Stereospecific Synthesis of the Rearrangement Product Obtained on Reaction of Penicillins with Methyl Chloroformate

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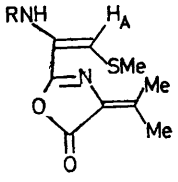
Summary The product from the interesting rearrangement of penicillins with methyl chloroformate has been shown to have the structure and stereochemistry (X) by total stereospecific synthesis; this is in keeping with mechanistic considerations.

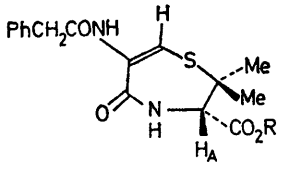
THERE has recently been considerable interest in the rearrangements of penicillins and cephalosporins.[1] Penicillin V (VIII; R = $PhOCH_2CO$) has been reported[2] to rearrange to (I; R = $PhOCH_2CO$) on treatment with methyl chloroformate and we have found that penicillin G (VIII; R = $PhCH_2CO$), under the same conditions, gives a product to which the structure (I; R = $PhCH_2CO$) might be assigned. The original workers[2] have implied that the stereochemistry of the product is that shown in (I) with the SMe group *cis* to the carbonyl of the enone unit and this implication has now entered the review literature[3] without comment. We have now synthesised the isomers (I;

TABLE

				(IV)			(V)		
R^1	R^2	R^3	R^4	λ_{max}/nm	ϵ	τ(HA)	λ_{max}/nm	ϵ	τ (HA)
$PhCH_2CO$	H	$PhCH_2$	Me	299	15,700	2·03	288	18,300	3·43
$PhCH_2CO$	H	Me	Me	297	10,500	2·01	285	19,200	3·23
$PhCH_2CO$	H	Me	H	298	6,985	—	285	13,600	—
Phthaloyl[8]		Me	Me	295	16,600	2·93	286	18,400	3·08



(I)



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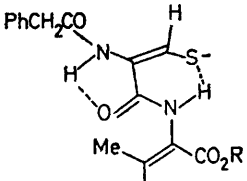

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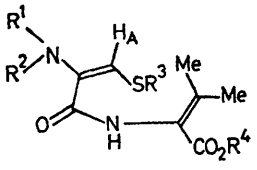

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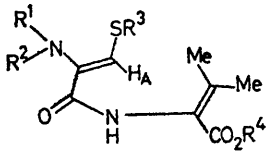
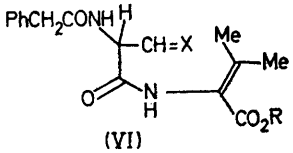
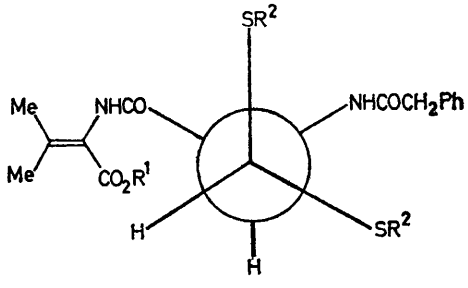


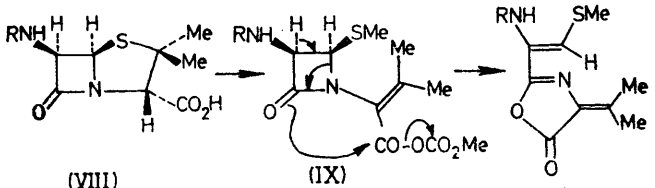
(V)



(VI)



(VII)



(VIII) (IX) (X)

R = $PhCH_2CO$) and (X; R = $PhCH_2CO$) by two separate stereospecific routes and have shown (X; R = $PhCH_2CO$) to be identical to the rearrangement product of penicillin G.

The thiazepine (II; R = Me) has been shown[4] to be amenable to base-catalysed ring opening, and alkylation of the anion (III) has yielded a series of compounds (IV).† Hydrolysis of the thiazepine (II; R = Me) with LiI in pyridine has yielded the acid (II; R = H),† but attempts to achieve the base-catalysed ring-opening reaction with this acid have failed, presumably owing to the proximity of the carboxylate anion to the acidic hydrogen H_A (in II). In order to obtain the acids (IV; R^4 = H), it was, therefore, necessary to protect the carboxy-group by synthesis of the t-butyl ester (II; R = Bu^t).† This readily underwent the ring-opening–alkylation sequence to yield (IV; R^1 = $PhCH_2CO$; R^2 = H; R^3 = Me; R^4 = Bu^t),† and hydrolysis yielded (IV; R^1 = $PhCH_2CO$; R^2 = H; R^3 = Me; R^4 = H).† It is significant that in each case, the ring-opening–alkylation reaction gave but one geometric isomer. Since the intermediate enethiolate would best be stabilised by hydrogen bonding as shown in (III), it was most likely that the stereochemistry of the products would be as in (IV) with the chromophore RS–C=C–C=O *cis*.

In attempts to obtain the *trans*-isomers (V), the acetal [VI; X = $(OEt)_2$; R = Me][5] was hydrolysed with acid to (VI; X = O, R = Me)† and with LiI in pyridine and then acid to (VI; X = O; R = H).† These aldehydes were readily converted into thioacetals [VI; X = $(SR^1)_2$, R = Me or H]† by reaction with thiols and a Lewis acid. Treatment of these thioacetals with base effected elimination of thiol and, in every case except one, this reaction proved totally stereospecific, the one exception providing but a small amount of a second isomer. The products from these reactions proved to be isomeric to the compounds obtained from the thiazepine (II) and so were assigned the structures (V).† This implies that *gauche*-interactions are minimised in conformation (VII) of the thioacetals and it is interesting that the only case where stereospecificity was not total was the base-catalysed elimination from [VI; X = $(SMe)_2$; R = Me)† where the sulphide had minimal steric requirements, and that the acid [VI, X = $(SMe)_2$; R = H],† which would be ionised in base, underwent elimination with complete stereospecificity.

The stereochemical assignments which we have made on the basis of theoretical considerations were borne out on consideration of the spectral data of these compounds as outlined in the Table. The isomers (IV) deemed to have a *cis*-chromophore absorbed with the expected[6] lower ϵ value and the expected[7] higher λ_{max}, than the isomers (V) deemed to have a *trans*-chromophore.

Reaction of (IV; R^1 = $PhCH_2CO$; R^2 = H; R^3 = Me; R^4 = H) with acetic anhydride yielded a product (I;

† All new compounds had satisfactory analytical and spectral data.

R = $PhCH_2CO$),† λ_{max} 273 and 348 nm, τ (HA) 1·92, while reaction of (V; R^1 = $PhCH_2CO$; R^2 = H; R^3 = Me; R^4 = H) yielded (X; R = $PhCH_2CO$),† λ_{max} = 271 and 333 nm, τ (HA) 2·81, which was identical in all respects to the compound derived from reaction of penicillin G with methyl chloroformate. The penicillin rearrangement is therefore stereospecific and the stereochemistry of (X) is more in keeping than that of (I) with a concerted mechanism; (VIII)→(IX)→(X), or with a mechanism in which the thermodyanamically more stable isomer would be the product.

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[2] S. Kukolja, R. D. G. Cooper, and R. B. Morin, *Tetrahedron Letters*, 1969, 3381.
[3] Ref. 1, pp. 243 and 245.
[4] N. J. Leonard and R. Y. Ning, *J. Org. Chem.*, 1967, **32**, 677.
[5] J. Cheney, C. J. Moores, J. A. Raleigh, A. I. Scott, and D. W. Young, *J.C.S. Chem. Comm.*, 1974, 47; *J.C.S. Perkin I*, in the press.
[6] A. E. Gillam and E. S. Stern, 'An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry,' Arnold, London, 1958, p. 267.
[7] H. P. Schad, *Helv. Chim. Acta*, 1955, **38**, 1117.
[8] Compound (IV; R^1, R^2 = phthaloyl, R^3 = R^4 = Me) was synthesised by base-catalysed ring opening and alkylation of the corresponding thiazepine, prepared by the method of M. H. Benn and R. E. Mitchell, *Canad. J. Chem.*, 1972, **50**, 2195, and the *trans*-isomer (V; R^1, R^2 = phthaloyl, R^3 = R^4 = Me)was obtained by photolysis of (IV; R^1, R^2 = phthaloyl, R^3 = R^4 = Me).