Some Lewis Acid-catalysed Reactions between 2,2,2-Trichloroethyl 6-Diazopenicillanate and Ketones

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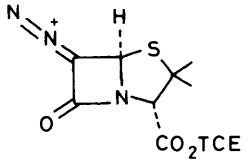
In the presence of boron trifluoride–diethyl ether, 6-diazopenicillanate (**1**) and acetone, cyclopentanone, and acetophenone, gave mixtures of 6α-alkyl-6β-acylpenicillanates and thiazolo-oxazinones, which had been formed *via* C(5)–C(6) bond cleavage.

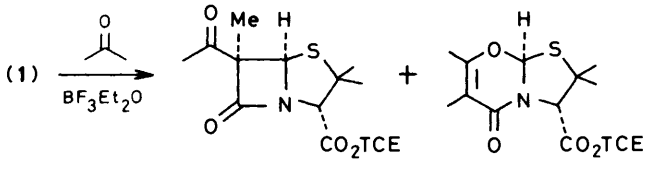
6-Diazopenicillanates have been found to be useful starting materials for the preparation of a range of penicillanates with novel substituents at C-6.[1] In particular, reactions with aromatic aldehydes and imines have provided routes to spiro-oxirane and spiro-aziridine-penicillanates.[2,3] We now report aspects of the Lewis acid-catalysed reaction between 2,2,2-trichloroethyl 6-diazopenicillanate (**1**) and ketones[4] which provide 6-acylpenicillanates of interest in view of the hydroxyalkyl side-chain present at C-6 in thienamycin[5] and the olivanic acids.[6]

Results and Discussion

Treatment of an ice-cold solution of the diazopenicillanate (**1**)[7] and acetone in dichloromethane with a catalytic amount of boron trifluoride–diethyl ether gave a penicillanate which was isolated by chromatography and identified as the 6β-acetyl-6α-methylpenicillanate (**2**) (*ca.* 30%). Attempts to improve the yield from this reaction by varying the reaction conditions and Lewis acid were unsuccessful. However when strictly anhydrous conditions were used, a second product was formed. This product could be isolated pure if the crude reaction product mixture was treated with sodium borohydride before chromatography. This reduced the oxopenicillanate (**2**) to give a mixture of the hydroxyethylpenicillanates (**4**), and enabled the second product to be isolated and identified as the thiazolo-oxazinone (**3**) (18%). The acetylpenicillanate (**2**) and thiazolo-oxazinone (**3**) were identified from spectroscopic data. In particular the C-6 configuration of the penicillanate followed from the observation of a strong n.O.e. enhancement of 5-H on irradiation of the 6-methyl substituent, whereas no n.O.e. enhancement of 5-H was observed on irradiation of the 6-acetyl methyl group. The thiazolo-oxazinone (**3**) was identified by comparison with other known penicillanate derived thiazolo-oxazinones.[2] Only one isomer was isolated which was assigned the 8a-configuration shown since this isomer is usually the major one formed under these conditions.[2,3] Rather unexpectedly the 6β-acetyl-6α-methylpenicillanate (**2**) was found to be relatively stable, and did not rearrange to the oxazinone (**3**) when treated with acids (silica gel, boron trifluoride–diethyl ether) in either toluene or chloroform, conditions which rapidly effected rearrangement of the 6β-formylpenicillanate (**5**) to the analogous oxazinone (**6**).[2]



(1)



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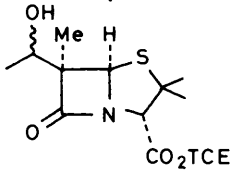

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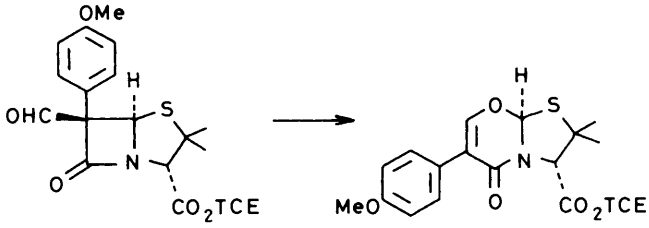

(5) (6)

6-Diazopenicillanate (**1**) was similarly treated with cyclopentanone and boron trifluoride–diethyl ether. Two products were isolated from this reaction, and identified as the spiro-oxocyclohexane-pencillanate (**7**) (20%) and the oxazinone (**8**) (13%). Acetophenone gave rise to the formation of three products which were separated and identified as the two 6β-acylpenicillanates (**9**) and (**10**), isolated in 11 and 4% yields, respectively, together with an oxazinone provisionally identified as (**11**), although the data available did not exclude the alternative possibility (**12**). Finally the reaction of 6-diazopenicillanate (**1**) with butan-2-one was studied; however in this case only a low yield (11%) of what appeared to be an inseparable mixture of penicillanates (**13**) and (**14**) was isolated.

It is difficult at this stage to provide a thorough mechanistic explanation of these 6-diazopenicillanate-ketone reactions which is consistent with that suggested for the analogous aldehyde reactions.[2] However one possible explanation is outlined in the Scheme. Attack of the ketone onto the less

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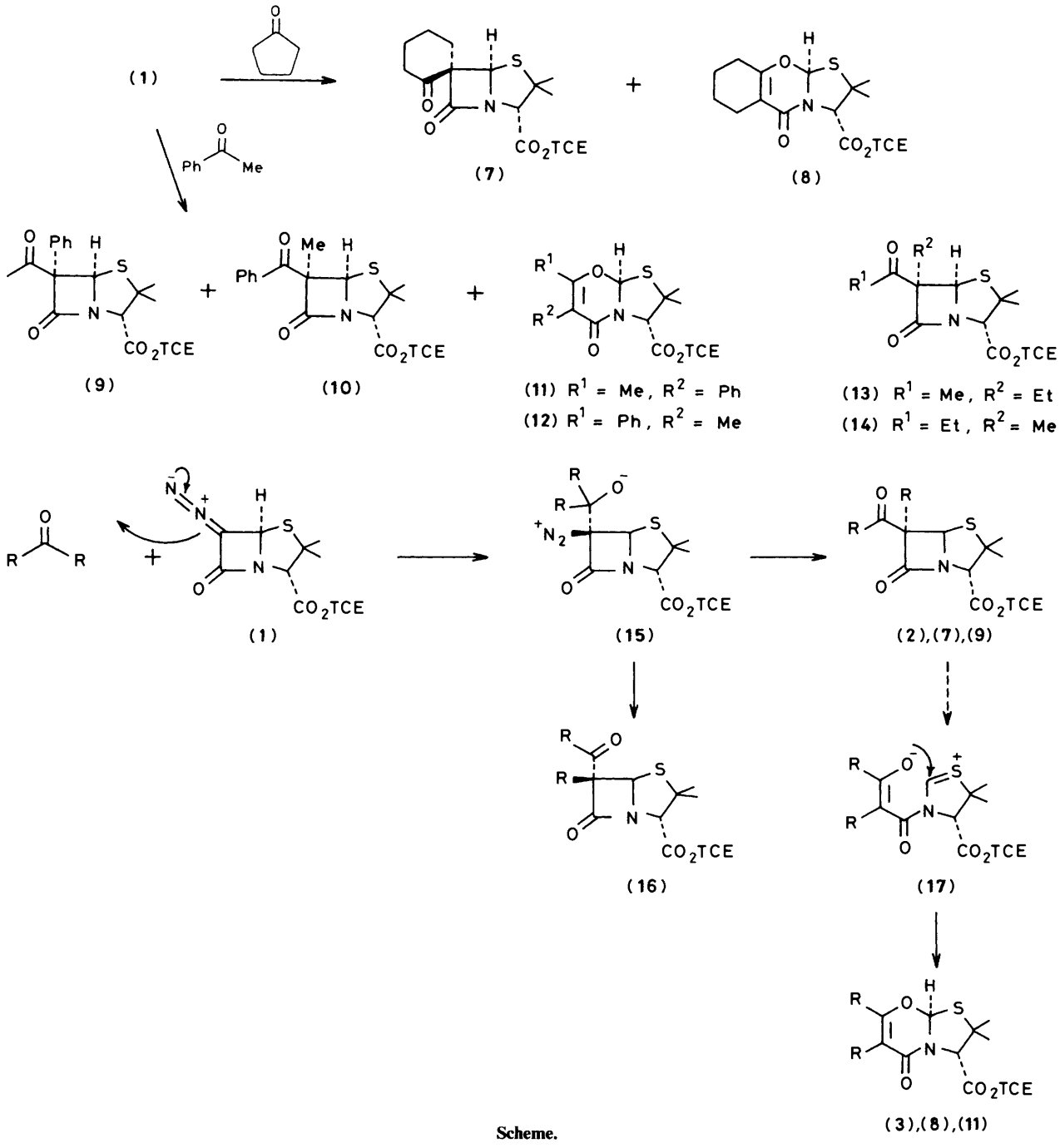

Scheme.

hindered 6α-face of the 6-diazopenicillanate would generate the zwitterionic intermediate (**15**). Alkyl migration with inversion of configuration at C-6 would then provide the 6β-acyl-6α-alkylpenicillanates which were isolated. The formation of the oxazinones (**3**), (**8**), and (**11**), involves a C(5)–C(6) cleavage which is usually believed to proceed *via* the equivalent of enolate-sulphenium ion (**17**). Since the isolated 6β-acylpenicillanates (**2**), (**7**), (**9**), and (**10**) were found, however, to be stable to rearrangement under the reaction conditions, it is tempting to suggest the oxazinones are derived from the isomeric 6α-acylpenicillanates (**16**) which rearrange as shown. It could be that steric hindrance between the 2β-methyl group and a bulky 6β-acyl substituent prevents the acyl substituent in the 6β-acyl isomers from adopting a configuration in which it can assist the C(5)–C(6) fragmentation. No such steric hindrance is present for the 6α-acyl epimers (**16**) which therefore fragment readily. For the 6β-formylpenicillanates, *e.g.* (**5**), generated in the aromatic aldehyde-diazopenicillanate reactions the size of the 6β-formyl group would appear to be insufficient to prevent the fragmentation configuration from being adopted. However these mechanistic speculations must be regarded as tentative until more experimental data are available.

Experimental

For general experimental details see the first full paper in this series.

Reactions between 6-Diazopenicillanate (**1**) *and Ketones.—With acetone.* Boron trifluoride–diethyl ether (2 drops) was added to a solution of 6-diazopenicillanate (**1**) (150 mg, 0.42 mmol) and acetone (30 μl, 0.42 mmol) in dichloromethane (10 ml) at 0—5 °C. After 30 min the mixture was concentrated under reduced pressure and the residue chromatographed on silica using ethyl acetate–light petroleum (1:9) as eluant, to give 2,2,2-*trichloroethyl* 6β-*acetyl*-6α-*methylpenicillanate* (**2**) (58 mg, 35%), m.p. 129—130 °C (from ethyl acetate–light petroleum) (Found: C, 39.5; H, 4.15; N, 3.35. $C_{13}H_{16}Cl_3NO_4S$ requires C, 40.15; H, 4.15; N, 3.6%); $\nu_{max.}$($CHCl_3$) 1 780, 1 770, and 1 710 cm^{-1}; δ_H($CDCl_3$) 1.54 and 1.67 (each 3 H, s, Me), 1.77 (3 H, s, CH_3CCOCH_3), 2.30 (3 H, s, CH_3CCOCH_3), 4.48 (1 H, s, 3-H), 4.71 and 4.87 (each 1 H, d, *J* 12 Hz $HCHCCl_3$), and 5.13 (1 H, s, 5-H); *m/z* 387 (M^+).

The reaction was repeated as above but using 1 g of 6-diazopenicillanate. The crude product mixture was treated with sodium borohydride and provided, after chromatography, (3S, 8aS)-2,2,2-*trichloroethyl* 2,3-*dihydro*-2,2,6,7-*tetramethyl*-5-*oxo*-5H,8aH-*thiazolo*[2,3-b][1,3]*oxazine*-3-*carboxylate* (**3**) (200 mg, 18%), a colourless oil (Found: M^+, 386.9855. $C_{13}H_{16}{}^{35}Cl_3NO_4S$ requires *M*, 386.9865); $\nu_{max.}$($CHCl_3$) 1 760, 1 660, and 1 410 cm^{-1}; δ_H($CDCl_3$) 1.54 and 1.79 (each 3 H, s, Me), 1.82 and 2.03 (each 3 H, s, vinylic Me), 4.80 (2 H, s, CH_2CCl_3), 4.90 (1 H, s, 3-H), and 6.64 (1 H, s, 8a-H); δ_C($CDCl_3$) 10.29, 17.07, 24.31, and 34.03 (each q, Me), 53.30 (s, 2-C), 70.03 (d, 3-C), 76.37 (t, CH_2CCl_3) 93.74 (d, 8a-C), 94.24 (s, CCl_3), 106.39 (s, 6-C), 161.87 (s, 5-C), 162.45 (s, CO_2), and 167.40 (s, 7-C); *m/z* 387 (M^+).

A mixture of the 6-acetylpenicillanate (**2**) and oxazinone (**3**) (526 mg, 1.35 mmol) was dissolved in dioxane (50 ml) and potassium dihydrogen phosphate–sodium hydroxide buffer (pH 7; 20 ml), was added followed by sodium borohydride (50 mg, 1.35 mmol). After 30 min brine was added, and the mixture extracted with ethyl acetate. After drying ($MgSO_4$), the organic phase was concentrated under reduced pressure, and the residue chromatographed on silica gel using ethyl acetate–light petroleum (1:9) as eluant, to provide firstly the oxazinone (**3**) (200 mg), followed by 2,2,2-*trichloroethyl* 6β-[(1RS)-1-*hydroxyethyl*]-6α-*methylpenicillanate* (**4**) (194 mg, 59%), a pale yellow oil, isomer ratio *ca.* 2.3:1; $\nu_{max.}$($CHCl_3$) 3 500, 1 780, 1 760, and 1 450 cm^{-1}; δ_H($CDCl_3$) major diastereoisomer: 1.33 (3 H, d, *J* 6 Hz, CH_3CHOH), 1.48 and 1.58 (each 3 H, s, Me), 1.69 (3 H, s, 6-Me), 4.39 (1 H, q, *J* 6 Hz, CH_3CHOH), 4.55 (1 H, s, 3-H), 4.73 and 4.84 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), and 5.18 (1 H, s, 5-H); minor diastereoisomer: 1.11 (3 H, d, *J* 6 Hz, CH_3CHOH), 1.50 and 1.56 (each 3 H, s, Me), 1.72 (3 H, s, 6-Me), 4.39 (1 H, q, *J* 6 Hz, CH_3CHOH), 4.56 (1 H, s, 3-H), 4.72 and 4.85 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), and 5.12 (1 H, s, 5-H).

With cyclopentanone. Boron trifluoride–diethyl ether (2 drops) was added to a solution of 6-diazopenicillanate (**1**) (1 g, 2.8 mmol) and cyclopentanone (0.24 ml, 2.8 mmol) in dichloromethane (40 ml) at 0—5 °C. After 30 min the mixture was concentrated under reduced pressure and the residue chromatographed on silica using ethyl acetate—light petroleum (1:9) as eluant. The first eluted product was identified as (3S, 10aS)-2,2,2-*trichloroethyl* 2,3,6,7,8,9-*hexahydro*-2,2-*dimethyl*-5-*oxo*-5H, 10aH-*thiazolo*[2,3-b][1,3]*benzoxazine*-3-*carboxylate* (**8**) (146 mg, 13%), m.p. 122—124 °C (from ethyl acetate—light petroleum) (Found: M^+, 413.0019. $C_{15}H_{18}{}^{35}Cl_3NO_4S$ requires *M*, 413.0022): $\nu_{max.}$($CHCl_3$) 1 760, 1 660, and 1 420 cm^{-1}; δ_H($CDCl_3$) 1.55 and 1.80 (each 3 H, s, Me), 1.58—2.34 (8 H, complex m, 4 × CH_2), 4.80 (2 H, s, CH_2CCl_3), 4.90 (1 H, s, 3-H), and 6.68 (1 H, s, 10a-H); δ_C($CDCl_3$) 21.38, 21.80, and 21.87 (each t, CH_2), 24.33 and 34.08 (each q, Me), 27.21 (t, 6-C), 53.28 (s, 2-C), 69.88 (d, 3-C), 74.92 (t, CH_2CCl_3) 93.98 (d, 10a-C), 94.27 (s, CCl_3), 108.62 (s, 5a-C), and 162.12, 164.00, and 167.49 (each s, 9a-C + two carbonyl C); *m/z* 413 (M^+). The second eluted product was identified as (6′R)-2,2,2-*trichloroethyl spiro*-(*cyclohexane*-2,6′-*penicillanate*) (**7**) (237 mg, 20%), m.p. 175—177 °C (decomp.) (from ethyl acetate–light petroleum) (Found: M^+, 413.0005. $C_{15}H_{18}{}^{35}Cl_3NO_4S$ requires *M*, 413.0022); $\nu_{max.}$($CHCl_3$) 1 780, 1 760, and 1 710 cm^{-1}; δ_H($CDCl_3$) 1.53 and 1.65 (each 3 H, s, Me), 1.67—2.66 (8 H, complex m, 4 × CH_2), 4.77 (1 H, s, 3-H), 4.73 and 4.84 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), and 5.20 (1 H, s, 5-H); δ_C($CDCl_3$) 22.53 (t, CH_2) 26.32 and 30.94 (each q, Me), 27.30, 35.71, and 40.78 (each t, CH_2), 63.76 (s, 2-C), 68.91 (d, 3-C), 69.47 (d, 5-C), 74.10 (s, 6-C), 74.87 (t, CH_2CCl_3), 94.09 (s, CCl_3), 166.44 (s, CO_2), 171.42 (s, 7-C), and 202.46 (s, CH_2CO); *m/z* 413 (M^+).

With acetophenone. Boron trifluoride–diethyl ether (12 drops) was added to a solution of 6-diazopenicillanate (**1**) (1.5 g, 4.18 mmol) and acetophenone (0.64 ml 4.18 mmol) in dichloromethane (60 ml) at 0—5 °C. After 1 h the mixture was concentrated under reduced pressure, and the residue chromatographed on silica using ethyl acetate–light petroleum (1:9) as eluant. The first eluted material was identified as 2,2,2-*trichloroethyl* 6β-*acetyl*-6α-*phenylpenicillanate* (**9**) (212 mg, 11%), m.p. 139—140 °C (from ethyl acetate–light petroleum) (Found: M^+, 449.0051. $C_{18}H_{18}{}^{35}Cl_3NO_4S$ requires *M*, 449.0020); $\nu_{max.}$($CHCl_3$) 1 780, 1 770, and 1 710 cm^{-1}; δ_H($CDCl_3$) 1.53 and 1.73 (each 3 H, s, Me), 2.24 (3 H, s, $COCH_3$), 4.54 (1 H, s, 3-H), 4.68 and 4.86 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), 5.45 (1 H, s, 5-H), and 7.38—7.50 (5 H, m, ArH); *m/z* 449 (M^+). The second eluted product was identified as (3S, 8aS)-2,2,2-*trichloroethyl* 2,3-*dihydro*-2,2,7-*trimethyl*-5-*oxo*-6-*phenyl*-5H, 8aH-*thiazolo*[2,3-b][1,3]*oxazin*-3-*carboxylate* (**11**) (87 mg, 5%), m.p. 155—157 °C (from dichloromethane–light petroleum) (Found: M^+ 449.0026. $C_{18}H_{18}{}^{35}Cl_3NO_4S$ requires *M* 449.0020); $\nu_{max.}$($CHCl_3$) 1 760, 1 660, 1 400, and 1 370 cm^{-1}; δ_H($CDCl_3$) 1.57 and 1.86 (each 3 H, s, Me), 1.98 (3 H, s, 7-CH_3), 4.77 (2 H, s, CH_2CCl_3), 4.96 (1 H, s, 3-H), 6.86 (1 H, s, 8a-H), and 7.27—7.40 (5 H, m, ArH); *m/z* 449 (M^+). The third eluted product was identified as 2,2,2-*trichloroethyl* 6β-*benzoyl*-6α-*methylpenicillanate* (**10**) (72 mg, 4%), m.p. 160—162 °C (from ethyl acetate–light petroleum); $\nu_{max.}$($CHCl_3$) 1 785 and 1 770 cm^{-1}; δ_H($CDCl_3$) 1.52 and 1.61 (each 3 H, s, Me) 1.99 (3 H, s, 6-CH_3), 4.53 (1 H, s, 3-H), 4.72 and 4.89 (each 1 H, d, *J* 12 Hz, $HCHCCl_3$), 5.43 (1 H, s, 5-H), and 7.48—8.01 (5 H, m, ArH); *m/z* 449 (M^+).

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