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SYNTHESIS OF (±)-PENICILLIN AND (±)-2-SPIROCYCLOPENTANOBISNORPENICILLIN SYSTEMS

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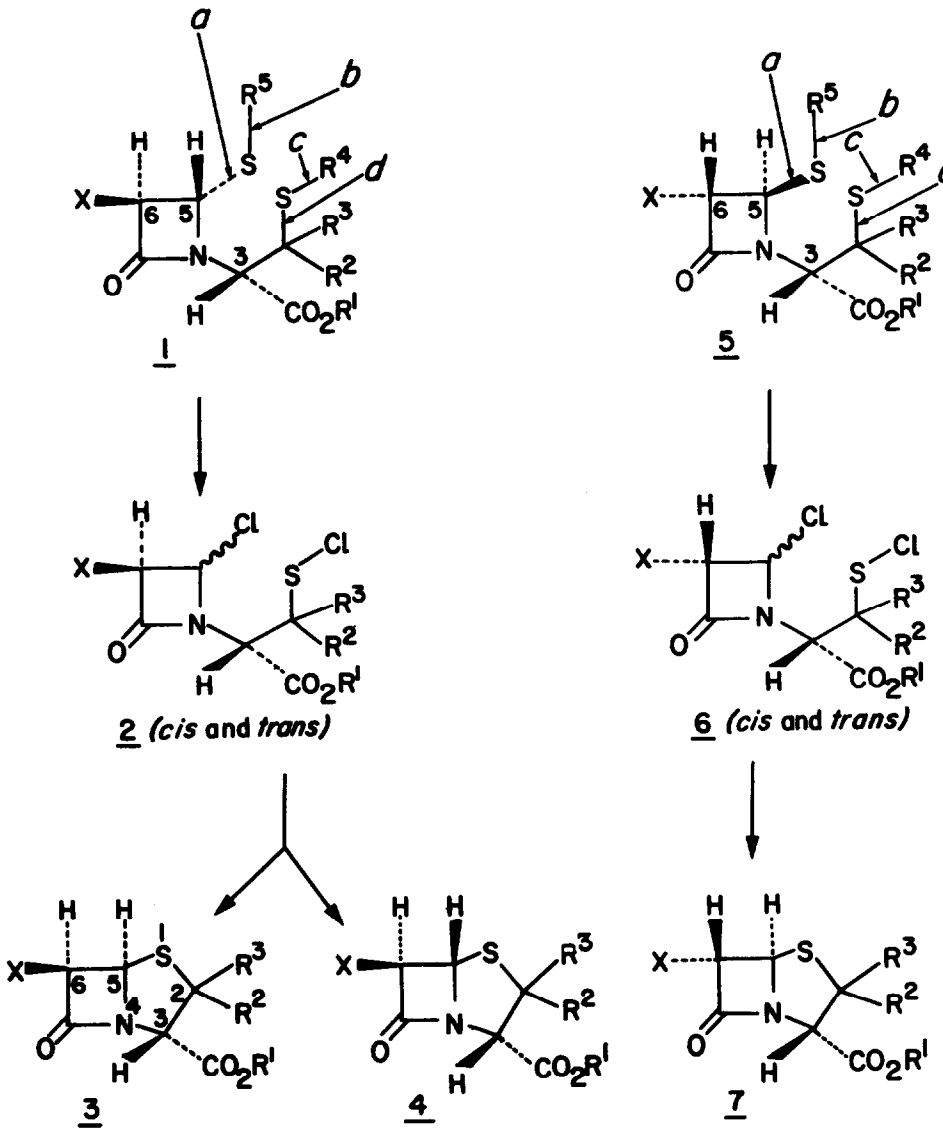
The synthesis of the penicillin bicyclic system meets with difficulties deriving from its particular structural features which embody multiple functional groups on a strained relatively small molecule. In fact, only a few total syntheses have been reported.[1] We now describe a new totally synthetic route to the penicillin system as well as to a new C-2 nuclear analogue thereof.

The β-lactams 1[2] which have the same relative configuration at positions C-3[3] and C-6[3] as the natural penicillins, and their diastereoisomers 5[2], which have at these centers the same relative configuration as 6-epipenicillins, are readily obtained from the corresponding β,β-dialkylcysteines by a procedure previously employed for the preparation of similar β-lactams from other α-aminocarboxylic acids.[4] The selection of groups R^4 and R^5 was guided by the requirement that simultaneous chlorinolysis of the two sulfide bonds in 1 or in 5 will result in the preferential cleavage of the bonds a and c, leaving the bonds b and d intact. Since the normal cleavage mechanism of a sulfide group seems to involve the formation of a chlorosulfonium ion followed by the unimolecular lysis of the bond between the sulfur atom and the alkyl group, and since this cleavage is aided by the ability of the alkyl group to stabilize a positive charge,[5] we have chosen groups "R^4" which favor formation of carbonium ions, namely t-butyl and p-methoxybenzyl groups, and a group "R^5" which does not favor the formation of a carbonium ion, namely methyl group. Thus, for example, addition of chlorine in carbon tetrachloride (80 ml, 0.092 M) at 0°C to 1d (0.003 mol) in methylene dichloride (65 ml), followed by evaporation, gave the bis-chloro compound 2d, presumably along with MeSCl and p-MeO.$C_6H_4CH_2Cl$ or secondary reaction products thereof. By the same procedure, the β-lactams 1a-c,e were converted into the corresponding bis-chloro-compounds 2[2], while the isomers 5c-e were converted into the corresponding isomeric bis-chloro-compounds 6.[2] The products of chlorinolysis were used immediately in the next step without purification. The cis and trans-β-lactams 2a exhibit the same ir and nmr spectra as that reported[6] for the chlorinolysis products of 3a, obtained from a natural penicillin.



a, X=phthalimido, R^1=R^2=R^3=R^5=Me, R^4=p-MeO.C_6H_5.CH_2

b, X=phthalimido, R^1=$CHPh_2$, R^2 and R^3= -$(CH_2)_4$-, R^4=p-MeO.C_6H_4.CH_2, R^5=Me

c, X=N_3, R^1=R^4=Bu^t, R^2=R^3=R^5=Me

d, X=N_3, R^1=$CHPh_2$, R^2 and R^3= -$(CH_2)_4$-, R^4=p-MeO.C_6H_5.CH_2, R^5=Me

e, X=N_3, R^1=R^4=Bu^t, R^2 and R^3= -$(CH_2)_4$-, R^5=Me

Compounds 2 were converted into the fused bicyclic systems 3[2] and 4,[2] and compounds 6 into 7[2] by treatment with stannous chloride in dioxane,[7] yields and nmr data are given in the Table. For example, stirring a mixture of 2d (obtained from the chlorinolysis of 0.003 mole 1d) in dioxane (60 ml) with anhydrous stannous chloride (0.003 mole), at 0°C, during 40 hr, under argon, afforded, after chromatography (silica gel, acetone-hexane as eluant) (±)-2-spirocyclopentanobisnorpenicillin 3d (2%) and its 5-epimer 4d (25%). Essentially the same procedure was used for the cyclisation of the other azidolactams 2c,e and 6c-e, while cyclisations of the phthalimidolactams 2a,b were carried out at 60-100°C during 90-100 min.

The conversion of penams 3 into potentially useful antibiotics require the removal of the carboxyl protecting group and conversion of the azido group into an acylamino group, and in the case of the 6-epipenams 7 inversion of the stereochemistry at the C-6 center is also required. Such transformations have been recently described[10] for the conversion of benzyl 6-α-azidopenicillanate 7 (R^1=$PhCH_2$, R^2=R^3=Me, X=N_3) into penicillin G and their applicability for the transformation of (±)-3d and (±)-7d into (±)-6-acylamino-3-carboxy-2-spirocyclopentanopenams [3 (X-acylamino, R^1=H, R^2 and R^3=-$(CH_2)_4$-], new C-2 penicillin analogs are now being examined.

Table. Yields[a] and Nmr Data[b] of Penicillanates

S.M.	Prod.[c]	(yield %)	3-H	5-H(J, Hz)[d]	6-H(J, Hz)[d]
1a	3a[e]	(16)	4.69	5.62 (4)	5.71 (4)
	4a[f]	(70)	3.92	5.59 (2)	5.47 (2)
1b	4b	(34)	4.11	5.60 (2)	5.40 (2)
1c	3c	(8)	4.38	5.50 (4)	4.92 (4)
	4c	(13)	3.64	5.00 (2)	4.64 (2)
5c	7c	(38)	4.44	5.25 (2)	4.62 (2
1d	3d	(2)	4.75	5.49 (4)	4.91 (4)
	4d	(25)	3.95	4.95 (2)	4.68 (2)
5d	7d[g]	(24)	4.75	5.27 (1.5)	4.59 (1.5)
1e	4e	(23)	3.75	4.94 (2)	4.69 (2)
5e	7e	(23)	4.53	5.22 (2)	4.57 (2)

[a] Of two steps 1 → 2 → 3 + 4 or 5 → 6 → 7. [b] In parts per million in $CDCl_3$. [c] Ms, ir, and complete nmr data are consistent with the assigned structures. [d] Of doublets. [e] Nmr data are consistent with that reported in Ref. 8 and 9. [f] Nmr data are consistent with that reported in Ref. 7 and 9. [g] Nmr data for 5-H and 6-H are consistent with that reported in Ref. 10 for benzyl 6-α azidopenicillanate.

It is assumed that the present synthesis can be readily extended for the preparation of various 2,2-dialkylpenames. So far only a few other C-2 penicillin analogs namely, the bis-norpenicillin V[11] and the 2S- and 2R-norpenicillin V,[12] have been obtained by total synthesis.

References and Notes

1. For a recent total synthesis of the penicillin system and references to previous ones see: J.E. Baldwin, M.A. Christie, S.B. Haber, and L.I. Kruse, J.Am.Chem.Soc., 98, 3045 (1976).
2. All chiral compounds in this work consist of racemic mixtures, for simplicity,only one enantiomer of each pair has been displayed in the formulas
3. Penicillin numbering system is employed (cf. 3).
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