Sulfur-free Penicillin Derivatives. I. Functionalization at C-5

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Direct chlorination of an anhydropenicillin produces a sulfur-free dichloride in which the two C—S bonds are replaced by two C—Cl bonds. The reaction is general for anhydropenicillins and proceeds with predominant retention of configuration at C-5 except in the case of anhydro-6-phthalimidopenicillin, which gives variable stereochemical results.

Hydrolysis of the COCl function to COOH, conversion of the acids or acid chlorides to methyl, *t*-butyl, and benzhydryl esters, and regeneration of the acids from the latter two esters are described.

Nucleophilic substitution at C-5 of these compounds proceeds smoothly and with inversion of configuration. The rate of the reaction depends on the C-6 substituent in the direction H_2N > acylamino > phthalimido.

La chloration directe de l'anhydropénicilline conduit à un dérivé dichloré avec absence de soufre, dans lequel les deux liaisons C—S sont remplacées par deux liaisons C—Cl. Cette réaction est générale pour les anhydropénicillines et se fait avec prédominance de rétention de configuration sur le C-5, sauf dans le cas de l'anhydro phtalimido-6 pénicilline qui donne des résultats variables concernant la stéréochimie.

L'hydrolyse de la fonction COCl en COOH, la conversion des acides ou chlorures d'acides en esters méthylique, t-butylique et diphenyl méthylique et la regénération des acides à partir de ces deux derniers esters, sont décrites.

La substitution nucléophile au niveau du C-5 de ces composés se fait de façon douce, avec inversion de configuration. La vitesse de la réaction dépend du substituant sur le C-6, avec dans l'ordre NH_2 > acylamino > phtalimido. [Traduit par le journal]

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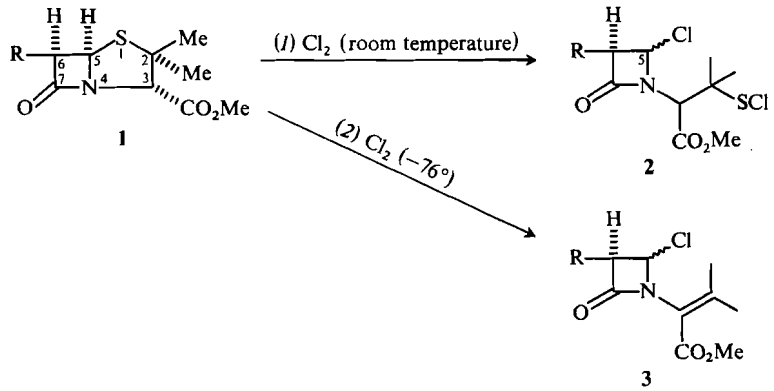
There is much current interest in chemical modifications of the penicillin nucleus which retain the β-lactam ring (1). Most of these transformations produce compounds which also retain the sulfur atom, but there are three exceptions (2–4) which are relevant to the work reported here and in the accompanying communications (5). In the work of Kukolja (4), shown in eq. 1, both C5-epimers[2] of **2** were obtained in crystalline form, but the epimers of **3** were not,[3] and the reaction conditions indicate that fission of the *thiazolidine* ring requires careful attention to experimental detail.

We report here a *general* reaction of *anhydro*-penicillins which, like that shown in eq. 1, involves a chlorinolysis. In the present reaction, quantitative conversion to sulfur-free compounds is achieved and, with the exception

[1]



[1]This work was presented in the Merck, Sharp and Dohme Award Lecture, Quebec City, Quebec, June, 1972.
[2]The penicillin numbering system is employed here (*cf.* **1**).
[3]A 4:1 mixture of 5S:5R epimers was obtained "in high yield".

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of anhydro-6-phthalimidopenicillin[4] (**4***a*; see below), the opposite stereoselectivity is observed, *i.e.*, the **R** configuration predominates at C-5. In addition, careful control of solvent composition, temperature, and chlorine concentration is not necessary. Thus, direct chlorination (excess chlorine, CH_2Cl_2, 20°, 3 min) of **4***a*, followed by removal of the solvent under reduced pressure, afforded a quantitative yield (by n.m.r.) of a 3:2 mixture of two isomeric compounds (**5***a* and **6***a*). The major isomer **5***a*, m.p. 210° (dec.), was crystallized from $CHCl_3$–petroleum ether, λ_{max} ($CHCl_3$) 242 (10 000).

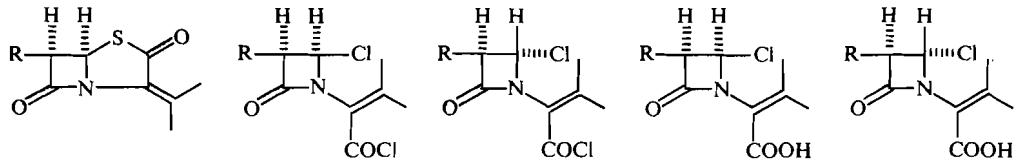
Anal. Calcd. for $C_{16}H_{12}N_2O_4Cl_2$: C, 52.3; H, 3.31; N, 7.69; Cl, 19.4. Found: C, 52.03; H, 2.96; N, 7.76; Cl, 19.53.

The i.r. spectrum (KBr) of **5***a* (and of the mixture of **5***a* and **6***a*) shows peaks at 5.48 (COCl), 5.55 (β-lactam), 5.62, 5.79 μ (phthalimido). The n.m.r. spectrum[5] has peaks at 2.13 (4H, d), 3.78 (1H, d, 4.2 Hz), 4.75 (1H, d, 4.2 Hz), 7.57 (3H, s), 7.65 (3H, s).

The relative amounts of **5***a* and **6***a* were not significantly affected by chlorination in the presence of excess $Et_4N^+Cl^-$ or by a change in the temperature of the reaction; other chlorinating agents (SO_2Cl_2, pyridinium trichloride, pyrrolidone hydrotrichloride) gave more complex mixtures.

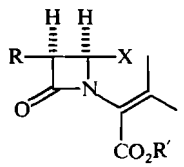
Interestingly, in some reactions, under otherwise identical experimental conditions, the opposite stereoselectivity[4] was obtained. The difference appears to be related to the origin and purity of the starting material **4***a*. The R stereoselectivity described above was achieved from **4***a* prepared by rearrangement (1*a*) of the penicillanic acid, and containing trace amounts (*ca.* 1%) of *N*-carboethoxyphthalimide (7). In contrast a 3:1 5S:5R ratio of epimers was obtained following chlorination of rigorously purified **4***a* or **4***a* prepared from anhydrotritylaminopenicillin (1*b*). The pure dichloride **6***a* could be isolated from such mixtures.

Hydrolysis of **5***a* (boric acid – borax buffer



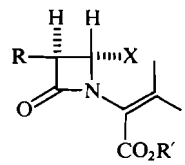
4 **5** **6** **7** **9**

4–9: *a*, R = $C_6H_4(CO)_2N$; *b*, R = $TsOH{\cdot}H_2N$; *c*, R = $C_6H_5CH_2CONH$; *d*, R = $C_6H_5CH_2OCONH$; *e*, R = CCl_3CH_2OCONH



8

a R = $C_6H_4(CO)_2N$; R′ = CH_3; X = Cl
b R = $C_6H_4(CO)_2N$; R′ = *t*-C_4H_9; X = Cl
c R = $C_6H_5CH_2CONH$; R′ = CH_3; X = Cl
d R = $TsOH{\cdot}H_2N$; R′ = CH_3; X = Cl
e R = H_2N; R′ = CH_3; X = Cl
f R = $C_6H_4(CO)_2N$; R′ = CH_3; X = N_3
g R = $C_6H_4(CO)_2N$; R′ = CH_3; X = OAc
h R = H_2N; R′ = CH_3; X = N_3
i R = $C_6H_5CH_2CONH$; R′ = CH_3; X = N_3



10

a R = $C_6H_5(CO)_2N$; R′ = CH_3; X = Cl
b R = $C_6H_5(CO)_2N$; R′ = $CH(C_6H_5)_2$; X = Cl
c R = $C_6H_5(CO)_2N$; R′ = *t*-C_4H_9; X = Cl
d R = $C_6H_5(CO)_2N$; R′ = CH_3; X = N_3
e R = H_2N; R′ = CH_3; X = Cl
f R = H_2N; R′ = CH_3; X = N_3
g R = $C_6H_5CH_2CONH$; R′ = CH_3; X = N_3

[4]Phthalimidopenicillanic acid and its derivatives often display different chemical properties from the (biologically more significant) 6-acylaminopenicillanic acids (2*b*, *c*, 6).

[5]Unless otherwise mentioned, all n.m.r. spectra were recorded in $CDCl_3$ at 60 MHz. Chemical shifts are given in τ values relative to internal TMS. Although, to conserve space, spectroscopic data are not quoted in detail for all new compounds, all of these gave i.r., n.m.r., and high resolution mass spectra in full accord with the assigned structures and stereochemistry. In addition, all crystalline compounds gave satisfactory elemental analyses (C, H, N, Cl).

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(8), aqueous acetone, or aqueous THF) gave the acid **7***a*, m.p. 168–174° (dec.) in 73–90% yield. Methylation of **7***a* (CH_2N_2, Et_2O–CH_2Cl_2) produced the ester **8***a*, m.p. 178–180° (dec.), $[\alpha]_D^{20}$ −8.9° ($CHCl_3$) in 97% yield. The same compound was obtained from **5***a* in 93% yield upon treatment with absolute methanol (30 min, 20°). Similarly, hydrolysis of **6***a* afforded the acid **9***a*, m.p. 164–166° (dec.), which was converted to the corresponding methyl ester **10***a*, m.p. 192–194°, $[\alpha]_D^{20}$ −144° ($CHCl_3$).

The *t*-butyl ester **8***b* was obtained in 33% yield by *refluxing* **5***a* in anhydrous *t*-BuOH for 21 h. The C5-epimer **10***c*, prepared similarly, melted at 170–172°. Dissolution of **8***b* in trifluoroacetic acid (TFA), and evaporation of the solvent after 3 min, gave **7***a* in quantitative yield. The benzhydryl ester **10***b*, prepared (Ph_2CN_2) in 99% yield from **9***a*, also underwent ready reconversion to **9***a* upon treatment with TFA.

Anhydrotritylaminopenicillin (1*b*) decomposed during chlorination. However the derived (1*b*) *p*-toluenesulfonic acid salt **4***b* reacted smoothly to give a 4:1 5R:5S mixture of **5***b* and **6***b* as a stable (below 20°) white powder, m.p. 148–149° (dec.). Hydrolysis of this powder afforded a 4:1 mixture of the acids **7***b* and **9***b*. Phenylacetylation of this mixture ($NaHCO_3$, $PhCH_2COCl$, H_2O–CH_3COCH_3) gave the penicillin G analog **7***c*, whose methyl ester **8***c* was crystallized in 51% yield (from **4***b*), m.p. 111–115° (dec.). Alternatively, methanol treatment of the mixture of **5***b* and **6***b*, and crystallization from chloroform–hexane, produced the pure 5R ester **8***d*, m.p. 125–130° (dec.), in 67% yield (from **4***b*).

Neutralization of **8***d* and reaction of the free base **8***e*, m.p. 67–70° (dec.), with Nefkens' reagent (7) yielded **8***a*, confirming that chlorinolysis proceeds in the same manner with both side chains. Phenylacetylation of **8***e* gave **8***c* in 82% yield. This provides an alternative to the sequence **5***b* → **7***b* → **7***c* → **8***c*, and indicates that **7***b* can serve as a general intermediate for acylamino members of this class of compounds.

The anhydro derivatives (**4***c*–*e*) of benzyl, benzyloxycarbonyl,[6] and trichloroethoxycarbonylpenicillin[7] underwent ready chlorination–hydrolysis to give quantitative yields of the acids **7***c* + **9***c*, **7***d* + **9***d*, and **7***e* + **9***e*. In each case a 3–4:1 mixture of 5R (**7**): 5S (**9**) epimers was obtained and the proportion of epimers was not significantly affected by changes in the experimental conditions. Methylation of the mixture of **7***c* + **9***c* afforded **8***c*, completing the interrelation of the phthalimido, amino and acylamino series of derivatives.[8]

Equilibration of **8***a* and **10***a* proceeded smoothly, upon refluxing (acetone, 12 h; 2-butanone, 4 h) in the presence of tetraethylammonium chloride. The same equilibrium mixture, containing in all cases an excess (1.5–2.5:1) of the *trans*-isomer **10***a* was obtained starting with either pure epimer, the position of equilibrium depending upon solvent, temperature, and concentration of tetraethylammonium chloride. The compounds recovered from equilibrium mixtures were identical in all respects to those prepared directly from **4***a*.

Reaction of **8***a* with sodium azide (DMF, 90°, 3 h) afforded the 5S azide **10***d*, m.p. 144–145°, in 67% yield, uncontaminated by the 5**R** isomer **8***f*. Under the same conditions **10***a* yielded **8***f*, m.p. 183–187° in 52% yield, uncontaminated by **10***d*. With tetraethylammonium acetate ($CHCl_3$, reflux, 17 h) **10***a* gave **8***g* in 62% yield. These various observations demonstrate that nucleophilic displacement on a β-lactam ring proceeds with inversion of configuration (9).

Equilibration of **8***e* and **10***e* was best achieved (**10***e*:**8***e* = 6:1) with tetramethylguanidinium chloride (CH_2Cl_2, reflux, 12 h). Reaction of **8***e* with tetramethylguanidinium azide (10) (2 equiv, $CHCl_3$, reflux) yielded **10***f* (90%); the epimer **8***h*, m.p. 116–117°, was obtained similarly from **10***e* in 85% yield. Phenylacetylation of **8***h* ($C_6H_5CH_2COOH$, DCC, CH_2Cl_2) afforded the 5-azidopenicillin G analog **8***i*, m.p. 102–103° (97%); the C5-epimer **10***g* was obtained similarly from **10***f* or by reaction of **8***c* with tetramethylguanidinium azide (2 equiv, $CHCl_3$, reflux).

Each of the reactions **8***a* → **10***d*, **8***e* → **10***f*, **8***c* → **10***g* represents the conversion of a 5R-chloro into a 5S-azido compound. Reaction

[6]Prepared in 90% yield from **4***b*.

[7]Prepared in 85% yield from **4***b*.

[8]Structure proofs of the benzyloxycarbonyl and trichloroethoxycarbonyl acids are based on their subsequent reactions (2).

8*e* → **10***f* was complete in 0.5 h; under the same conditions **8***c* → **10***g* was complete in 2 h and **8***a* was recovered unchanged. Consequently the effect of the C6-substituent on the rate of nucleophilic displacement from C-5 is H_2N > acylamino > phthalimido.

The sequences established here provide general routes to carboxyl-protected sulfur-free penicillin derivatives, with control over the substituent at C-6 and the functionality and stereochemistry at C-5.

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1. See *inter alia* (*a*) S. WOLFE, J. C. GODFREY, C. T. HOLDREGE, and Y. G. PERRON. Can. J. Chem. **46**, 2549 (1968); (*b*) S. WOLFE. Can. J. Chem. **46**, 459 (1968); (*c*) S. WOLFE and W. S. LEE. Chem. Commun. 262 (1968); (*d*) Y. G. PERRON, L. B. CRAST, J. M. ESSERY, R. R. FRASER, J. C. GODFREY, C. T. HOLDREGE, W. F. MINOR, M. E. NEUBERT, R. A. PARTYKA, and L. C. CHENEY. J. Med. Chem. **7**, 483 (1964); (*e*) J. C. SHEEHAN and K. G. BRANDT. J. Am. Chem. Soc. **87**, 5468 (1965); (*f*) R. B. WOODWARD and K. HEUSLER. Chem. Abstr. **72**, 100689*m* (1970); (*g*) J. A. WEBBER, E. M. VAN HEYNINGEN, and R. T. VASILEFF. J. Am. Chem. Soc. **91**, 5674 (1969); (*h*) R. B. MORIN, B. G. JACKSON, R. A. MUELLER, E. R. LAVAGNINO, W. B. SCANLON, and S. L. ANDREWS. J. Am. Chem. Soc. **91**, 1401 (1969); (*i*) R. D. G. COOPER and F. L. JOSÉ. J. Am. Chem. Soc. **92**, 2575 (1970); (*j*) D. O. SPRY. J. Am. Chem. Soc. **93**, 5008 (1970); (*k*) G. V. KAISER, C. W. ASHBROOK, and J. E. BALDWIN. J. Am. Chem. Soc. **93**, 2344 (1971); (*l*) D. H. R. BARTON, D. G. T. GREIG, G. LUCENTE, P. G. SAMMES, M. V. TAYLOR, C. M. COOPER, G. HEWITT, and W. G. E. UNDERWOOD. Chem. Commun. 1683 (1970); (*m*) D. H. R. BARTON, D. G. T. GREIG, P. G. SAMMES, and M. V. TAYLOR. Chem. Commun. 845 (1971); (*n*) R. D. G. COOPER. J. Am. Chem. Soc. **94**, 1018 (1972); (*o*) R. D. G. COOPER and F. L. JOSÉ. J. Am. Chem. Soc. **94**, 1021 (1972); (*p*) L. D. CAMA, W. J. LEANZA, T. R. BEATTIE, and B. G. CHRISTENSEN. J. Am. Chem. Soc. **94**, 1408 (1972); (*q*) R. A. FIRESTONE, N. SCHELECHOW, D. B. R. JOHNSTON, and B. G. CHRISTENSEN. Tetrahedron Lett. 375 (1972).
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