mmol) in dry benzene (25 ml) at 5 °C was added phosphorus pentachloride (2.08 g, 10 mmol) over a 10-min period. When evolution of hydrogen chloride had ceased, the solution was cooled to 4 °C and a solution of stannic chloride (3.35 g, 13 mmol) in benzene (50 ml) was added dropwise with stirring over a 30-min period. The magenta colored mixture was allowed to warm up to room temperature and was stirred for 2 h. Decomposition of the complex with 0.1 M HCl and ice, followed by benzene extraction with washing and drying ($MgSO_4$), gave, upon removal of the solvent, a yellow oil. This was chromatographed on silica gel using 3:1 benzene–chloroform as eluent to give yellow crystals (1.9 g, 68%) mp 161–162 °C. An analytical sample (mp 162.5–163 °C) was obtained by recrystallization from benzene–hexane as bright yellow prisms with a brilliant green fluorescence: ir (KBr) 1625 cm^{-1}; NMR (Unisol-D) δ 7.0–8.3 (m, 8 H, aromatic), 4.6 (s, 2 H, CH_2), 4.0 (s, 3 H, OCH_3). Anal. Calcd for $C_{17}H_{12}O_2S$: C, 72.83; H, 4.32; S, 11.43. Found: C, 73.09; H, 4.25; S, 11.60.

Attempted Synthesis of 11-Acetoxy-6-methoxynaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (2b). A stirred mixture of 1-(3′-carboxy-2′-thenyl)-2-methoxynaphthalene (**7**, 1.0 g, 3.36 mmol), acetic anhydride (25 ml), acetic acid (20 ml), and freshly fused zinc chloride (1.2 g, 8.8 mmol) was heated under reflux for 0.5 h. To the hot solution was added water (25 ml) dropwise and the reaction mixture was cooled in ice. Yellow needles separated and were removed by filtration (0.8 g, 71%), mp 207–208.5 °C. This substance gave a positive iodoform test. Recrystallization from benzene–hexane followed by sublimation in vacuo gave **8** as pale yellow needles: mp 208–208.5 °C; ir (KBr) 1660 (C=O), 1645 cm^{-1} ($ArCOCH_3$); NMR (acetone-d_6) δ 7.5–6.9 (m, 7 H, aromatic), 4.55 (s, 2 H, CH_2); 4.0 (s, 3 H, OCH_3), 2.45 (s, 3 H, $COCH_3$). Anal. Calcd for $C_{19}H_{14}O_3S$: C, 70.79; H, 4.38; S, 9.95. Found: C, 70.59; H, 4.35; S, 10.06.

6-Methoxy-7,11-dihydronaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (9). To a cooled, stirred suspension of lithium aluminum hydride (0.23 g, 6.0 mmol) in ether (25 ml) was added, with cooling and stirring, a solution of aluminum chloride (0.80 g, 6 mmol) in 25 ml of anhydrous ether. To this was added a solution of 6-methoxynaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophen-11(7*H*)-one (1.0 g, 3.5 mmol) in ether (35 ml). The mixture was stirred under reflux for 16 h. Careful addition of 5% H_2SO_4 followed by extraction with ether, washing with $NaHCO_3$, and drying ($MgSO_4$) gave upon removal of the solvent a white solid (0.5 g, 54%), mp 130–132 °C. Sublimation gave an analytical sample: mp 129–130 °C; NMR ($CDCl_3$) δ 6.9–7.8 (m, 7 H, aromatic), 4.7 (s, 2 H, CH_2), 4.4 (s, 2 H, CH_2), 4.0 (s, 3 H, OCH_3). Anal. Calcd for $C_{17}H_{14}OS$: C, 76.66; H, 5.30; S, 12.04. Found: C, 76.41; H, 5.31; S, 12.13.

6-Methoxy-11,11-dideuterio-7,11-dihydronaphtho-[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (10). From the ketone **3b** (2.0 g), lithium aluminum deuteride (1.0 g), and aluminum chloride (32 g) there was obtained 1.85 g (98%) of **10**: mp 129.5–130 °C; NMR ($CDCl_3$) δ 6.8–7.7 (m, 7 H, aromatic), 4.6 (s, 2 H, CH_2), 3.9 (s, 3 H, OCH_3); mol wt by mass spectrum, 268 (calcd for $C_{17}H_{12}D_2OS$, 268).

6-Methoxy-11-isopropylidene-7,11-dihydronaphtho[1′,8′:4,5,6]cyclohepta[1,2-*b*]thiophene (11). To a filtered ethereal solution of isopropylmagnesium bromide from isopropyl bromide (12.37 g, 0.1 mmol) and magnesium (2.67 g, 0.11 g-atom) was added a solution of 1.0 g (3.5 mmol) of the ketone **3b** in 50 ml of 1:1 benzene–ether. The mixture was stirred under reflux for <1.5 hr. and was then hydrolyzed with 10% NH_4Cl solution (200 ml). The organic layer was separated, washed with water and Na_2CO_3, and dried ($MgSO_4$). Evaporation of the ether left a red oil which was taken up in methanol (30 ml) containing 2 drops of 12 M HCl and heated under reflux for 12 h. Removal of the methanol gave a yellow oil (2.0 g) which was freed from traces of acid and was then chromatographed on alumina (50 g) using hexane as the eluent. A colorless oil (0.2 g) was obtained which solidified after 5 days to white prisms (0.2 g, 19%), mp 119.5–120 °C. Recrystallization from hexane followed by sublimation gave an analytical sample: mp 119–120 °C; NMR ($CDCl_3$) δ 7.3–7.7 (m, 6 H, aromatic), 6.95 (s, 1 H, aromatic C_5H), 4.6 (2 H, quartet, 2 H), 4.0 (s, 3 H, OCH_3), 1.93 (s, 3 H, CH_3), 1.85 (s, 3 H, CH_3). The AB quartet centered at 4.6 has J_{AB} = 16 Hz and δ_{AB} = 34 Hz. Anal. Calcd for $C_{20}H_{18}OS$: C, 78.39; H, 5.92; S, 10.47. Found: C, 78.46; H, 6.06; S, 10.22.

Registry No.—**3b**, 59463-61-5; **5**, 59463-62-6; **6**, 59463-63-7; **7**, 59463-64-8; **8**, 59463-65-9; **9**, 59463-66-0; **10**, 59463-67-1; **11**, 59463-68-2; 2,3-dibromothiophene, 3140-93-0; 2-methoxynaphthaldehyde, 5392-12-1; isopropyl bromide, 75-26-3.

References and Notes

(1) We are indebted to Dr. Kurt L. Loening of Chemical Abstracts Service for information pertaining to the naming of this system.
(2) M. P. Cava and R. H. Schlessinger, *Tetrahedron*, **21**, 3073 (1965).
(3) J. Blackwell and W. J. Hickinbottom, *J. Chem. Soc.*, 1405 (1961).
(4) D. W. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.*, **36**, 3999, 4004 (1971).
(5) P. T. Lansbury, *Acc. Chem. Res.*, **2**, 210 (1969).
(6) D. W. H. MacDowell and F. L. Ballas, *J. Org. Chem.*, **39**, 2239 (1974).
(7) All temperatures are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as an internal standard (δ 0) and solvents as specified.
(8) N. P. Buu-Hoï and D. Lavit, *J. Chem. Soc.*, 2776 (1955).

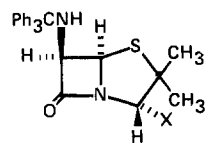
A Reaction of Chlorosulfonyl Isocyanate and 6-Tritylaminopenicillanic Acid Leading to the Anhydropenicillin Rearrangement

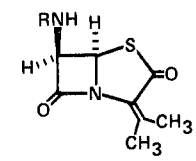
Hermann Faubl

Pfizer Central Research, Pfizer Inc., Groton, Connecticut 06340

Received April 12, 1976

Since their initial preparation,[1] anhydropenicillins have continued to attract interest.[2] We now report a reaction of 6-tritylaminopenicillanic acid (1) with chlorosulfonyl isocyanate (CSI) that leads to the formation of anhydro-6-tritylaminopenicillanic acid (**5**).





1, X = COOH
2, X = CN
3, X = $CO_2CONHSO_2Cl$
4, X = $CONHSO_2Cl$

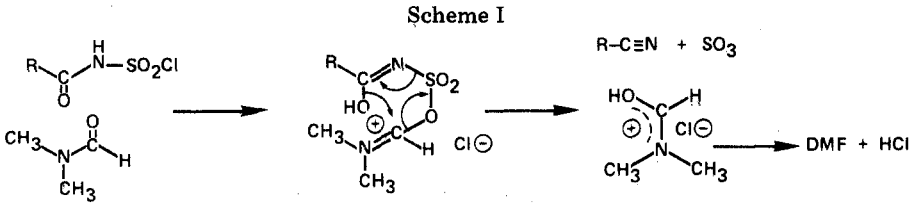
5, R = $-CPh_3$
6, R = $-H$, $CH_3(C_6H_4)SO_3H$

In connection with other work, we attempted a synthesis of the penicillin nitrile **2** from carboxylic acid **1** by application of the methods of Lohaus[3] and Vorbrüggen.[4] These involve, respectively, treatment of a chlorosulfonylamide with either an amide such as dimethylformamide (DMF, Scheme I) or a base such as triethylamine (Scheme II). In favorable cases, the chlorosulfonylamide is readily obtained by reacting a carboxylic acid with CSI.

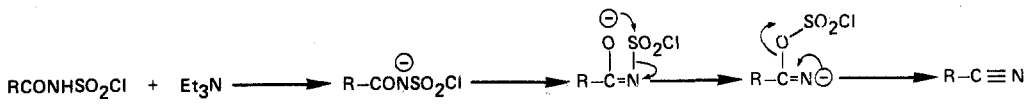
When **1** was treated with a 5% molar excess of CSI in acetonitrile, followed by either DMF or triethylamine, no β-lactam containing materials were isolated with the neutral fraction. Various speculations may be proposed to account for the failure of these straightforward approaches patterened after the successful conditions of Lohaus and Vorbrüggen. The β-lactam moiety perhaps interacted with the chlorosulfonylamide **4**[3,5] or it reacted directly with the CSI.[5] The possibility of other undesirable reactions involving CSI and compounds **1**, **2**, **3**, or **4** may also be inferred.[5] Finally, the fact that penicillins are relatively strong acids[6] may have hampered the $CO_2H \rightarrow CN$ conversion because, according to results of both Lohaus and Vorbrüggen, the CSI reaction is sluggish with strong acids.

On the assumption that the β-lactam amide was the major cause of our difficulties, we treated **1** with CSI in the presence of either DMF or triethylamine. Neither small nor large amounts of DMF were useful, likely because the rate of CSI reaction with DMF[5] was faster than that with the penicillin carboxyl group. When, however, triethylamine was present during the CSI addition, we isolated[7] a fairly pure penicillin derivative contaminated by some triphenylcarbinol[8] according to ir, NMR, and TLC analysis. The presence of two vinylic methyl group resonances suggested that the anhydropenicillin rearrangement had occurred to afford anhydro-6-tritylami-

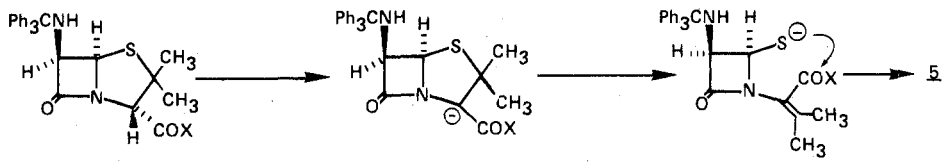
Scheme I



Scheme II



Scheme III



nopenicillanic acid (**5**). This was confirmed by comparison of the analytical data for **5** and for the detritylated derivative **6** with published data for these compounds[9] (see Experimental Section).

Our highest conversion from **1** to **5** was at least 45% without any attempt at optimization.[10] The isolated yields likely suffered because we routinely employed an isolation procedure that would have been satisfactory for our original synthetic goal, the nitrile **2**. This procedure included an aqueous extraction to which anhydropenicillins are reported to be sensitive.[11,12]

Although various speculations may be entertained about the reaction of **1** with CSI, the mechanism for the **1** to **5** conversion is likely analogous to that proposed by Wolfe,[1] which involves base abstraction of the C-3 proton of a suitably activated penicillin 3-carboxyl group (Scheme III) followed by elimination of thiolate and subsequent attack on the activated acid.

Experimental Section

Ir spectra were measured with a Perkin-Elmer Model 21 spectrometer. ^{1}H NMR spectra were recorded on a Varian Model T-60 spectrometer with a dilute solution in deuteriochloroform and tetramethylsilane as an internal standard.

Anhydro-6-tritylaminopenicillanic Acid (5). A solution of 9.16 g (20 mmol) of 6-tritylaminopenicillanic acid (**1**) and 13.9 ml (100 mmol) of triethylamine in 50 ml of acetonitrile was cooled to −35 °C under nitrogen. Then 1.84 ml (21 mmol) of chlorosulfonyl isocyanate (Aldrich Chemical Co., Milwaukee, Wis.) was added over a 5-min period.[13] The dry ice bath was removed and the mixture warmed to 22 °C over 35 min. Then the reaction mixture was heated at 40 °C. Evolution of CO_2 was monitored by sweeping the reaction surface with nitrogen and bubbling the effluent into an aqueous $Ba(OH)_2$ solution. After 20 h the reaction mixture was worked up; although the CO_2 evolution had not entirely ceased, it had greatly diminished. The reaction mixture was concentrated to half volume, diluted with 1:1 ether/saturated aqueous sodium bicarbonate, and partitioned between ether and water. The combined ethereal extracts were washed with a brine solution, dried over sodium sulfate, and concentrated, affording 5.7 g of a beige-colored foam. An ir spectrum showed the distinctive bands of **5** plus some triphenylcarbinol; by NMR analysis this material was about 69% pure **5** (corresponding to a corrected isolated yield of 45%) contaminated mainly by triphenylcarbinol plus a small amount of triethylamine and traces of other components.

The above crude product (2 g) was chromatographed on silica gel with a 7:3 hexane/chloroform solution. According to the ir and NMR spectra, **5** was not effectively separated from the triphenylcarbinol impurity. Adapting methodology suggested by Wolfe,[9] 394 mg from the early eluate were combined in chloroform and isopropyl alcohol and concentrated to a yellow, granular material. This was then triturated with cold acetic acid to afford an off-white solid which was filtered, washed with hexane, and dried to afford 194 mg of pure anhydro-6-tritylaminopenicillanic acid (**5**), mp 157–160 °C (lit.[9] 165–166 °C).

Anal. Calcd for $C_{27}H_{24}N_2O_2S$: C, 73.61; H, 5.49; N, 6.36; S, 7.27. Found: C, 73.71; H, 5.60; N, 6.15; S, 7.10.

The ir spectrum matched that published.[9] The NMR spectrum showed only resonances consistent with **5**: δ_{Me_4Si} ($CDCl_3$) 2.00 (3 H, s), 2.12 (3 H, s), 3.18 (NH, d, J = 11.8 Hz), 4.40 (C-7, 1 H, d, J = 4.0 Hz), 4.81 (C-6, 1 H, dd, J = 4.0, 11.8 Hz), and 7.1–7.7 ppm (Ph_3C, 15 H).

***p*-Toluenesulfonic Acid Salt of Anhydro-6-aminopenicillanic Acid (6).** **5** (50 mg) was dissolved in 0.25 ml of acetone and processed with *p*-toluenesulfonic acid hydrate according to Wolfe[9] to afford 30 mg of **6**, mp 155–157 °C dec (lit.[9] 153–154 °C dec). The ir spectrum matched that published.[9]

Acknowledgment. The expert technical assistance of Mr. Ralph Breitenbach is gratefully acknowledged.

Registry No.—**1**, 40124-92-3; **5**, 17276-71-0; chlorosulfonyl isocyanate, 1189-71-5.

References and Notes

(1) S. Wolfe, J. C. Godfrey, C. T. Holdredge, and Y. G. Perron, *J. Am. Chem. Soc.*, **85**, 643 (1963).
(2) References to other methods for preparing anhydropenicillins and their uses may be found in D. N. McGregor in "Progress in the Chemistry of Organic Natural Products", Vol. 31, W. Herz, H. Grisebach, and G. W. Kirby, Ed., Springer-Verlag New York, New York, N.Y., 1974, p 1; P. G. Sammes, *Chem. Rev.*, **76**, 113 (1976); J. H. Sellstedt, U. S. Patent 3 879 408 (1975).
(3) G. Lohaus, *Chem. Ber.*, **100**, 2719 (1967).
(4) H. Vorbrüggen, *Tetrahedron Lett.*, 1631 (1968).
(5) R. Graf, *Angew. Chem., Int. Ed. Engl.*, **7**, 172 (1968).
(6) H. D. C. Rapson and A. E. Bird, *J. Pharm. Pharmacol., Suppl.*, **15**, 222T (1963).
(7) As judged by ir and NMR of the total reaction mixture, the anhydropenicillin **5** is already present before workup.
(8) Although secondary amines can react with CSI,[5] it was assumed that the trityl group would effectively block that of **1**. Isolation in good yield of **5** shows that this was largely the case. However, spectral and TLC identification of triphenylcarbinol in mixtures where solvolysis should not have occurred does indicate adverse behavior of the 6-tritylamino group under the reaction conditions.
(9) S. Wolfe, *Can. J. Chem.*, **46**, 459 (1968).
(10) Addition of CSI at 0 °C instead of at −35 °C led to a reduction in yield of **5** to 32% from 45%. Using 2 equiv of CSI (added at 0 °C) led to a yield of only 19% for **5** associated with the production of much more triphenylcarbinol.[8] Using pyridine in place of triethylamine led to an isolated mixture that contained only traces of **5** at best.
(11) H. Bundgaard and H. R. Angelo, *Tetrahedron Lett.*, 3001 (1974).
(12) S. Wolfe, J. C. Godfrey, C. T. Holdredge, and Y. G. Perron, *Can. J. Chem.*, **46**, 2549 (1968).
(13) Adding CSI to solutions of **1** in acetonitrile at 0 °C led to an exotherm, suggesting rapid formation of **3**; however CO_2 evolution (**3** → **4?**) continued for a long time although the reactions were heated at 40 or 60 °C.