 (br s, 1, NH).

Anal. Calcd for $C_{17}H_{17}N_3O_5S$: C, 54.39; H, 4.51; N, 11.19. Found: C, 54.39; H, 4.64; N, 10.98.

(4-Nitrophenyl)methyl 2,3,5,6-Tetrahydro-8-amino-6,6-dimethyl-1,3-dioxo-1*H*-imidazo[5,1-*c*][1,4]thiazine-5-carboxylate (5a). A solution of **3a** (2.6 g, 5 mmol) in 200 mL of a methanolic hydrogen chloride was refluxed until no evidence of **3a** could be detected by thin-layer chromatography (ether eluent on silica gel plates). The solvent was flash evaporated, and the residue was dissolved in ethyl acetate and washed with water. The organic phase was dried and evaporated to an oil which was crystallized from dichloromethane–ether to give 1.2 g (65% yield) of **5a**: mp 221–223 °C; $[\alpha]^{24}_{546}$ −215.2° (*c* 1.059, acetone); NMR (Me_2SO) δ 1.50 (s, 3), 1.52 (s, 3), 4.90 (s, 1, 5-H), 5.38 (s, 2, CO_2CH_2), 6.9 (s, 2, NH_2), 7.92 (q, 4, J_{AB} = 68 Hz), 10.8 (s, 1, NH).

Anal. Calcd for $C_{16}H_{16}N_4O_6S$: C, 48.97; H, 4.11; N, 14.28; S, 8.17. Found: C, 49.30; H, 4.39; N, 13.92; S, 8.27.

(4-Methylphenyl)methyl 2,3,5,6-Tetrahydro-8-amino-6,6-dimethyl-1,3-dioxo-1*H*-imidazo[5,1-*c*][1,4]thiazine-5-carboxylate (5b). The title compound was obtained in 70% yield from **3c** by a procedure similar to that described for **5a**. It decomposed above 80 °C: $[\alpha]^{26}_{546}$ −192.73° (*c* 0.991, acetone); NMR ($CDCl_3$) δ 1.5 (s, 6), 2.32 (s, 3), 4.71 (s, 1, 5-H), 5.17 (s, 2, CO_2CH_2), 5.91 (s, 2, NH_2), 7.20 (s, 4), 9.9 (s, 1, NH).

Anal. Calcd for $C_{17}H_{19}N_3O_4S$: C, 56.16; H, 5.20; N, 11.33; S, 8.87. Found: C, 56.49; H, 5.30; N, 11.63; S, 8.90.

2,3,5,6-Tetrahydro-8-amino-6,6-dimethyl-1,3-dioxo-1*H*-imidazo[5,1-*c*][1,4]thiazine-5-carboxylic Acid (6). Method I. From 4a. A solution of **4a** (1 g, 2.55 mmol) in 200 mL of a methanolic solution of hydrogen chloride was stirred at room temperature for 2 h. The solvent was flash evaporated, and the residue was washed repeatedly with ether and then crystallized from acetone/ether/pentane to give 350 mg (54% yield) of solid **6** which did not melt sharply but decomposed above 150 °C: $[\alpha]^{26}_{546}$ −175.15° (*c* 0.982, acetone); NMR (Me_2SO) δ 1.41 (s, 3), 1.53 (s, 3), 4.53 (s, 1, 5-H), 6.7 (br s, 2, NH_2), 10.59 (s, 1, NH).

Anal. Calcd for $C_9H_{11}N_3O_4S$: C, 42.01; H, 4.31; N, 16.33. Found: C, 42.44; H, 4.35; N, 14.65. The NMR spectrum indicated the presence of a small amount of *p*-aminotoluene which may account for the high C and low N values.

Method II. From 5a. A solution of **5a** (2.5 g, 6.38 mmol) in 150 mL of 2:1 methanol/ethanol was hydrogenolyzed in the presence of 2.5 g of 5% palladium on alumina catalyst. Within 40 min the theoretical amount of hydrogen was absorbed. The catalyst was filtered, and the filtrate was flash evaporated to give a gum which solidified in dichloromethane. Crystallization from acetone–ether afforded the desired product (800 mg, 49% yield)

(9) (a) T. S. Chou, W. A. Spitzer, D. E. Dorman, S. Kukolja, I. G. Wright, N. D. Jones, and M. O. Chaney, *J. Org. Chem.*, **43**, 3835 (1978); (b) R. Thomas, *J. Chem. Soc., Chem. Commun.*, 1176 (1979); (c) A. G. M. Barrett, *J. Chem. Soc., Perkin Trans. 1*, 170 (1979).

whose NMR spectrum was identical with that described in Method I.

Registry No. 1a, 41625-65-4; **1b**, 54275-93-3; **1c**, 77646-76-5; **2**, 19617-43-7; **3a**, 77589-57-2; **3b**, 77589-58-3; **3c**, 77589-59-4; **4a**, 77589-60-7; **4b**, 77589-61-8; **5a**, 77589-62-9; **5b**, 77589-63-0; **6**, 77589-64-1.

Supplementary Material Available: Atomic coordinate and numbering for the crystallographic analysis and a table of mass spectral data of compounds **3b** and **4b** (8 pages). Ordering information is given on any current masthead page.

Properties of Phenolic and Thiophenolic Surfactant Micelles

Robert A. Moss* and Frank M. Dix

Wright and Rieman Laboratories, Department of Chemistry, Rutgers, The State University of New Jersey, New Brunswick, New Jersey 08903

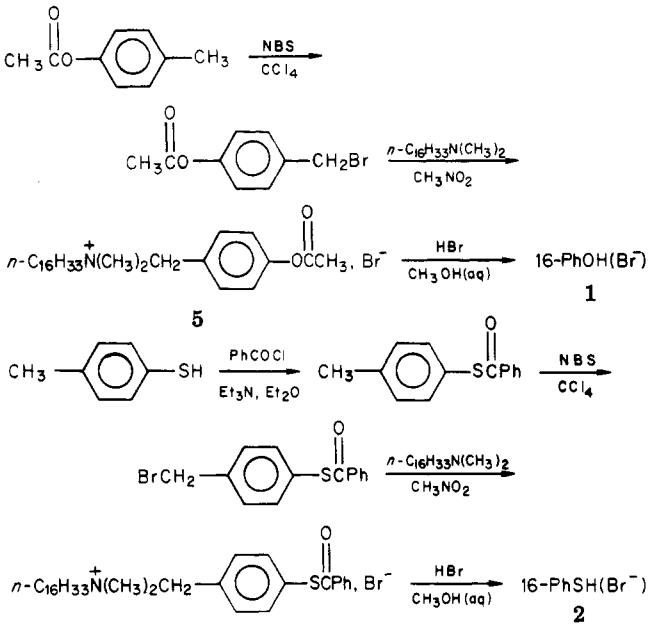
Received February 4, 1981

The phenol and thiophenol functionalized surfactants *N*-*n*-cetyl-*N*,*N*-dimethyl-*N*-(*p*-hydroxy[or *p*-mercapto]benzyl)ammonium bromide (**1** and **2**) were synthesized. Under micellar conditions at pH 8, 1.0×10^{-2} M **1**, comicellized with equimolar cetyltrimethylammonium bromide (CTABr), cleaved 2×10^{-5} M *p*-nitrophenyl acetate (PNPA) with $k_\psi = 0.0123$ s^{-1}, whereas 7.5×10^{-3} M **2**, comicellized with 1.33 equiv of CTABr, cleaved PNPA with $k_\psi = 0.034$ s^{-1}. Relative to suitable model reactions with nonmicellar Me_3N^+ analogues of **1** and **2**, micellar enhancements of 27 and 65, respectively, were observed for **1** and **2**. The origins of these factors are discussed, and the esterolytic reactivities of **1** and **2** are compared to related micellar reagents.

Several years ago, Inoue et al. studied the esterolytic cleavage of *p*-nitrophenyl acetate (PNPA) by various lauroylamino acids solubilized in micellar cetyltrimethylammonium bromide (CTABr).[1] They reported the phenolic amino acid derivative *N*-lauroyltyrosine to be a somewhat more efficient reagent for the cleavage of PNPA than the imidazolyl derivative, *N*-lauroylhistidine. For example, in 0.05 M Tris buffer (pH 8.7, 25 °C) with the [lauroylamino acid]/[CTABr] ratio fixed at 0.125 and [PNPA] = 1×10^{-5} M, rate constant vs. [lauroylamino acid] + [CTABr] profiles gave data from which the pseudo-first-order rate constants for PNPA cleavage by the micelle-solubilized lauroylamino acids were calculated to be 0.168 and 0.26 s^{-1}, respectively, for the histidine and tyrosine systems.[1]

The prevailing interest in the remarkable esterolytic properties of imidazolyl surfactant systems[2] prompted us to take a closer look at the comparative reactivities of phenolic and imidazolyl micellar reagents toward PNPA. In this paper, we report the syntheses and comparative esterolytic kinetic properties of phenolic, thiophenolic, and imidazolyl micellar surfactants and appropriate model compounds.

Scheme I



Results

Synthesis. The surfactants of interest were **1** (16-PhOH) and **2** (16-PhSH); these targets also required the corresponding model compounds **3** (1-PhOH) and **4** (1-PhSH). The syntheses of 16-PhOH and 16-PhSH are outlined in Scheme I.

Commercially available *p*-methylphenyl acetate was brominated with NBS, affording the *p*-bromomethyl derivative. This was used to quaternize *N*,*N*-dimethylcetylamine, affording salt **5**, a protected form of the desired surfactant. Deprotection with aqueous methanolic HBr afforded 16-PhOH,Br$^-$ in a 25% overall yield for the three steps. The surfactant was characterized by NMR and

(1) T. Inoue, K. Nomura, and H. Kimizuka, *Bull. Chem. Soc. Jpn.*, **49**, 719 (1976).

(2) The imidazole moiety can be supplied as an hydrophobic acylhistidine or benzimidazole solubilized by a "carrier" micelle (e.g., CTABr): (a) A. Ochoa-Solano, G. Romero, and C. Gitler, *Science*, **156**, 1243 (1967); (b) C. Gitler and A. Ochoa-Solano, *J. Am. Chem. Soc.*, **90**, 5004 (1968); (c) P. Heitmann, R. Husung-Bublitz, and H. J. Zunft, *Tetrahedron*, **30**, 4137 (1974); (d) A. P. Osipov, K. Martinek, A. K. Yatsimirski, and I. V. Berezin, *Dokl. Akad. Nauk SSSR*, **215**, 914 (1974); (e) K. Martinek, A. P. Osipov, A. K. Yatsimirski, V. A. Dadali, and I. V. Berezin, *Tetrahedron Lett.*, 1279 (1975); (f) K. Martinek, A. P. Osipov, A. K. Yatsimirski, and I. V. Berezin, *Tetrahedron*, **31**, 709 (1975). Or, the imidazole moiety can be part of the surfactant itself: (g) W. Tagaki, M. Chigira, T. Ameda, and Y. Yano, *J. Chem. Soc., Chem. Commun.*, 219 (1972); (h) J. M. Brown and C. A. Bunton, *ibid.*, 969 (1974); (i) J. M. Brown, C. A. Bunton, and S. Diaz, *ibid.*, 971 (1974); (j) D. G. Oakenfull and D. E. Fenwick, *Aust. J. Chem.*, **27**, 2149 (1974); (k) R. A. Moss, R. C. Nahas, S. Ramaswami, and W. J. Sanders, *Tetrahedron Lett.*, 3379 (1975); (l) U. Tonellato, *J. Chem. Soc., Perkin Trans. 2*, 771 (1976); (m) R. A. Moss, R. C. Nahas, and S. Ramaswami, *J. Am. Chem. Soc.*, **99**, 627 (1977); (n) W. Tagaki, S. Kobayashi, and D. Fukushima, *Chem. Commun.*, 29 (1977); (o) U. Tonellato, *J. Chem. Soc., Perkin Trans. 2*, 821 (1977); (p) R. A. Moss, T. J. Lukas, and R. C. Nahas, *Tetrahedron Lett.*, 3851 (1977); (q) W. Tagaki, D. Fukushima, T. Eiki, and Y. Yano, *J. Org. Chem.*, **44**, 555 (1979); (r) J. M. Brown, P. A. Chaloner, and A. Colens, *J. Chem. Soc., Perkin Trans. 2*, 71 (1979).

0022-3263/81/1946-3029$01.25/0