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NEW SPIRO DERIVATIVES OF PENICILLIN

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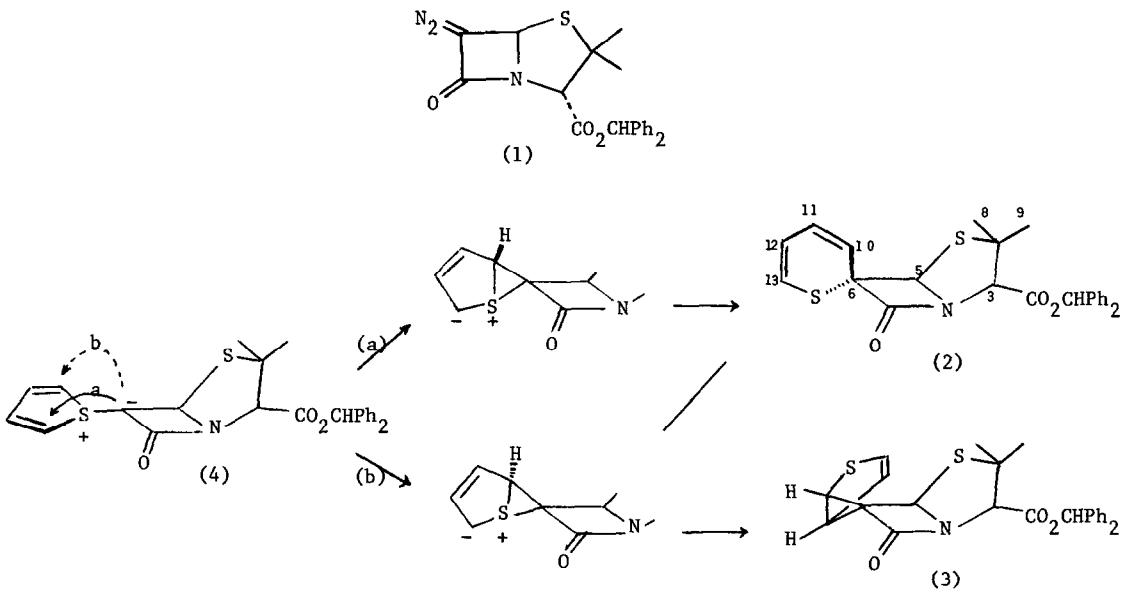
Summary *The first example of carbenoid ring expansion of thiophene to a 2H-thiopyran has been observed in its Rh-catalysed reaction with benzhydryl 6-diazopenicillanate. Buchner ring expansion of anisole with the same carbenoid gives two isomeric methoxy-cycloheptatrienes by attack on the upper face of the β-lactam ring. In one of the isomers, the methoxyl group shows a strong conformational preference in solution, revealed by n.O.e. difference spectroscopy.*

The reactions of carbenes with thiophene have previously been reported to afford either thiophenium ylides, cyclopropanes, or 2-substituted thiophenes.[1] When benzhydryl 6-diazopenicillanate[2] (1) was dissolved in thiophene containing rhodium acetate, rapid evolution of nitrogen occurred and only two β-lactam containing products could be isolated by chromatography on silica.[3] These proved to be the spiro adducts (2) and (3), in yields of 11% and 22% respectively. The structure of the 2H-thiopyran (2) followed from its ^{1}H nmr spectrum, which revealed the presence of four vinylic C-H groups (5 55δ, d, J = 9.5Hz, C_{10}-H; 6.1δ, m, C_{11}-H and C_{12}-H; 6.25δ, d, J = 8Hz, C_{13}-H), and was confirmed by n.O.e. difference spectroscopy and decoupling difference spectroscopy.[4] The stereochemistry of compound (2) was shown by the n.O.e. difference technique, which revealed the close spatial proximity between the C_8 CH_3 group (1.48δ) and the vinylic proton adjacent to the spiro junction (C_{10}-H). Similarly, the stereochemistry of the spiro-cyclopropyl adduct (3) was established with great ease and complete certainty by n.O.e. difference spectroscopy, using the C_5-H and C_8 CH_3 groups as sensitive probes for the orientation of the C_6 spiro ring. The product (2) is unique in being the first recorded example of a 2H-thiopyran formed by carbenoid ring expansion of thiophene. Both products are considered to be formed via a thiophenium ylide which then suffers internal attack at C_α. This is followed either by ring expansion or by bond migration (Scheme 1). This mechanistic picture requires movement of the thiophenium ring towards the α-face from the ylide (4).

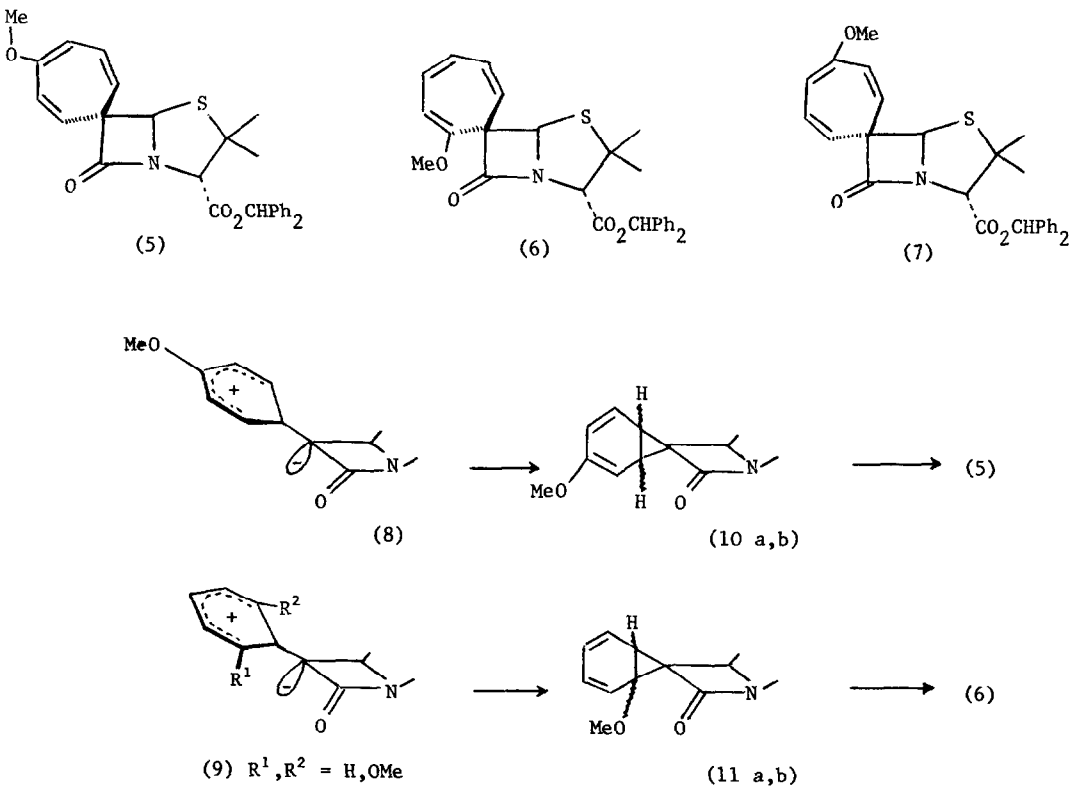
The ring expansion of thiophene to the 2H-thiopyran (2) is a heterocyclic analogue of the Buchner reaction,[5] in which a carbenoid derived from a diazo compound inserts into a benzene

ring to give a cycloheptatriene. For comparison, the Buchner reaction was carried out between the diazo compound (1) and anisole (10 equiv.) in dichloromethane at room temperature. Use of $Rh_2(OAc)_4.2H_2O$ (2%) as catalyst led to the formation of two isomeric adducts (5) and (6) in very low yields (4% and 1% respectively). In agreement with the recent report by Anciaux et al.,[5] $Rh_2(CF_3CO_2)_4$ was a more efficient catalyst, furnishing the adducts (5) and (6) in yields of 13% and 2% respectively. No other products containing a β-lactam ring were detected in either reaction. The structure of adduct (5) follows from ^1H nmr (400MHz, $CDCl_3$), which revealed, in addition to signals for the penicillin nucleus and benzhydryl function, five vinylic protons, consisting of a vicinal pair (5.85δ, d, J = 10Hz, C_{15}-H; 6.18δ, dd, J = 10Hz and 2Hz, C_{14}-H) and a separate system of three protons (5.31δ, d, J = 9.5Hz, C_{10}-H; 6.31δ, dd, J = 9.5Hz and 7.3Hz, C_{11}-H; 5.75δ, dd, J = 7.3Hz and 2Hz, C_{12}-H). In order to distinguish between the two possible isomers (5) and (7), the product was submitted to n.O.e. difference spectroscopy.[4,6] This clearly established two important spacial proximities: one between the C_{15}-H and the C_5-H, the other between the C_{10}-H and the C_8 CH_3 at 1.45δ. Thus, n.O.e. difference spectroscopy allows an unambiguous assignment of stereochemistry (5) to the main product. In the course of this determination, it was observed by the n.O.e. difference method that the methoxyl group in (5) has a strongly preferred orientation,[6] with the methyl group spending approximately 90% of its time syn-periplanar to the C_{12}-H. This is the first time that the observation of such a preference has been made in solution. The structure of the second isomer (6) was also established by ^1H nmr spectroscopy and its stereochemistry demonstrated by the n.O.e. difference technique.

The formation of both the observed products is explained by the attack of anisole (o- or p-) on the *upper* face of a rhodium-complexed carbenoid to give the dipolar species (8) and (9). Collapse of each of these can take place to give two possible norcaradienes (10a,b) and (11a,b) respectively, but the subsequent ring opening of each pair of stereoisomers leads to a single cycloheptatriene (Scheme 2). Thus, the observed specificity in the formation of the products (5) and (6) stems entirely from the initial attack of anisole from the β-face of the penicillanate. Presumably, the bulky rhodium catalyst is complexed at the less hindered α-face of the β-lactam ring, preventing attack from this side, and collapse of the intermediate dipolar species (8) and (9) is faster than inversion at C_6. This contrasts with the thiophene reaction, in which the thiophene must also be presumed to attack from the upper face of the β-lactam but the greater stability of the thiophenium ylide[1,7] allows time for inversion through to the lower face as the reaction proceeds (Scheme 1).



Scheme 1



Scheme 2

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