Downloaded from rstb.royalsocietypublishing.org

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Penems and Related Substances

R. B. Woodward

Phil. Trans. R. Soc. Lond. B 1980 **289**, 239-250
doi: 10.1098/rstb.1980.0042

Email alerting service

Receive free email alerts when new articles cite this article - sign up in the box at the top right-hand corner of the article or click **here**

To subscribe to *Phil. Trans. R. Soc. Lond. B* go to: **http://rstb.royalsocietypublishing.org/subscriptions**

This journal is © 1980 The Royal Society

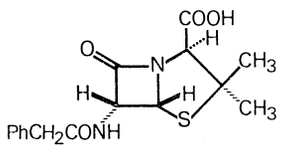
Downloaded from rstb.royalsocietypublishing.org

Phil. Trans. R. Soc. Lond. B **289**, 239–250 (1980)
Printed in Great Britain

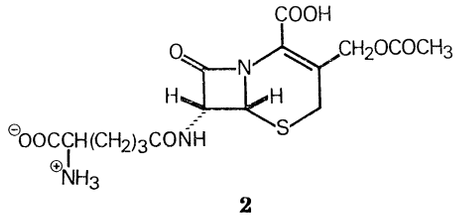
Penems and related substances

By R. B. Woodward, For.Mem.R.S.†
Woodward Research Institute, Basle, Switzerland

The discovery of the penicillins, as exemplified by penicillin G (**1**) – one of the earliest known members of the class – and of the cephalosporins, of which the first to be isolated was cephalosporin C (**2**), laid the basis for one of the most spectacular chapters in the history of medicine.



1



2

The initial observations of Fleming, made 50 years ago, provided the stimulus for further investigations, taken up at Oxford a decade later by Florey, Chain, Abraham, Robinson, Baker and their collaborators, and these in turn gave results of sufficient promise to justify the initiation of a gigantic Anglo-American effort during World War II; this programme had as its objectives the improvement of methods for the production and isolation of penicillins, the determination of their structures, and their synthesis. At the conclusion of the war, most of these aims had been achieved, but the subtlety and novelty of penicillin chemistry placed obstacles in the way of penicillin synthesis which were not overcome until many years later by Sheehan and his associates.

For some time after 1945, there followed a period of consolidation, marked especially by the adoption of the penicillins as one of the most powerful tools in the armoury of modern medicine. Then, with the isolation and determination of the structure of cephalosporin C during the period 1953–61 by Abraham and his collaborators, a new efflorescence began, which has if anything gained momentum during the ensuing years; the excitement of and interest in the β-lactam antibiotics is at this time – fully half a century after the saga began – at a peak unrivalled throughout the fascinating history of the subject.

It was my great good fortune to participate in the wartime effort, and, in September 1944, to contribute conclusive arguments in favour of the β-lactam structure of the penicillins, which only a short time later was confirmed by the beautiful X-ray crystallographic studies of Dorothy Hodgkin and her associates. The deduction of the structure from chemical evidence rested in large measure on theoretical considerations which will be shown in the sequel to be of continuing relevance in the discussion of chemical reactivity and biological activity of the penicillins and related substances.

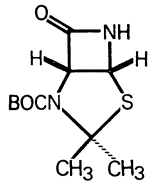
After 1946, our activities in the field were for some time desultory, until in 1963 we took up in Basle studies on the synthesis of cephalosporin C (**2**), which were crowned with success in late 1965. In that investigation, a key intermediate was the lactam (**3**), which we synthesized from L-cysteine. It will be noted that our approach was novel in that we began our work with

† Deceased 8 July 1979.

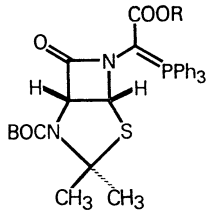
The Royal Society is collaborating with JSTOR to digitize, preserve, and extend access to *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences.* www.jstor.org

Downloaded from rstb.royalsocietypublishing.org

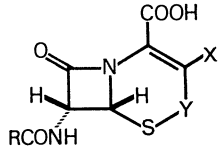
the construction of the β-lactam ring, and *later* effected the fusion of the six-membered ring which was needed to complete the construction of the cephalosporin molecule. From the first, it had been an important consideration in our planning that we might use this same principle to construct numerous new structural types, by building new rings, of structures limited only by the imagination, upon our monocyclic template. Shortly after the completion of the synthesis



3

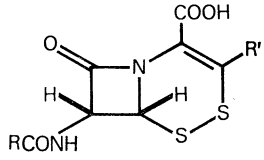


4

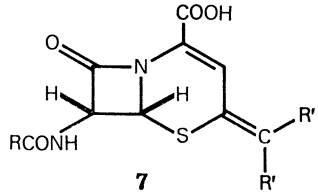


5

of cephalosporin C, that general aim was much facilitated by our discovery of the unusual phosphoranes of the general type **4**. These versatile intermediates, in our hands and those of others, have permitted the construction of numerous novel fused bicyclic β-lactams of the general structure **5**; the power of the method may be exemplified here by two (**6** and **7**) of the many prepared in Basle.

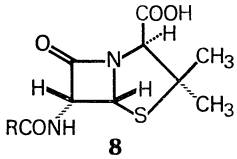


6

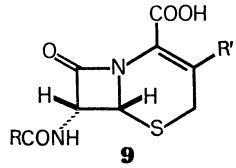


7

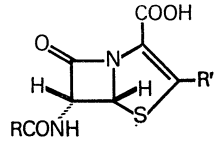
For a long time we regarded as a desirable objective the preparation of *penems*, as exemplified by **10**; it will be noted that such structures contain at once the five-membered ring of the penicillins (**8**), and a double bond similarly situated to that incorporated within the six-membered ring of the cephalosporins (**9**). These features are closely associated with the biological activity of the two classes; what would the effect be of incorporating both structural elements within the same molecule? We approached the task of synthesizing penems with no little diffidence, since we supposed that the desired substances might be even more sensitive than the already very sensitive penicillins. In the early stages of our studies, our apprehensions seemed to be justified, when a number of plausible approaches failed. But ultimately a successful path was found, in which, gratifyingly, phosphoranes of the type (**4**) mentioned above played a key role.



8



9



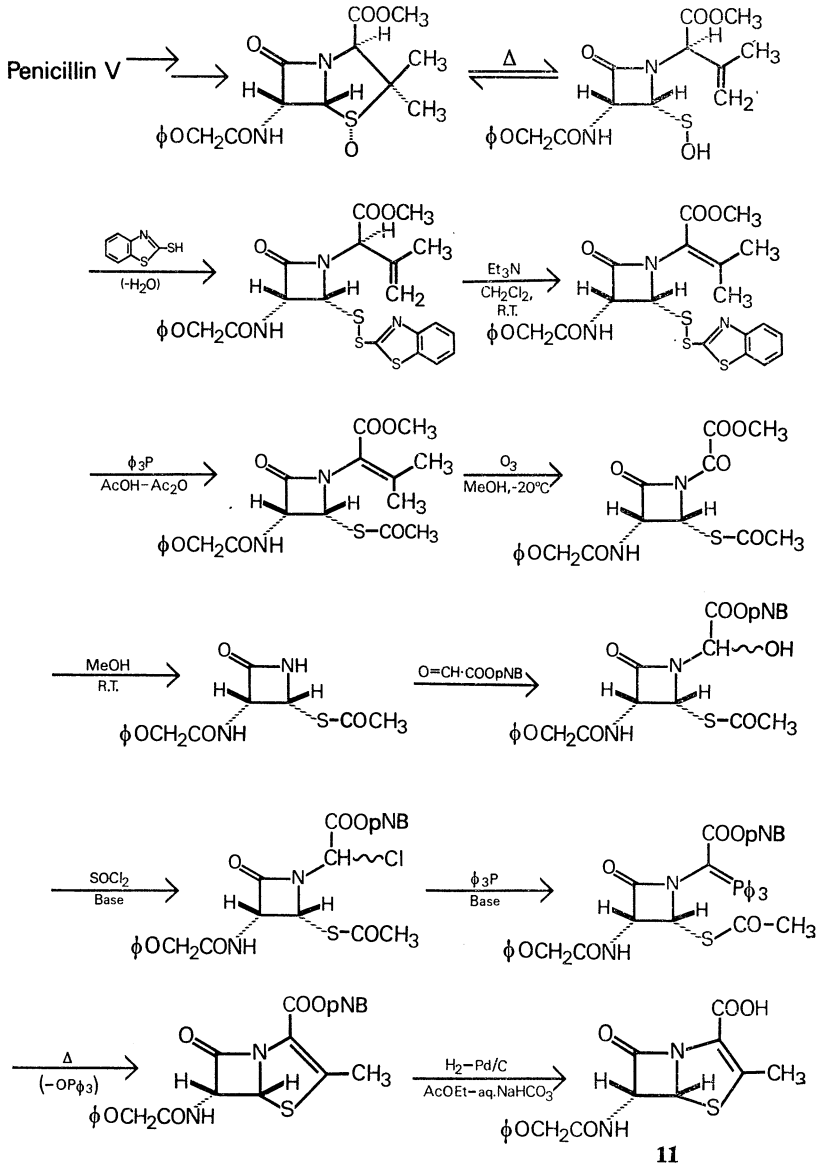
10

Not surprisingly, our first attempts were directed to the preparation of 6-acylamino substituted penems, since it was clear that such substituents were important in conferring biological activity on the penicillins and cephalosporins. Indeed, the first penem synthesized was the 6-phenoxyacetylamino derivative (**11**), which was prepared by the sequence shown in chart 1.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org



11

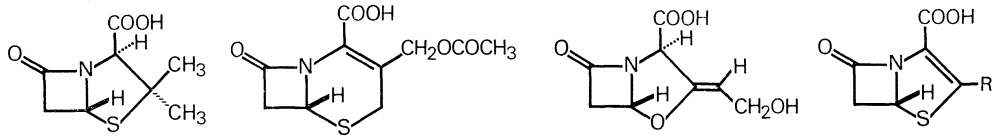
(pNB = -CH_2-C$_6$H$_4$-NO_2)

CHART 1

The first penem (**11**) was found to be active against pathogenic organisms, but in a quantitative sense the level of activity was disappointing. Nevertheless, we had shown that the penem system was one of sufficient stability to permit isolation, and we felt it was our responsibility to extend our knowledge of the basic chemistry of the new system. Although the 6-unsubstituted penicillin (**12**) and the corresponding cephalosporin (**13**) are totally devoid of biological activity, we embarked upon the preparation of the simple penems (**15**). The desirability of taking this course was heightened by the possibility that we foresaw that these substances might be relatively readily accessible by total synthesis, and further, by the appearance upon the scene of clavulanic acid (**14**), which while not possessed of antibiotic properties, is highly active as an inhibitor of certain penicillinases.

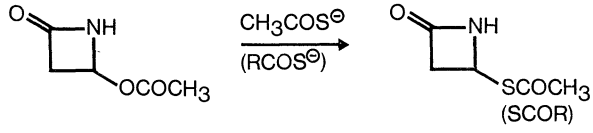
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org



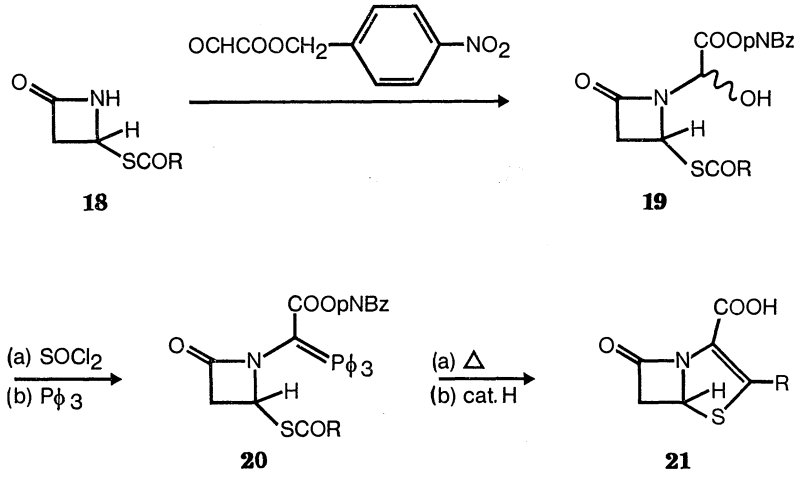
12 13 14 15

The total synthesis of simple penems is based upon the ready availability of the acetoxyazetidinone (**16**) (Clauss *et al.* 1974), whose acetoxy group had been shown to be readily replaceable by nucleophiles. We found that this substitution could be smoothly effected by a wide variety of thioacid anions, to give the thioesters (**17**). We then attached our versatile phosphorane grouping to the β-lactam nitrogen atom in the usual way (cf. **18** → **19** → **20**),



16 **17**

and were gratified to find that the resulting substances underwent smooth thermal conversion to penems. Although numerous ester groups were utilized in sequences of this sort, the *p*-nitrobenzyl group was found to afford special advantages, particularly in that it could be relatively smoothly removed by hydrogenolysis without damage to the nucleus. In figure 1, the result of an X-ray crystallographic study of the simple penem ester (**22**) is portrayed: the structure of the penem is confirmed in detail, and certain interesting structural facets are revealed, to which we shall return later.



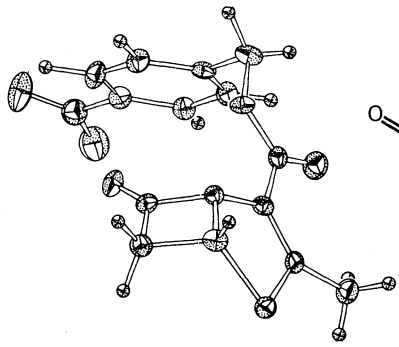
18 **19** **20** **21**

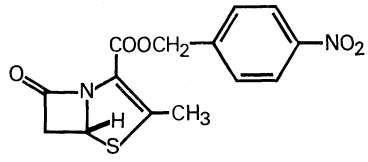
Astonishingly, the simple 6-unsubstituted penems were found to exhibit powerful antibiotic activity against a wide range of organisms. In table 1, the *in vitro* activity of three simple racemic derivatives is portrayed, in comparison with cephalexin and penicillin V. More than a dozen further derivatives of the class, with some breadth in the structural character of the substituents in the 2-position, are shown in table 2. It will suffice here to mention that all of these substances are biologically active, though not surprisingly there is some – though not marked – variation in the individual antibacterial spectra.

In view of the striking simplicity of the new penems, and the fact that they contain only one chiral centre, it was clearly now desirable to prepare an optically active representative of the

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

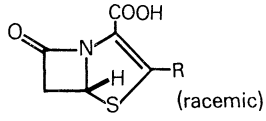




22

FIGURE 1

TABLE 1. M.i.c. (MINIMUM INHIBITORY CONCENTRATION IN micrograms/ml)

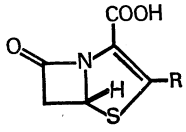


(racemic)

	R				
	CH_3	phenyl	n-pentyl	cephalexin	penicillin V
Gram-positive strains					
Staphylococcus aureus (Smith) 14	1	1	0.2	1	0.05
Staphylococcus aureus 2999 (resistant)	1	4	2	8	64
Streptococcus pyogenes Aronson/K 1129	0.5	0.05	0.05	1	0.05
Streptococcus pneumoniae/III/84	0.5	0.1	0.05	1	0.05
Gram-negative strains					
Neisseria meningitidis/K 1316	0.1	0.1	0.05	0.5	0.5
Haemophilus influenzae NCTC 4560	4	4	2	32	4
E. coli 205	8	8	32	8	128
Salmonella typhimurium 277	4	8	16	4	64
Proteus rettgeri/K 856	8	4	32	128	—†
Pseudomonas aeruginosa/K 1118	8	—‡	64	—†	—†

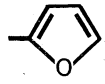
† No inhibition at 128 μg/ml.
‡ Not measured.

TABLE 2

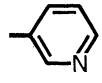


R

—H, —CH_2Ph,
—CH_2SCH_3,
—$CH_2NHCOCH_2OPh$,
—$CH_2CH_2CH_2NH_2$,
—SCH_2CH_3,



—CH_2OCOCH_3
—$CH_2SC(CH_3)_3$
—$CH_2CH_2NH_2$
—$CH_2CH_2CH_2NHCOOCH_2Ph$
—$SCH_2CH_2NHCOCH_3$



6-unsubstituted series. This objective was first realized when the 2-methylpenem (**23**) of the 'natural' configuration was prepared from penicillin V by a sequence of steps which need not be shown here. In a parallel antibacterial test, with 24 Gram-positive and Gram-negative strains, the new, optically active acid (**23**) was twice as active as the corresponding racemic substance in 20 cases, while equal activity was found in the remaining four instances.

The clear stereochemical implications of these results received unequivocal confirmation when both enantiomers, **24** and **25**, of the simplest penem were synthesized, by the method

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

depicted in abbreviated form in chart 2. The isomer **24**, possessing the 'natural' absolute configuration, was found to be highly active, while its enantiomer, **25**, was devoid of any activity whatsoever. These circumstances are vividly portrayed in the agar plate inhibition tests shown in figure 2, whose display here may be regarded as especially appropriate to this occasion.

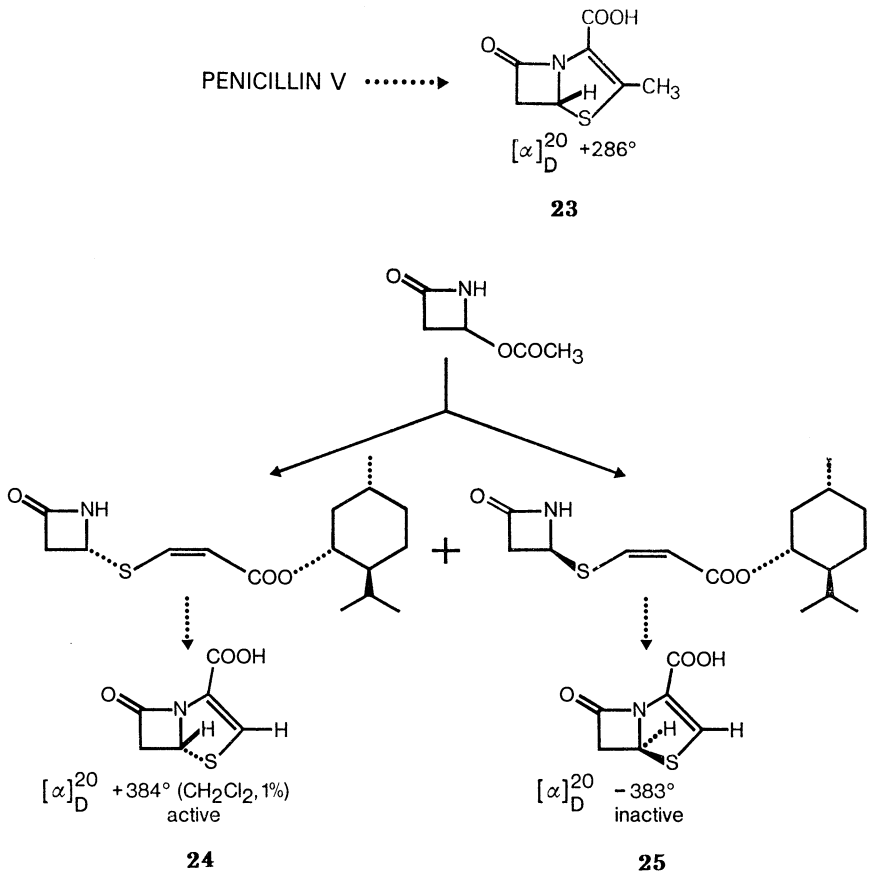


CHART 2

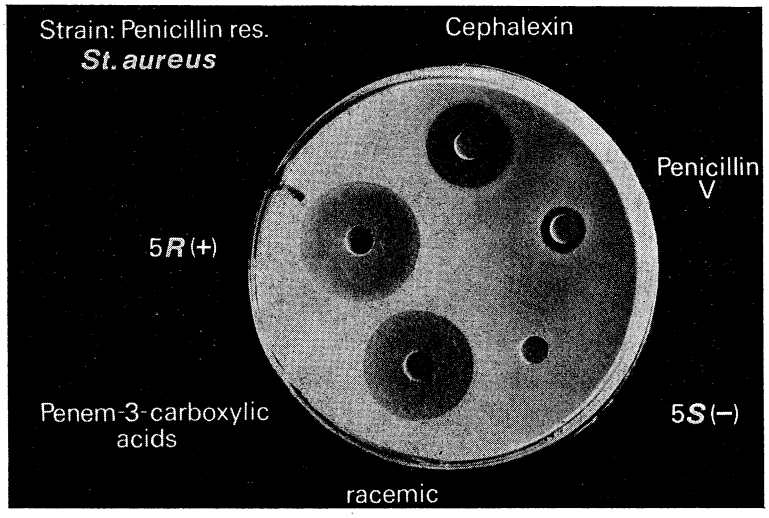
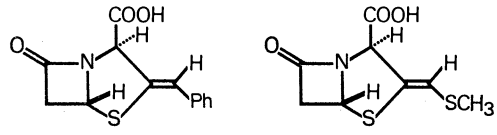


FIGURE 2

Downloaded from rstb.royalsocietypublishing.org

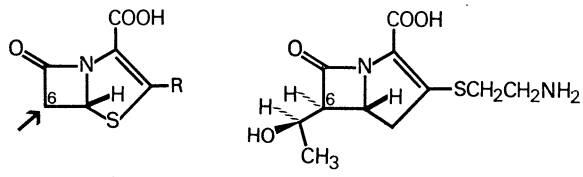
Certainly it is tempting to suggest an important generalization: the absolute configuration at C-5 (in penicillins and penems), or C-6 (in cephalosporins) is of definitive significance for biological activity of the β-lactam antibiotics.

It was found possible to effect the transformation, by basic catalysis, of some of our penems into exo-cyclic isomers, for example **26** and **27**. For the moment, we note that these substances are devoid of antibacterial activity.



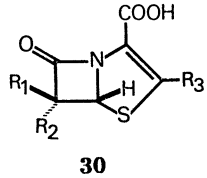
26 **27**

We turn now to one of those remarkable coincidences that seem to defy the laws of chance, and which not infrequently lead to episodes of high drama in science. Coincident with our discovery of the penems, the Merck group (Albers-Schönberg *et al.* 1978) isolated from natural sources the exceptionally interesting novel substance thienamycin (**29**). The structural resemblance to the penems (cf. **28**) is obvious: the skeletal system of thienamycin is that of a 1-carbapenem. Further, while there is a substituent at the 6-position of thienamycin, that substituent is a simple one, in no way reminiscent of those present in – and important for the activity of – the classical β-lactam antibiotics. Beyond that, the substituents on the β-lactam ring are disposed in a *trans* sense: note that the *trans* isomers of the classical penicillins are uniformly biologically inactive. And finally, thienamycin exhibits antibacterial activity of a very high order against a wide range of pathogenic microorganisms.



28 **29**

TABLE 3



30

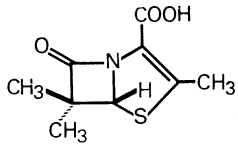
R_1	R_2	R_3
$-CH_3$	$-H$	$-CH_3$
$-CH_2CH_3$	$-H$	$-SCH_2CH_2NHCOCH_3$
$-H$	$-CH_2CH_3$	$-SCH_2CH_2NHCOCH_3$
$-CH_2CH_3$	$-H$	$-CH_2CH_2CH_2NH_2$
$-CH_2C_6H_5$	$-H$	$-CH_3$
$-CH(CH_3)_2$	$-H$	$-CH_3$
$-CH(CH_3)_2$	$-H$	$-SCH_2CH_3$
$-OCH_3$	$-H$	$-CH_3$
$-CH_3$	$-CH_3$	$-CH_3$
$-CH_3$	$-CH$	$-n\text{-}C_5H_{11}$

In the light of this remarkable development, it is perhaps pertinent to mention briefly the third class of penems that we prepared by synthesis: those (**30**) substituted at the 6-position with groupings having no relation to the classical substituents. A group of such substances is shown in table 3. In respect of their biological activity, it is only necessary to mention here

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

that all except the last two are active antibiotics. We did not find the latter result surprising. As substitution at C-6 is increased, the penems become increasingly stable – the β-lactam ring is less easily cleaved – and the 2,6,6-trimethyl compound (**31**) survives *indefinitely* in phosphate buffer at pH 7.0. Nevertheless, even here a surprise was in store for us, and it seems worth

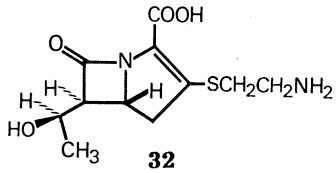


31

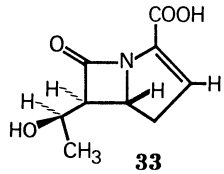
Inhibitor of β-lactamases from *Pseudomonas aeruginosa* 18SA and *Enterobacter* P99
Inactive against β-lactamases from *Staphylococcus aureus* K506 and *Escherichia coli* K1260

noting, though its significance can hardly be assessed at this time. Dr J. Regös found that the chemically inert **31** is an inhibitor of the β-lactamases from *Pseudomonas aeruginosa* 18SA and *Enterobacter* P99, though by contrast, inactive against those from *Staphylococcus aureus* K506 and *E. coli* K1260.

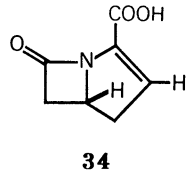
As indicated above, the structure of the substituent in the 2-position of penems can be varied over a considerable range without marked effect on biological activity. A similar situation in the class of carbapenems is suggested by the fact that the 2-unsubstituted compound (**33**) prepared by the Merck group – both by degradation from thienamycin (**32**) and by synthesis (Shih *et al.* 1978; Cama & Christensen 1978) – is highly active. Even the simplest carbapenem, **34**, prepared by synthesis both in Basle and in Rahway, retains activity – a fact not surprising in view of the activity of the simple penem (**24**).



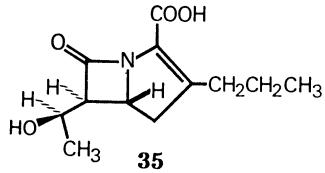
32



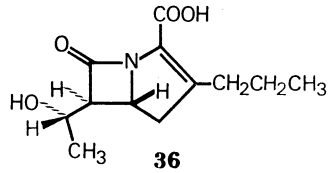
33



34

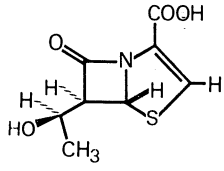


35

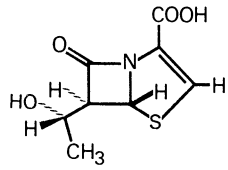


36

So far, the impression may have been given that the biological activity of the penems and the carbapenems is not greatly susceptible to variation in substitution pattern. But it should be noted that although the 6-substituent in thienamycin is a simple one, it is chiral, and that the Merck group has found that diastereomers, epimeric at the chiral centre of the side chain, are substantially less active than thienamycin itself. Similar results have been obtained in Basle; of the diastereomers **35** and **36**, synthesized by Dr P. Schneider, **35** is at least an order of magnitude more active than **36**. These circumstances conferred special interest on the comparable pair of penems, **37** and **38**: indeed, we found that **37** is by far the more active substance, as



37



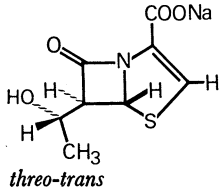
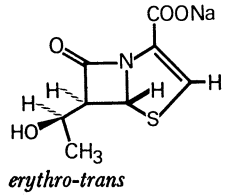
38

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

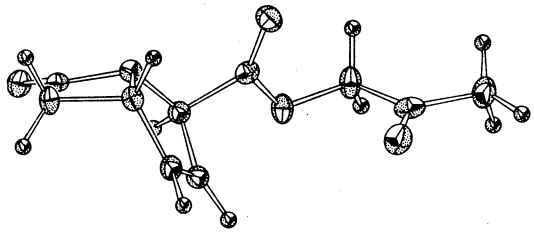
shown by the data presented in table 4. It may be mentioned parenthetically that in all of the total syntheses by which the various penems and carbapenems alluded to were prepared, *N*-azetidinonylphosphoranes of the type originally introduced by us were utilized.

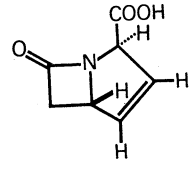
TABLE 4. INHIBITION DIAMETERS OF RACEMIC SODIUM 6-α-HYDROXYETHYLPENEM-3-CARBOXYLATES*

	Staph. aureus Smith 14	*S. aureus*-resistant 2999i+p+	*E. coli* 205	*Proteus vulg.* ATCC 9484	*Pseudom. aer.* ATCC 12055	*Pseudom. aer.* Richmond
 *threo-trans*	33	29	23	30	17	22
 *erythro-trans*	22	14	8	14	0	0
Penicillin V	35	12	11	23	0	0

* 0.5% solutions in H_2O (DMSO).

In the case of the carbapenems, there exists a possibility for isomerism which is denied to the penems, and indeed we were able to prepare the Δ^1-carbapenem (**39**) through base-catalysed isomerization of the acetonyl ester of **34**, followed by hydrolysis. It was something of a surprise that **39** was found to exhibit no antibacterial activity whatsoever. The detailed structure of the molecule, as revealed by X-ray crystallographic studies of the corresponding acetonyl ester, is shown in figure 3, and the possible relevance of structural factors there revealed to the matter of biological activity will be discussed shortly.





39

FIGURE 3

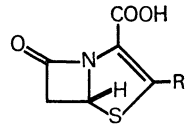
Since the biologically active penems are relatively simple substances which represent a considerable departure, in structural terms, from the classical penicillins, it will be of much interest to know the extent to which their mode of action parallels that of their better known progenitors. The information presented in table 5, summarizing the results obtained by Dr W. Zimmermann in examining the affinity of some penems for penicillin-binding proteins in the Spratt system, suggests that the parallelism may be close. It is perhaps especially noteworthy that the compound **24**, of the 'natural' optical series, is strongly bound, while no binding whatsoever is observed for its enantiomer, **25**.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

Throughout the history of the penicillins it has seemed clear that there is some relation, though not necessarily a simple one, between the high *chemical* reactivity of the β-lactam ring, and biological activity. The basic structural circumstances that lead to high β-lactam lability in the penicillins were first recognized by me in 1944; indeed this recognition was the crucial factor in the chain of reasoning that led to the deduction of the β-lactam structure for penicillins on the basis of chemical evidence, only just before the X-ray crystallographic studies that provided unassailable physical evidence for that same structure. The nub of the matter is that steric constraints within the fused bicyclic system make it impossible for the four groups attached to the carbon–nitrogen bond of the β-lactam grouping to lie in a common plane;

TABLE 5. SPRATT SYSTEM



$R = CH_3$ $R = C_6H_5$	high affinity to PBP2 moderate to good affinity to PBP1a and PBP3 } from *E. coli* high affinity to PBP1 PBP2 PBP4 } from *Ps. aeruginosa* K799
R = H	optically active compound of natural series strongly bound enantiomer *not* bound

in these circumstances the bond-strengthening interaction, between the lone electron pair of the nitrogen atom, and the carbonyl group – which strengthens the carbon–nitrogen bond in simple amides and in monocyclic β-lactams – is severely inhibited, with consequent marked labilization of the system. This interpretation, which was critical for the understanding of the lability of the penicillins in 1944, has stood the test of time. In 1970, Sweet & Dahl introduced a convenient formalism (cf. **40** in table 6) for defining the critical departure from coplanarity: a trigonal pyramid is imagined, the corners of whose base are C-3, C-5 and C-7, while N-4 is at its apex; the altitude *h*, from the apex to the base, will be larger as the departure from coplanarity increases.

In the light of the foregoing remarks, the data collected from a number of X-ray crystallographic studies, and presented in table 6, are of much interest. The distortion in the penicillins is considerable, and quite sufficient to account for their lability. The penems are more distorted, and more labile, as expected. The distortion in the carbapenems is even greater, as is, again, the lability. Finally, in the Δ^1-carbapenems, the pyramidal nature of N-4 is extreme, and the chemical reactivity is extraordinarily high.

Now, what can we conclude about the relation between chemical reactivity and biological activity? We feel reasonably certain that *below* a certain level of chemical reactivity, biological activity will not be observed. We suspect that the reactivity of the simple penicillin system is below the requisite level, and that the 6-acylamino substituent – which is known to have a marked effect in increasing the lability of the β-lactam system – is required to bring the reactivity of the classical penicillins to the operative level. In this light, the total lack of antibacterial activity in **12** (and **26** and **27**, whose relevant geometry is very probably closely similar to that of the penams) becomes explicable, as does the high biological activity of the simple penems and carbapenems.

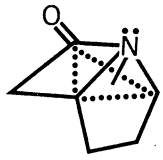
Now we suspect that there is another, and very important, side to this coin. With increasing lability of the β-lactam ring and its concomitant possibility of increased biological activity,

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

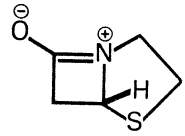
Downloaded from rstb.royalsocietypublishing.org

there are also inevitable dangers associated with instability. In particular there is the possibility that the potential antibiotic will react randomly with the numerous nucleophiles that it may encounter, with the result that it never reaches its target, the transpeptidase whose role in cell wall construction it must inhibit or destroy. That is to say, we suspect that there is a level of β-lactam reactivity *above* which antibacterial activity will be weak or non-existent. In this light, our first penem, **11**, possesses disappointing activity because the chemical activation provided by the 6-acylamino substituent has brought the already highly reactive *penem* system into too high a range. Similarly, **34**, probably the most highly chemically reactive of the carbapenems we have encountered, exhibits only moderate biological activity, while the truly exceptionally reactive Δ^1-carbapenem (**39**) is devoid of antibacterial properties.

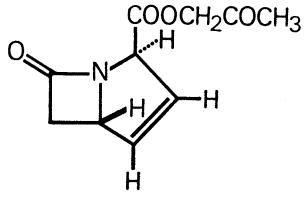
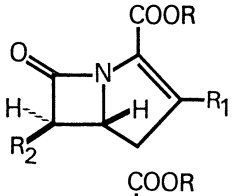
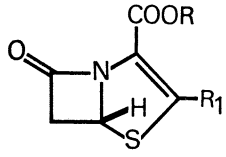
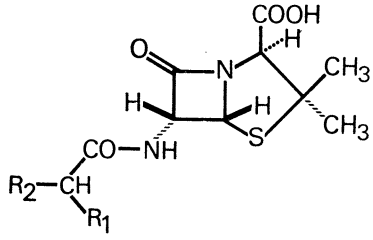
TABLE 6



40



Woodward *et al.* (1949)
Sweet & Dahl (1970)

	h
	0.54*
 R = —CH_2COCH_3 $R_1 = R_2$ = —H	0.50*
R = —CH_3 R_1 = —$SCH_2CH_2NHCOCH_3$ R_2 = —$CH(OH)CH_3$	0.49
 R = —CH_2COCH_3 R_1 = —H	0.44*
R = *p*-$CH_2C_6H_4NO_2$ R_1 = —CH_3	0.43*
 R_1 = —H R_2 = —OC_6H_5	0.40
R_1 = —NH_2 R_2 = —C_6H_5	0.38

* Mrs G. Ribs.

In short, a good case can be made that there is an optimal range of β-lactam reactivity, below *or* above which antibacterial activity may be expected to be diminished or absent. Of course, this picture is oversimplified. Other factors, probably most particularly aspects of structural complementarity – or the lack of it – with the target enzyme(s), will alter the situation

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

for good or ill; should one doubt that, one need only contemplate the high activity of **24**, as contrasted with the total lack of activity of its enantiomer, **25**.

One point remains. Clearly, antibacterial activity is inherent in the bicyclic nuclear structures, both of the penems and the carbapenems. In constructing thienamycin, has Nature utilized the millions of years available to her, to endow the carbapenem nucleus with substituents which modulate the inherent activity of the nucleus in a manner upon which we cannot improve? We may doubt it. But we may not doubt that the chemist will accept the challenge provided by these fascinating new nuclei, and explore the opportunity to prepare new and perhaps superior antibiotics.

It gives me great pleasure to acknowledge the creative intellectual contributions, as well as the exceptionally skilful and devoted collaboration, of the men who carried out the work it has been my privilege to describe here: Dr I. Ernest, Dr J. Gosteli, Dr C. W. Greengrass, Dr W. Holick, Dr D. E. Jackman, Dr M. Lang, Dr H. R. Pfaendler and Dr K. Prasad.

References (Woodward)

Albers-Schönberg, G., Arison, B. H., Hensens, O. D., Hirshfield, J., Hoogsteen, K., Kaczka, E. A., Rhodes, R. E., Kahan, J. S., Kahan, F. M., Ratcliffe, R. W., Walton, E., Ruswinkle, L. J., Morin, R. B. & Christensen, B. G. 1978 *J. Am. chem. Soc.* **100**, 6491–6498.

Cama, L. D. & Christensen, B. G. 1978 *J. Am. chem. Soc.* **100**, 8006–8007.

Clauss, K., Grimm, D. & Prossel, G. 1974 *Justus Liebigs Annln Chem.*, pp. 539–560.

Shih, D. H., Hannah, J. & Christensen, B. G. 1978 *J. Am. chem. Soc.* **100**, 8004–8006.

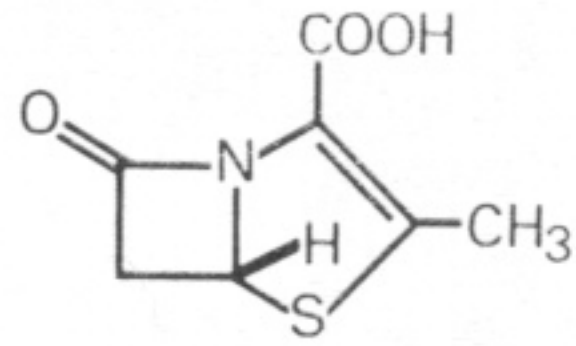
Sweet, R. M. & Dahl, L. F. 1970 *J. Am. chem. Soc.* **92**, 5489–5507.

Woodward, R. B., Newberger, A. & Trenner, N. R. 1949 In *Chemistry of penicillins* (ed. H. T. Clarke, J. R. Johnson & R. Robinson), p. 415. Princeton: Princeton University Press.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

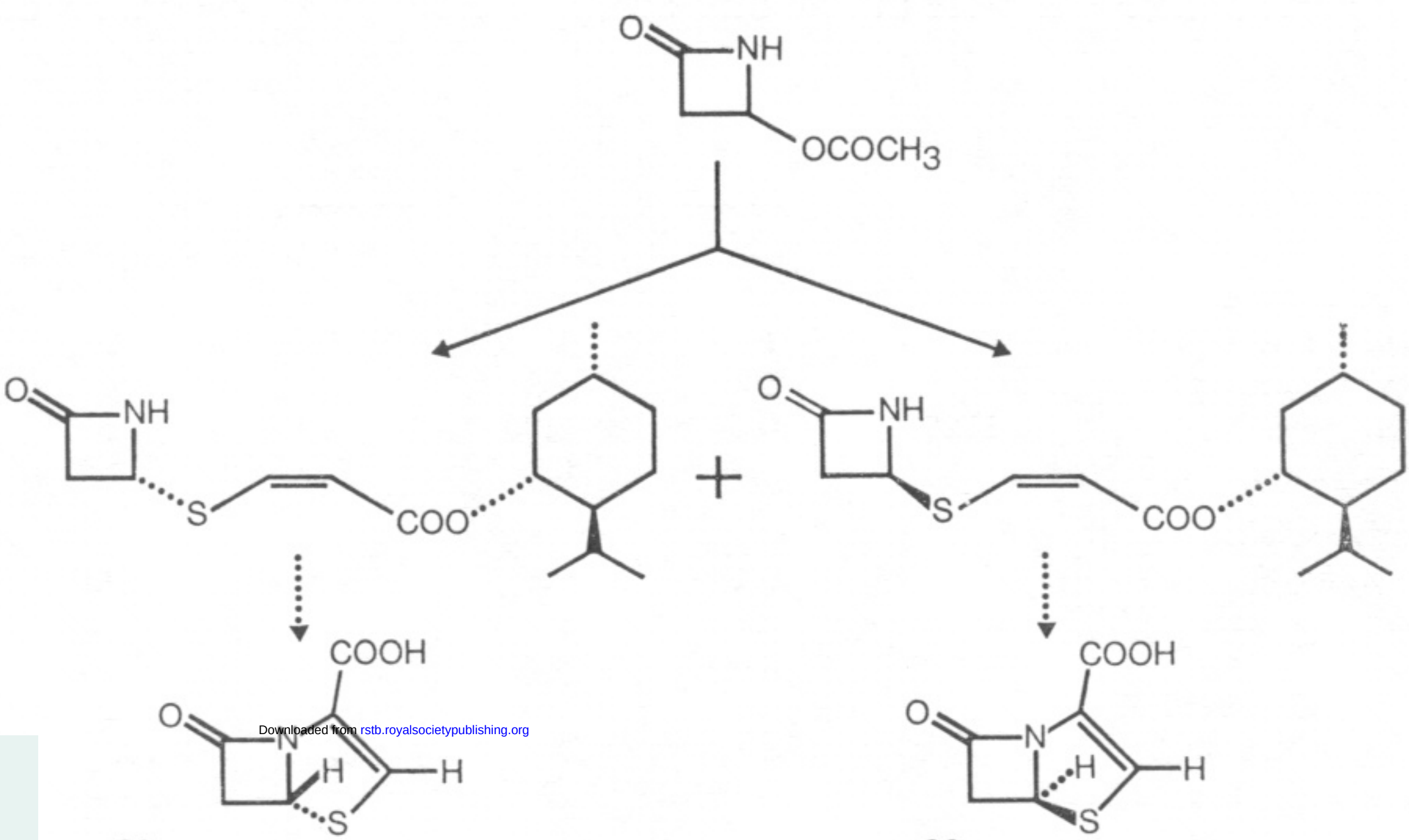
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

PENICILLIN V ·····▸



$[\alpha]_D^{20}$ +286°

23



$[\alpha]_D^{20}$ +384° (CH_2Cl_2, 1%)
active

24

$[\alpha]_D^{20}$ −383°
inactive

25

CHART 2

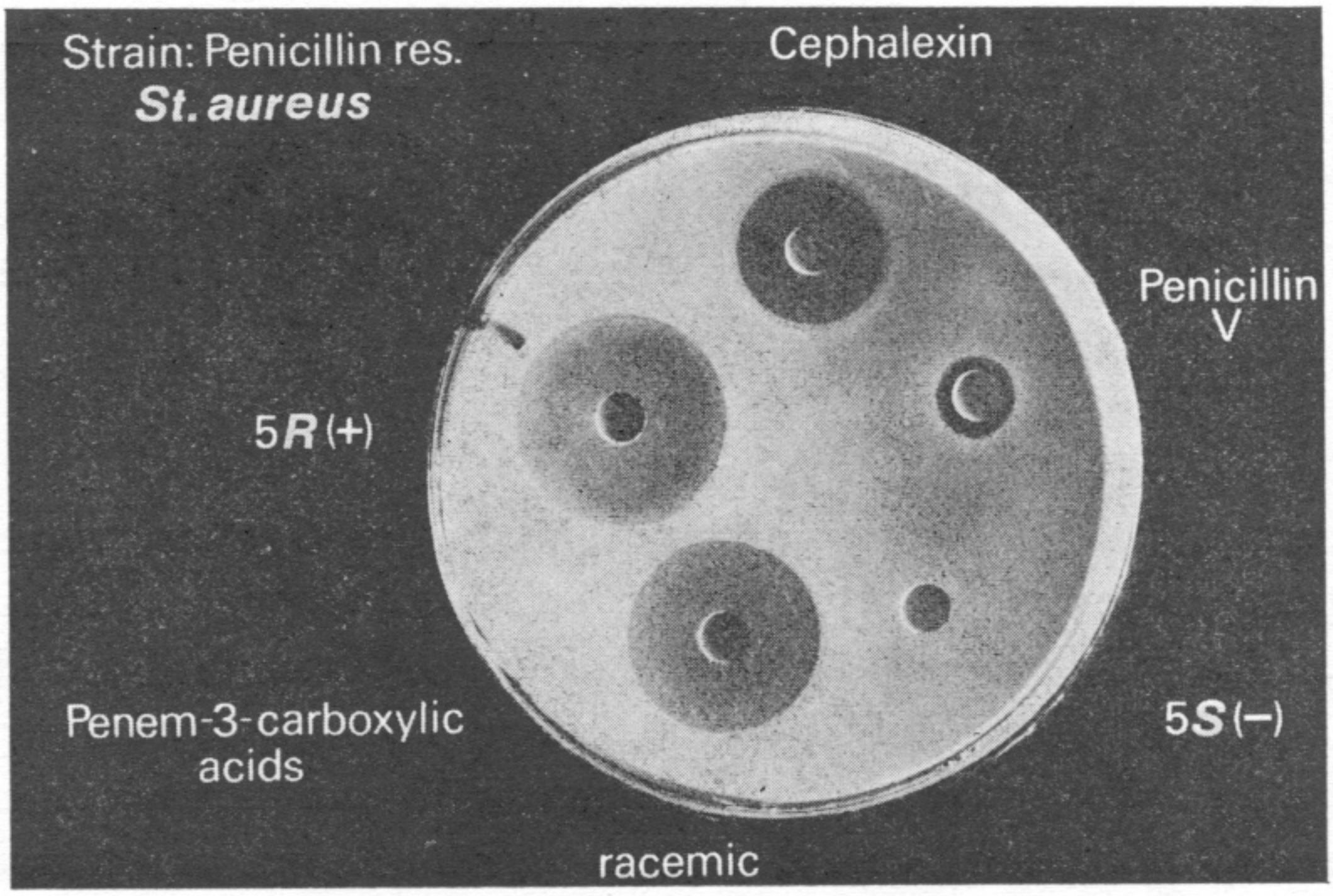


FIGURE 2

Downloaded from rstb.royalsocietypublishing.org

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES