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PHTHALIDYL ESTERS OF CEPHALOSPORINS[1]

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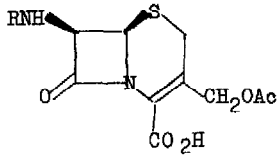
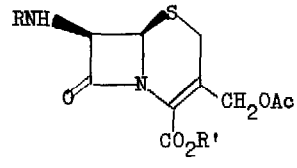
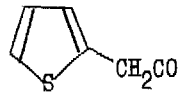
Esterification of cephalosporins e.g. 1 often presents problems associated with the isomerisation of the nuclear double bond resulting in a mixture of the $\Delta 3$-ester, 2 and the $\Delta 2$-ester, 3.[2] Fractional crystallisation often gives acceptable yields of 2 and in addition an elegant method exists for converting 3 to 2 via the sulphoxide.[3] However avoidance of the formation of 3 is clearly desirable. Such a problem confronted us in attempting to esterify various cephalosporins 1 with the phthalidyl moiety, R' = 4 (X = •).



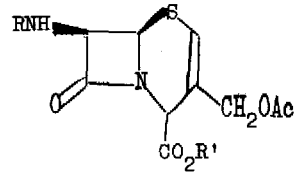
1



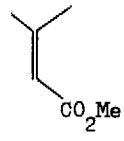
2

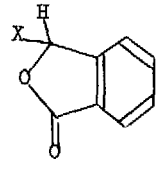
a R = 

b R = D-PhCH-CO
NHCO$_2$Bu^t



3

c R = Me 



4 a X = Br
b X = OH
c X = I

Substrate		Reagent note		Ratio 2:3	Yield 2+3(%)	
1a	Na salt	4a	i	60:40	83-90	2aA: m.p. 174-6°; $[\alpha]_D^{20}$ -40.8° (c, 0.72, acetone) 2aB: m.p. 169-171; $[\alpha]_D^{20}$ 43.8° (c, 0.94, acetone)
1a		4b	ii	ca90:10	10	Isolated Δ3-ester was 2aB
1a	Na salt	4c	iii	95:5	64	
1a	Na salt	4c	iv	95:5	81-90	
1b	Na salt	4a	i	50:50	73	2bA[v] : m.p. 182-4° ; $[\alpha]_D^{20}$ -62.9° (c, 0.91, acetone) 2bB[v] : m.p. 154-7° ; $[\alpha]_D^{20}$ + 22.2° (c, 1.03, acetone).
1b		4b	ii	ca90:10	26	
1b	Na salt	4c	iii	95:5	58	
1b	Et_3N salt	4c	iv	95:5	77	
1c	Na salt	4a	i	70:30	78	
1c	Na salt	4c	iv	95:5	83	

i 1 equiv. dry DMF, 1 hr, 20°

ii DCCI in MDC, 3 - 5 hrs, 20°

iii 1 equiv, dry DMF, 3 - 5 mins, 20°

iv 1 equiv, dry CH_3CN or acetone added to DMSO solution of substrate, 10 - 15 mins, 20°

v Pure 2bA and 2bB were synthesised from 2aA and 2aB respectively by chemical deacylation (PCl_5-quinoline; PrOH; H^+) and reacylation with D-PhCH($NHCO_2Bu^t$)$CO_2CO_2Bu^i$.

An added complication arises in this case since R' contains a new chiral centre. Thus when the Na salt of 1a was treated with bromophthalide, 4a in dry DMF a mixture containing the desired Δ3-ester, 2a as a 1:1 mixture of epimers was obtained together with the corresponding Δ2-epimers, 3a. Fractional crystallisation from aq. Methanol afforded one epimer of 2a, referred to as 2aA, in 10 - 20% yield and from the liquors the other epimer, 2aB (11%) was isolated.[4] The proportion of the Δ3-ester, 2a in the crude product was readily ascertained from the p.m.r. spectrum by integration of the resonance for the C2-methylene protons in 2a, which appeared as an AB quartet centred at δ 3.5 p.p.m. ($CDCl_3$, TMS as internal standard). An independent figure was obtained by measuring the extinction of the U.V. absorption at approximately 270nm, associated with 2a and not 3a[2] and comparing this with the value for the pure Δ3-isomers, 2aA (λ_{max}^{Dioxan} 272.5 nm, ε, 8150) or 2aB (λ_{max}^{Dioxan} 270 nm, ε, 7850). Separation of the two epimers, 2aA and 2aB was indicated by their differing polarities on T.L.C. and the appearance of separate resonances for the acetoxy methyl (at

δ 2.05, 2.10 p.p.m.) and phthalide methine protons (at δ 7.45, 7.50 p.p.m.). Other relevant data is presented in the table. The proportion of 2a was not significantly increased by change of solvent (DMSO, HMPA, DMA) or of countercation (K^+, $Et_3\overset{+}{N}H$, $PhCH_2Me_3N^+$). Attempts to esterify 1a with phthalaldehydic acid, 4b using acid chloride, carbodiimide, carbonyl diimidazole or mixed anhydride techniques generally failed or gave poor yields of esters. Interestingly a N,N'-dicyclohexylcarbodiimide mediated esterification of 1a with 4b produced a 10% yield of 2aB and only a trace of the epimer 2aA. These general observations with 1a were essentially duplicated with other cephalosporins including 1b (See Table).

When a solution of iodophthalide[6], 4c generated by stirring 4a with NaI in acetonitrile or acetone for 4-5 mins. was filtered into a solution of 1a, 1b or 1c[7], as their Na or Et_3N salts, in DMSO and the reaction allowed to proceed for 15 mins, the products isolated in high yield were largely free of any Δ2-isomers (See Table). Slightly lower yields were found when DMF only was used as solvent.

Cleavage of the protecting t-butyloxycarbonyl group from 2bA or 2bB or from the mixed epimers arising from the iodophthalide reaction was readily achieved using approximately N-hydrogen chloride in glacial acetic acid or dry ethyl acetate, which precipitated adequately pure phthalidyl D-phenylglycylcephalosporinate as a hydrochloride salt upon the addition of dry ether. Similarly, treatment of 2c (mixed epimers) with N-hydrochloric acid in aqueous acetone provided phthalidyl 7-aminocephalosporinate after work up.

It was of some interest to determine the cause of the isomerisation observed with 4a and not 4c. When dry DMF solutions of the pure Δ3-esters 2aA and 2aB were each stirred at 20° with NaBr, NaI, 4a and the Na salt of 1a only the latter resulted in isomerisation. Equilibrium was reached after 20 mins. when the ratio of Δ3 : Δ2 isomers was approximately 1:1. Since 1a or its Na salt were unchanged on similar treatment with NaBr or NaI, we conclude that the carboxylate ion itself isomerises the Δ3-ester as it is formed. We thus attribute the success of the reaction with 4c to the rate of reaction, allowing complete and fast removal of the carboxylate ion from the reaction mixture to be achieved.[8]

References and notes:

1. "Phthalidyl" refers to the 1-oxo-(3H)-isobenzfuranyl group. This group was expected to confer favourable oral absorbtion properties to the parent cephalosporin, which is liberated subsequently by enzymatic hydrolysis.
2. R.R. Chauvette and E.H. Flynn. J.Med.Chem. 1966, 9, 741. A more general account is presented in "Cephalosporins and Penicillins", ed. E.H. Flynn, Academic 1972, p.172.
3. G.V. Kaiser, R.D.G. Cooper, R.E. Koehler, C.F. Murphy, J.A. Webber, I.G. Wright and E.M. Van Heyningen, J.Org.Chem., 1970, 35, 2430.
4. All new compounds had satisfactory analytical and spectroscopic data.
5. These generally poor results may be a consequence of the unique reactivity of 4b. See D.D. Wheeler, D.C. Young and D.S. Erley, J.Org. Chem. 1957, 22, 547.
6. 4c is unstable and was used immediately.
7. 1c sodium salt was prepared by stirring a methanol solution of ACA sodium salt with methyl acetoacetate in the presence of molecular sieve (4a). The product (69%), which was isolated after 5 hrs. by filtration, evaporation and trituration with ether, was used without further purification.
8. It is assumed that the carboxylate anion is acting as a base promoting loss of a C2-hydrogen, resulting in isomerisation of the double bond: