Synthesis of C-2–C-3-Tricyclic Cephalosporins

By DOUGLAS O. SPRY

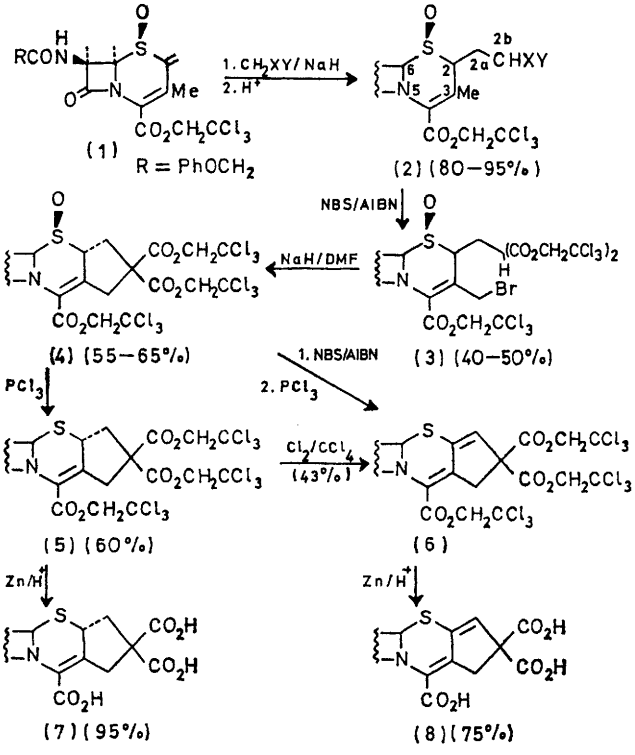
(*The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana* 46206)

Summary C-2–C-3-Tricyclic cephalosporins were synthesized *via* a Michael functionalization at C-2 followed by displacement of the bromomethyl group at C-3′.

STRUCTURAL modifications of the cephalosporin molecule have been centred at the C-7 side chain,[1a] at C-3′,[1b] and more recently at C-7α[2] and at C-2.[3] To our knowledge, however, there has been no description of C-2–C-3′ bridging to yield tricyclic structures. We now report the synthesis of the tricyclic cephalosporins (**7**) and (**8**).

The general synthetic approach to these derivatives was to functionalize at C-2 followed by displacement and ring closure at C-3′. Derivatization at C-2 was accomplished *via* a Michael reaction on the readily available,[3a] electrophilic[3a,d] C-2 exomethylene sulphoxide (**1**). The reaction takes place readily with nucleophiles such as $CH_2(CO_2R)_2$, $CH_2(CN)_2$, $MeNO_2$, and CH_2CNCO_2R to give (**2**) in good yield.

Allylic bromination of (**2**; X=Y=$CO_2CH_2CCl_3$) with *N*-bromosuccinimide (NBS) catalysed by azobisisobutyronitrile (AIBN) provided the 3′-bromomethyl derivative (**3**) which when treated with sodium hydride afforded the tricyclic derivative (**4**) [ν_{max} ($CHCl_3$) 1808 cm^{-1} (β-lactam); δ ($CDCl_3$) 2·3—3·3 (2H,m,2′-CH_2), 3·76 (3H,m,3′-CH_2 + 2-H) 4·92 (1H, d, *J* 4 Hz, 6-H), 6·11 (1H, q, *J* 4, 10 Hz, 7-H)]. Reduction of the sulphoxide using PCl_3 gave (**5**) and subsequent ester cleavage with zinc–acetic acid resulted in the tricyclic triacid (**7**).



Attempts to functionalize C-3′ further *via* the allylic bromination of (**4**) resulted in C-2 derivatization giving the C-2 bromo-derivative. Subsequent reaction with PCl_3 resulted in sulphoxide reduction with concomitant elimination of HBr to give the diene (**6**) [λ(EtOH) 325 (ϵ 12,500); ν_{max} ($CHCl_3$) 1795 cm^{-1} (β-lactam); δ ($CDCl_3$) 3·83 and 4·10 (2H, AB, J 18 Hz, 3′-CH_2), 5·15 (1H, d, J 4 Hz, 6-H), 5·90 (1H, q J 4, 10 Hz, 7–H), 6·59 (1H, s, 2′-H)] in low yield (16%). A better route to (**6**) was provided in the reaction of the sulphide (**5**) with chlorine *via* the carbosulphonium ion.[4] Ester cleavage of (**6**) then yields the diene triacid (**8**).

N.m.r. benzene shielding studies[5] on (**4**) and (**5**) show that the 2-H proton is slightly deshielded [δ ($CDCl_3$) − δ (C_6D_6)] by approximately −0·1 to −0·2 p.p.m. implying a β configuration for the proton and thus an α configuration for the ring juncture.

The tricyclic triacids (**7**) and (**8**) as well as the corresponding sulphide acids of (**2**) display significantly reduced microbiological activity in comparison to 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid.

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