The Removal and Displacement of the Thiazolidine Ring of Penicillin. III.[1] Reconstruction of the Penam Ring System

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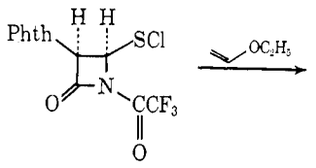
Received May 21, 1973

The sulfenyl chloride **1** reacts with ethyl vinyl ether to give **2** and with appropriate ketones to give **6**. The ring-closed form (**3**) of **2** can be trapped by treatment with acetic anhydride–pyridine. Compounds **6** reacted with mercuric chloride in methanol to give the penam ring structures **9**.

In 1963, after the numerous side chain variations of penicillin had been demonstrated to produce medically useful modifications in activity, and after the biological activity of the cephalosporins had shown that the thiazolidine ring was not inviolate, it was suggested that penicillin research could be directed toward modification of the ring system to produce clinically useful compounds.[2] Since that time, considerable effort has been expended in this direction.[3] Much of it has focused on the conversion of the thiazolidine ring of the penicillins to the dihydrothiazine ring of the cephalosporins. In contrast, very little progress has been reported in making modifications of the thiazolidine ring itself.[4] This paper reports some recent efforts toward that goal.

In the conversion of penicillin to cephalosporin, the most economical methods are those which utilize rearrangements of the five-carbon, fused ring system. In order to make substantial modifications of the thiazolidine ring, it becomes necessary to remove the five-carbon skeleton, replacing it with a new carbon framework. Several methods now exist for removal of the skeleton while retaining the sulfur atom and the requisite cis stereochemistry of the azetidine ring.[1,5] The utilization of the sulfenyl chloride **1**[1] is unique in providing an isolable, reactive intermediate which can be treated with a number of different types of reagents, two of which have already been reported.[1]

Details of the preparation of the sulfenyl chloride **1** are given in the Experimental Section. The potential of this intermediate for reconstruction of the thiazolidine ring is demonstrated in the reaction of **1** with ethyl vinyl ether. The course of the reaction is easily followed by watching the disappearance of the characteristic yellow color of a solution of **1**. In this case the color was discharged immediately upon addition of the vinyl ether,[6] and chromatography of the addition product effected hydrolysis of the sensitive α-



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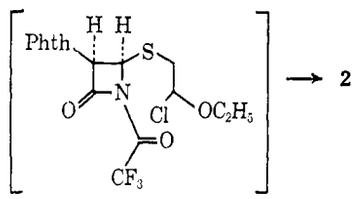
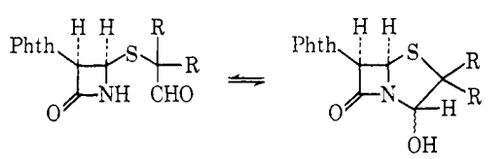


Phth = phthalimido

chloro ether function as well as removal of the trifluoracetyl group.

No NH or aldehyde proton is detectable in the nmr spectrum of the product. It shows a simple AB pattern in the δ 5–6 region (J = 4 Hz), a straightforward ABX pattern for the thiazolidine ring protons, and an aryl proton multiplet and OH singlet. In contrast, **3**[7] shows characteristic aldehyde and NH absorptions



2, R = H
3, R = CH_3

as well as an AB pattern with a larger coupling constant (5 Hz) and further splitting of the low-field portion by NH ($J \cong 1$ Hz). From this data it appears that the aldehyde–carbinolamide equilibrium is shifted well toward the ring-closed form in **2** as compared to **3**. This equilibrium has been discussed by Heusler.[5b] Based on variations of the C_6 substituent, he postulated that larger substituents shift the equilibrium toward the aldehyde owing to increased interaction between $C_{2\beta}$ and C_6 substituents in the carbinolamide. The comparison of **2** and **3** supports this view, in that removal of the $C_{2\beta}$ methyl shifts the equilibrium toward the carbinolamide. The unexpected favoring of the closed penam system in the absence of steric interference is encouraging when considering the prospect of reconstruction of the penam system from a monocyclic β-lactam.

Further encouragement was obtained when it was found that the reaction of **3** with acetic anhydride–

(1) Part II: J. C. Sheehan, D. Ben-Ishai, and J. U. Piper, *J. Amer. Chem. Soc.*, **95**, 3064 (1973).

(2) J. C. Sheehan, "Molecular Modifications in Drug Design," Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, p 15.

(3) For a review, see R. D. G. Cooper and D. O. Spry in "Cephalosoporins and Penicillins," E. H. Flynn, Ed., Academic Press, New York, N. Y., 1972, Chapter 5.

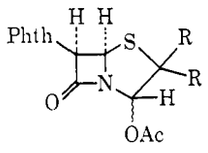
(4) For an exception see R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **85**, 1896 (1963); **91**, 1401 (1969).

(5) (a) J. C. Sheehan, U. S. Patent 3,487,074 (1969); *Chem. Abstr.*, **72**, 66933z (1969); (b) K. Heusler, *Helv. Chim. Acta*, **55**, 388 (1972); (c) R. D. G. Cooper and F. L. Jose, unpublished results cited in ref 3, pp 235–236; (d) I. Ager, D. H. R. Barton, G. Lucente, and P. G. Sammes, *Chem. Commun.*, **601** (1972); (e) J. H. C. Naylor, M. J. Pearson, and R. Southgate, *ibid.*, **57**, 58 (1973).

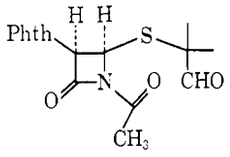
(6) The reaction of **1** with cyclohexene takes *ca.* 1 hr to lose the yellow color, and with ethyl acrylate several hours are required. This is the order expected for the electrophilic sulfenyl chloride.

(7) J. C. Sheehan and K. G. Brandt, *J. Amer. Chem. Soc.*, **87**, 5468 (1965).

pyridine produced **4a** as an oil containing only about 10% of **5** as a contaminant. The faster rate of O-



4a, R = CH_3
b, R = H



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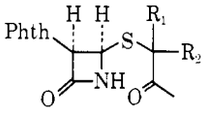
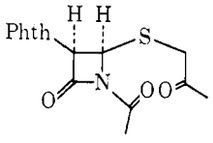
acylation *vs.* N-acylation serves to pull the equilibrium toward the closed system. Thus it became of interest to investigate the applicability of this type of ring closure to other systems.

In a known reaction of sulfenyl chlorides,[8] **1** reacted with acetone at room temperature to give, after chromatography, **6a** in 77% yield. Similarly, methyl



6a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



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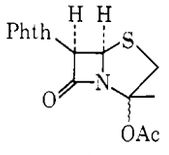

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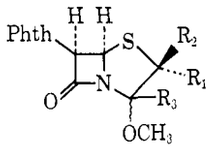
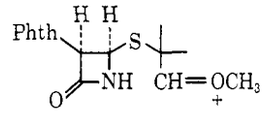
ethyl ketone and methyl isopropyl ketone gave **6b** and **6c**, respectively. In the latter two cases the crude products were slightly contaminated by the products resulting from attack of **1** at the methyl group of the ketones, but recrystallization gave pure products. Ketone **6b** was obtained as a mixture of C_2 epimers (penam numbering) in unequal amounts. The nmr spectra of these three compounds give no indication of the presence of any carbinolamide. Further, treatment of **6a** with acetic anhydride–pyridine gave **7** as the only isolated product. The distinction between structures **7** and **8** is easily made in several ways. In the nmr spectrum the chemical shifts of the *O*- and *N*-acetyl methyl protons are δ 2.1–2.2 and 2.5, respectively. As indicated above, the coupling constant for the azetidine ring protons decreases from *ca.* 5 Hz in **3** and **6** to 4 Hz in **2**, **4a**, and **4b**. On the other hand, N-acylation causes an increase in the coupling constant to *ca.* 6 Hz. In the ir spectra of compounds **2** and **4** the β-lactam carbonyl occurs at 1790–1795 cm^{-1}. The most obvious difference between **7** and **8**, that of the presence or absence of a ketone carbonyl, is not useful in the phthalimido derivatives, since the ketone carbonyl is usually masked by the lower frequency imide band.

The failure of the acetylation procedure to effect closure of **6a** to a penam system indicates that the difference in rates between O- and N-acylation is not large enough to offset the low concentration of carbinolamide.

In considering alternative ring closure methods, an earlier attempt at 1–5 bond cleavage was useful. The use of mercuric salts had been investigated for this purpose, in a manner similar to that recently reported by Stoodley.[9] In contrast to these authors the reaction of **3** with mercuric chloride in methanol gave mainly the dimethyl acetal of **3**. Reinvestigation of this reaction resulted in the isolation of **9a** in 28% yield when equimolar amounts of **3** and mercuric chloride were stirred at 50° in methanol. An intermediate related to **10** in which the electrophilic char-



9a, $R_1 = R_2 = CH_3$; $R_3 = H$
b, $R_1 = R_2 = H$; $R_3 = CH_3$
c, $R_1 = R_3 = CH_3$; $R_2 = H$



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acter of the potential C_3 is increased may be involved, although it is not clear whether the ring closure is a kinetic or equilibrium process.

Application of this procedure to ketone **6a** gave **9b** in 40% yield. Assignment of the penam structure is in accordance with the criteria used above: a lack of NH absorption in the ir and nmr spectra, β-lactam carbonyl absorption at 1780–1785 cm^{-1}, and azetidine ring proton coupling constants of 4 Hz. When **6c** was similarly treated, the corresponding penam system was not formed in isolable quantities. The difference in reactivity of **6a** and **6c** is directly analogous to the previous comparison made between **2** and **3**. Here again, the $C_{2\beta}$ methyl inhibits ring closure because of its spatial proximity to the bulky phthalimido group in the penam system[10]

In view of this, it is not surprising that the reaction of the epimeric mixture of ketones **6b** gives a single closed product, and on steric grounds the structure **9c** with the $C_{2\alpha}$ methyl group can be assigned. This assignment is supported by the chemical shift data presented in Table I. There is a substantial differ-

TABLE I
CHEMICAL SHIFTS FOR THE C_2 PROTONS IN PENAM SYSTEMS

Structure	δ ($H_{2\alpha}$)	δ ($H_{2\beta}$)
2	3.25	3.78
4b	3.26	3.86
9b	3.31	3.51
9c		4.06

ence in the chemical shifts of the α and β protons at C_2. Taking the effect of a methyl group into account, the C_2 proton of **9c** absorbs within the range of the $C_{2\beta}$ protons. On the basis of the above steric arguments, the lower field absorptions should be assigned to the β protons. (In the case of C_2 *gem*-dimethyl groups in the penam system, the lower field absorption has been assigned to the β-methyl.[11])

This assignment is also consistent with the H_2–H_3 couplings observed in the nmr spectra of **2** and **4b** if the following two assumptions are made: (1) the

(8) For a review, see I. B. Douglass in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, Elmsford, N. Y., 1961, Chapter 30.

(9) R. J. Stoodley and N. R. Whitehouse, *J. Chem. Soc., Perkin Trans. 1*, 32 (1973).

(10) That **3** should close more readily than **6c** follows from the comparison of carbinolamide equilibria in **2** and **6a** and from the expected greater reactivity of the aldehyde *vs.* the ketone.

(11) R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969).

C_3 substituent occupies the less crowded α side of the molecule, and (2) $J_{cis} > J_{trans}$. The latter assumption is usually reliable for five-membered rings which do not deviate appreciably from planarity,[12] a situation dictated here by the fused β-lactam ring. In both **2** and **4b** the C_2 and C_3 protons give rise to an ABX pattern with $J_{AX} \cong 0$ and $J_{BX} = 5$ Hz (A is the higher field C_2 proton, X is H_3). This leads to the conclusion that, if H_3 is β (assumption 1), the higher field proton at C_2 must be α (trans) and the lower field proton β (cis). Examination of models for the conformation which has been assigned to phenoxymethylpenicillin[11] indicates that a dihedral angle between H_2 and H_3 of 90–100°, for which J would be expected to approach 0 Hz, is not unreasonable. The arguments presented here are self-consistent and follow the expected pattern for "well-behaved" molecules. The assignments remain tentative, however, and the configuration at C_3 in **9b** and **9c** remains ambiguous.

Experimental Section

Melting points, determined on a Fisher-Johns hot stage, are corrected. Ir spectra were recorded in methylene chloride solution on a Perkin-Elmer Model 237 spectrophotometer. Nmr spectra were determined in deuteriochloroform unless otherwise noted, using tetramethylsilane as an internal standard. Nmr spectra were recorded on Varian T-60 or Hitachi Perkin-Elmer R-20B spectrometers. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Sulfenyl Chloride 1. 3-Phthalimido-4-(2′-hydroxy-1′,1′-dimethylethylthio)azetidin-2-one.—A solution of 3.0 g (9.4 mmol) of **3**[7] in 50 ml of tetrahydrofuran was cooled in an ice bath, and 2.0 ml (4.1 mmol) of a solution of 386 mg of sodium borohydride in 5 ml of water was added. The solution was stirred in the ice bath for 3 min and brought to pH 3–4 with 1 *N* hydrochloric acid. The resulting solution was poured into 150 ml of methylene chloride and washed with three 50-ml portions of water. The methylene chloride solution was dried and evaporated to a white foam. This was redissolved in methylene chloride and the solution was concentrated to give 2.6 g (97%) of white solid. Recrystallization from methylene chloride–hexane gave the crystalline alcohol: mp 196–197°; $[\alpha]^{23}D$ −6° (*c* 0.91, $CHCl_3$); ir 3600–3420 (broad), 3400, 1785, 1770, 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 7.04 (broad s, 1, NH), 5.65 (dd, 1, $J_{1,4}$ = 1 Hz, $J_{3,4}$ = 4.8 Hz, H-4), 5.40 (d, 1, J = 4.8 Hz, H-3), 3.50 (s, 2, CH_2), 2.40 (broad s, 1, OH), 1.08 and 1.07 [two s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74; S, 10.01. Found: C, 55.99; H, 5.13; N, 8.60; S, 10.00.

***N*-Trifluoroacetyl-3-phthalimido-4-(2′-trifluoroacetoxy-1′,1′-dimethylethylthio)azetidin-2-one.**—A solution of 2.0 g of the above alcohol and 10 ml of trifluoroacetic anhydride in 200 ml of methylene chloride was stirred with 1.5 g of anhydrous potassium carbonate for 64 hr at room temperature. The mixture was filtered and the filtrate was evaporated to a white solid. This was recrystallized from methylene chloride–hexane at −78° to give 2.67 g (83%) of the trifluoroacetyl derivative: mp 148–149°; $[\alpha]^{23}D$ −125° (*c* 1.2, $CHCl_3$); ir 1825, 1775, 1730 sh, and 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 5.80 (AB quartet, 2, J = 6.4 Hz, H-3 and H-4), 4.31 (AB quartet, 2, J = 11 Hz CH_2), 1.45 and 1.35 [two s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{19}H_{14}N_2O_6SF_6$: C, 44.54; H, 2.75; N, 5.47; S, 6.26; F, 22.25. Found: C, 44.57; H, 2.73; N, 5.55; S, 6.41; F, 22.36.

To a solution of 500 mg (0.98 mmol) of the above trifluoroacetyl derivative in 10 ml of methylene chloride was added 3.5 ml (2.1 mmol) of a solution of chlorine in carbon tetrachloride (44 mg/ml). The solution stood for 9–16 hr at room temperature and was concentrated *in vacuo* to a yellow oil: ir 1830, 1775, 1725 sh, and 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 6.06 (s, 2, H-3 and H-4); in C_6D_6 an AB quartet appeared at δ 5.25 (J = 6.8 Hz). This oil was used without further purification.

(12) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 288.

3-Hydroxy-6-phthalimidopenam (2).—The sulfenyl chloride 1 from 500 mg of the trifluoroacetyl derivative was dissolved in 5 ml of methylene chloride and 0.2 ml of ethyl vinyl ether was added. The yellow color of the solution disappeared immediately. The solution stood for 1 hr and was concentrated to a colorless oil which was chromatographed on 25 g of Florisil. After washing the column with 200 ml of methylene chloride, the product eluted in 2.5 l. of 9:1 methylene chloride–ethyl acetate. Evaporation of the solvents left an oil which crystallized from methylene chloride–hexane to give 96 mg (34%) of amorphous white solid. Recrystallization gave an analytical sample: mp 146–147°; $[\alpha]^{23}D$ 134° (*c* 0.67, $CHCl_3$); ir 3600, 1790, 1770 and 1720 cm^{-1}; nmr (acetone-d_6) δ 7.98 (s, 4, aryl), 6.06 (d, 1, J = 5 Hz, H-3), 5.77 and 5.52 (two d, 2, H = 4 Hz, H-5 and H-6), 3.68 (dd, 1, J_{gem} = 11 Hz, J_{vic} = 5 Hz, H-2β), 3.22 (d, 1, J = 11 Hz, H-2α), 2.95 (s, 1, OH).

Anal. Calcd for $C_{13}H_{10}N_2O_4S$: C, 53.79; H, 3.47; N, 9.65; S, 11.05. Found: C, 53.57; H, 3.36; N, 9.54; S, 11.03.

2,2-Dimethyl-3-acetoxy-6-phthalimidopenam (4a).—A solution of 66 mg of **3** in 0.6 ml of acetic anhydride and 0.1 ml of pyridine stood at room temperature for 3 hr and was concentrated at 0.5 mm to a clear oil. This was dissolved in methylene chloride and reconcentrated to a white foam. A 50-mg sample was chromatographed on 6 g of Florisil. After the column was washed with 100 ml of methylene chloride, the product was eluted with 9:1 methylene chloride–ethyl acetate. Evaporation of the solvents left an oil: ir 1795, 1775 sh, and 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 6.50 (s, 1, H-3), 5.65 and 5.50 (two d, 2, H = 4 Hz, H-5 and H-6), 2.20 (s, 3, OAc), 1.81 and 1.55 [two s, 6, $(CH_3)_2$]. Small signals (±10%) are visible which correspond to those expected for the *N*-acetyl derivative of **3**.

3-Acetoxy-6-phthalimidopenam (4b).—A solution of 50 mg of **2** in 0.6 ml of acetic anhydride and 0.1 ml of pyridine stood for 3 hr at room temperature and was concentrated at 0.5 mm to a white solid. This was chromatographed on 6 g of Florisil. The product eluted in the first 50 ml of 9:1 methylene chloride–ethyl acetate and was recrystallized from methylene chloride–hexane to give 35 mg (61%) of white crystals: mp 195–196°; $[\alpha]^{23}D$ 179° (*c* 0.89, $CHCl_3$); ir 1795, 1775, 1745, and 1720 cm^{-1}; nmr δ 7.8 (m, 4, aryl), 6.89 (d, 1, J = 5 Hz, H-3), 5.68 and 5.47 (two d, 2, J = 4 Hz, H-5 and H-6), 3.86 (dd, 1, J_{gem} = 11, J_{vic} = 5 Hz, H-2β), 3.26 (d, 1, J = 11 Hz, H-2α), 2.14 (s, 3, OAc).

Anal. Calcd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.63; N, 8.42; S, 9.64. Found: C, 54.28; H, 3.65; N, 8.35; S, 9.51.

3-Phthalimido-4-(2′-keto-1′-propylthio)azetidin-2-one (6a).—The sulfenyl chloride 1 from 500 mg of trifluoroacetyl derivative was dissolved in 5 ml of benzene, and 0.5 ml of acetone was added. The solution stood for 24 hr and was concentrated to a yellow oil, which was chromatographed on 25 g of Florisil. After the column was washed with 125 ml of 9:1 methylene chloride–ethyl acetate, the product was eluted with 750 ml of 4:1 and 100 ml of 7:3 methylene chloride–ethyl acetate. Evaporation of the solvents left a solid which was recrystallized from methylene chloride–hexane to give 228 mg (77%) of white crystals: mp 189–90°; $[\alpha]^{23}D$ −26° (*c* 0.55, $CHCl_3$); ir 3380, 1790, 1770, and 1725 cm^{-1}; nmr (pyridine-d_5) δ 7.5–8.0 (m, 4, aryl), 6.16 (dd, $J_{1,4}$ = 1, $J_{3,4}$ = 4.8 Hz, H-4), 5.50 (d, 1, J = 4.8 Hz, H-3), 5.05 (broad, s, 1, NH), 3.58 (s, 2, CH_2), 2.07 (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{12}N_2O_4S$: C, 55.26; H, 3.98; N, 9.21; S, 10.54. Found: C, 55.26; H, 3.99; N, 9.00; S, 10.61.

3-Phthalimido-4-(2′-keto-1′-methyl-1′-propylthio)azetidin-2-one (6b).—In the same manner as for **6a**, the sulfenyl chloride from 500 mg of trifluoroacetyl derivative in 5 ml of benzene and 0.5 ml of 2-butanone gave a colorless oil. After chromatography and recrystallization, 210 mg (68%) of white crystals were obtained: mp 154–155°; ir 3380, 1790, 1770, and 1725 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 7.17 (broad s, 1, NH), 5.71 (broadened doublet, 1, J = 5 Hz, H-4), 5.20 (d, 1, J = 5 Hz, H-3, 3.5 (two overlapping q, 1, J = 7 Hz, SCHCO), 2.25 (s, 3, CH_3CO), 1.4 (two overlapping d, 3, J = 7 Hz, CH_3CS).

Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.79; S, 10.07. Found: C, 56.65; H, 4.64; N, 8.78; S, 10.29.

3-Phthalimido-4-(2′-keto-1′,1′-dimethyl-1′-propylthio)azetidin-2-one (6c).—In the same manner as for **6a**, the sulfenyl chloride from 500 mg of trifluoroacetyl derivative in 5 ml of benzene and 0.5 ml of 3-methyl-2-butanone gave a black oil. After chromatography and recrystallization, 170 mg (52%) of white crystals were obtained: mp 176–177°; $[\alpha]^{23}D$ −35° (*c* 0.99, $CHCl_3$); ir 3390, 1790, 1770, 1725, and 1690 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 6.82 (broad s, 1, NH), 5.70 (dd, 1, $J_{1,4}$ = 1, $J_{3,4}$ = 5 Hz, H-4),

5.05 (d, 1, J = 5 Hz, H-3), 2.26 (s, 3, CH_3CO), 1.46 and 1.38 [two s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.42; S, 9.64. Found: C, 57.64; H, 4.90; N, 8.38; S, 9.74.

N-Acetyl-3-phthalimido-4-(2′-keto-1′-propylthio)azetidin-2-one (7).—A suspension of 60 mg of **6a** in 1 ml of acetic anhydride and 0.5 ml of pyridine was stirred at 52° for 16 hr. The resulting light-brown solution was concentrated at 0.5 mm to an oil which was chromatographed on 15 g of Florisil. After the column was washed with 125 ml of methylene chloride, the product was eluted with 250 ml of 9:1 methylene chloride–ethyl acetate. Evaporation of the solvents left an oil which crystallized from methylene chloride–hexane to give 30 mg (44%) of delicate crystals: mp 181–182°; $[\alpha]^{23}D$ −77° (c 1.1, $CHCl_3$); ir 1800, 1775, 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 5.73 and 5.45 (two d, 2, J = 6 Hz, H-3 and H-4), 3.73 (AB quartet, 2, J = 16 Hz, CH_2), 2.50 (s, 3, NAc), 2.23 (s, 3, CAc).

Anal. Calcd for $C_{16}H_{14}N_2O_5S$: C, 55.48; H, 4.07; N, 8.08; S, 9.25. Found: C, 55.29; H, 3.92; N, 7.98; S, 9.12.

2,2-Dimethyl-3-methoxy-6-phthalimidopenam (9a).—A solution of 250 mg (0.7 mmol) of **3** and 190 mg (0.7 mmol) of mercuric chloride in 12 ml of methanol was stirred at 52° for 16 hr. Evaporation of the solvent left an oily residue which was triturated with benzene. The benzene extracts were concentrated to an oil which was chromatographed on 20 g of Florisil. The column was washed with 650 ml of methylene chloride, and the product was eluted with 9:1 methylene chloride–ethyl acetate. Evaporation of the solvents left an oil which crystallized from ethyl acetate–hexane to give 65 mg (28%) of long needles: mp 125–126°; $[\alpha]^{23}D$ 215° (c 1.2, $CHCl_3$); ir 1790, 1775, 1720 cm^{-1}; nmr δ 7.8 (m, 4, aryl), 5.60 and 5.40 (two d, 2, J = 4.0 Hz, H-5 and H-6), 4.97 (s, 1, H-3), 3.52 (s, 3, OCH_3), 1.64 and 1.54 [two s, 6, $(CH_3)_2$].

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.42; S, 9.64. Found: C, 58.00; H, 4.90; N, 8.40; S, 9.80.

3-Methyl-3-methoxy-6-phthalimidopenam (9b).—In the same manner as for **9a**, the oil from 144 mg (0.47 mmol) of **6a** and 129 mg (0.47 mmol) of mercuric chloride was chromatographed on 14 g of Florisil. After the column was washed with 125 ml of methylene chloride, the product began to elute. The solvent was changed to 9:1 methylene chloride–ethyl acetate, and evaporation left a crystalline solid. Recrystallization from ethyl acetate–hexane gave 60 mg (40%) of needles: mp 170–172°; $[\alpha]^{23}D$ 149° (c 0.91, $CHCl_3$); ir 1785, 1770, and 1720 cm^{-1}; nmr δ 7.9 (m, 4, aryl), 5.63 and 5.33 (two d, 2, J = 4 Hz, H-5 and H-6), 3.41 (AB quartet, 2, J = 10.5 Hz, CH_2), 3.36 (s, 3, OCH_3), 1.96 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.69; H, 4.43; N, 8.79; S, 10.07. Found: C, 56.29; H, 4.34; N, 8.57; S, 10.31.

2,3-Dimethyl-3-methoxy-6-phthalimidopenam (9c).—In the same manner as for **9a**, the oil from 134 mg (0.42 mmol) of **6b** and 115 mg (0.42 mmol) of mercuric chloride was chromatographed on 13 g of Florisil. After the column was washed with 110 ml of methylene chloride, the product began to elute. The solvent was changed to 9:1 methylene chloride–ethyl acetate, and the product was obtained as an oil which crystallized from ethyl acetate–hexane to give 23 mg (16%) of needles: mp 130–131°; $[\alpha]^{23}D$ 191° (c 1.1, $CHCl_3$); ir 1785, 1770, and 1720 cm^{-1}; nmr δ 7.8 (m, 4, aryl), 5.57 and 5.25 (two d, 2, J = 4 Hz, H-5 and H-6), 4.06 (q, 1, J = 7 Hz, H-2), 3.36 (s, 3, OCH_3), 1.83 (s, 3, C_3 CH_3), 1.32 (d, 3, J = 7 Hz, C_2 CH_3).

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.42; S, 9.64. Found: C, 57.55; H, 4.85; N, 8.17; S, 9.77.

Acknowledgment.—We wish to thank the Sloan Basic Research Fund No. 27609 for support of this work. J. U. P. acknowledges partial support by Simmons College for a leave of absence.

Registry No.—**1**, 41189-52-0; **2** open form, 41189-53-1; ring form, 41189-54-2; **3** open form, 41189-55-3; **3** ring form, 41189-56-4; **4a**, 41189-57-5; **4b**, 41189-58-6; **6a**, 41189-59-7; **6b**, 41189-60-0; **6c**, 41189-61-1; **7**, 41189-62-2; **9a**, 41189-63-3; **9b**, 41189-64-4; **9c**, 41189-65-5; 3-phthalimido-4-(2′-hydroxy-1′,1′-dimethylethylthio)azetidin-2-one, 41189-66-6; *N*-trifluoroacetyl-3-phthalimido-4-(2′-trifluoroacetoxy-1′,1′-dimethylethylthio)azetidin-2-one, 41189-67-7; acetone, 67-64-1; 2-butanone, 78-93-3; 3-methyl-2-butanone, 563-80-4.

Benzimidazoles from Preformed Imidazoles. A Novel Approach

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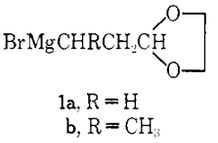
Received May 17, 1973

Benzimidazole derivatives **5a–e** are prepared in a two-step procedure by successive reactions of readily available imidazole-5-carboxaldehydes with reagents $BrMgCHRCH_2CHOCH_2CH_2O$ (R = H, CH_3) and cyclization of the resulting carbinols **3a–e** under controlled conditions. Alcohol $ArCHOHCH_2CH_2CHOCH_2CH_2O$ (Ar = 1-benzyl-2-methyl-5-imidazolyl) has been oxidized (MnO_2) to the ketone; addition of Grignard reagents thereto and ring closure of the new carbinols to compounds **9** and **10** illustrates a general preparation of 7-substituted benzimidazoles.

Benzimidazoles are traditionally synthesized by ultimate construction of the imidazole moiety, whereby the prerequisite *o*-phenylenediamines are cyclized with carboxylic acids and/or derivatives thereof. An alternative assembly, commencing with preformed and suitably functionalized imidazoles, has, to the best of our knowledge, hitherto escaped attention. Such an approach is herewith illustrated. It is, by its nature, complementary to existing methods, thereby allowing entry into systems otherwise found to be difficultly accessible.

In a recent[1] report concerning the hydroxymethylation of 1,2-disubstituted imidazoles, the preparation of the imidazolyl-5-methanols and 4,5-dimethanols was described. The reaction, carried out in refluxing aqueous CH_2O, proved to be pH sensitive and produced satisfactory results only in buffered (NaOAc–AcOH) milieu. Subsequent oxidation [$Pb(OAc)_4$] of the products to the aldehydes proceeded cleanly, thus providing an efficient and cheap two-step route to many imidazole-5-carboxaldehydes.

Grignard reagents **1a** and **1b** have, since 1969, found application in the synthesis of (±)-nuciferal[2]



1a, R = H
b, R = CH_3

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(2) G. Büchi and H. Wüest, *J. Org. Chem.*, **34**, 1122 (1969).