C(3)-Carboxy-cephem

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Summary C(3)-carboxy-cephem and its subsequent conversion into C(3)-ketones, amides, and various *N*-cephem acylamines is described.

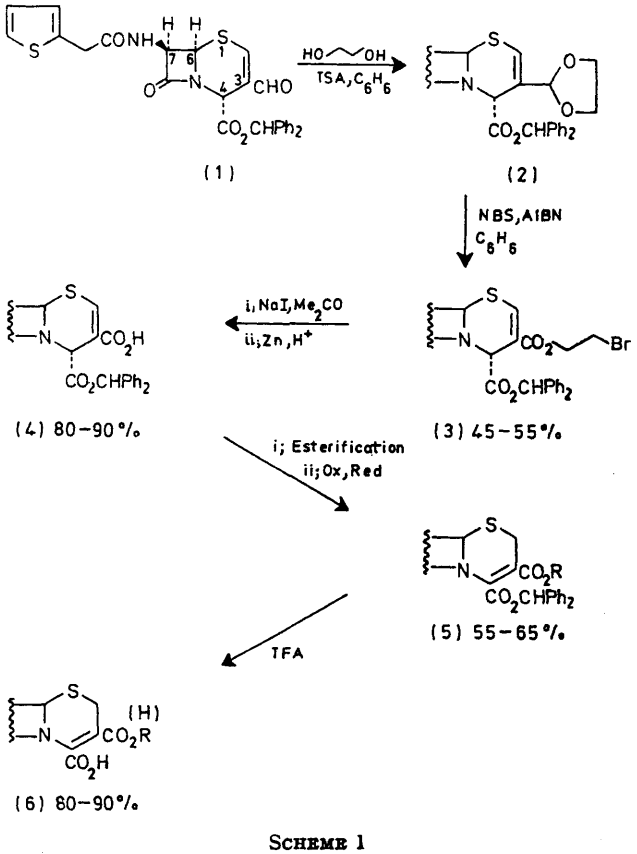
ALTHOUGH the C(3)-formyl group of the cephem molecule was reported in 1966 by Woodward[1] *et al.* in the total synthesis of cephalosporin C, its conversion into the C(3)-carboxylic acid has not been reported.[2]

We now describe the synthesis of C(3)-carboxy-cephem and its subsequent conversion into other C(3)-derivatives, for example, ketones, amides, and various *N*-cephem acylamines.

Treatment of the ethylene acetal (**2**) [m.p. 142—143°] with 1·1 equiv. of *N*-bromosuccinimide (NBS) and a trace of azobisisobutyronitrile (AIBN) in refluxing benzene, followed by chromatography on silica gel, gave 45—55% of the β-bromoethyl ester (**3**) [m.p. 129—130°] plus 10—20% of (**1**) (Scheme 1). Conversion of the β-bromo- into the β-iodo-compound (>95%) followed by zinc–acetic acid cleavage gave the C(3)-carboxy-Δ^2-cephem (**4**).

Esterification of (**4**) with diazoalkanes (CH_2N_2, Ph_2CN_2, p-$N_2CH{\cdot}C_6H_4{\cdot}NO_2$) or with the sodium carboxylate† of (**4**) and an alkyl iodide [*e.g.*, n-propyl (75%) or isopropyl (70%) iodide] in HMPA[3] followed by shifting the double bond (ox–red of S-1) gave (**5**; R=Me) [ν_{max} ($CHCl_3$) 1795—1800 cm^{-1}] m.p. 201° decomp., p-nitrobenzoate (PNB) m.p. 165—166°. Cleavage (PCl_5) of the C(7)-side chain provided the nucleus of (**5**), which was then acylated to provide the various C(7)-derivatives. Cleavage of the benzhydryl ester with trifluoroacetic acid (TFA) then gave (**6**), the C(3), C(4)-diacid (pK_a = 4·0,8·0) resulting from the cleavage of the dibenzhydryl ester.

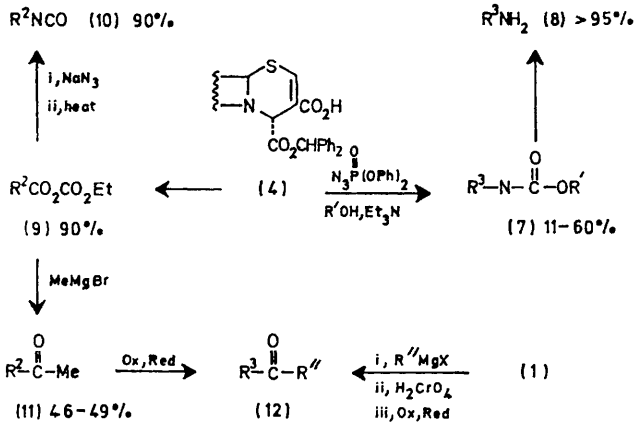
Biological tests show that, in general, the electron withdrawing effect of the C(3)-esters enhances both the gram negative and the gram positive activity, however, the compounds show significantly reduced activity against penicillin resistant *Staph. aureus*.



SCHEME 1

† The sodium carboxylate of (**4**) is soluble in EtOAc.

The synthesis of the C(3)-carboxylic acid allows the preparation of many previously unreported C(3)-derivatives of the cephem molecule. Various Δ^3-*N*-cephem-*O*-alkyl carbamates (**7**) [R′ = Me (11%), Et (34%), PNB (60%)‡], for example, have been obtained using the modified Curtius reaction of Yamada;[4] the presence of base causes complete double-bond isomerization from Δ^2 to Δ^3 (Scheme 2). Hydrogenolysis of the *p*-nitrobenzylcarbamate of (**7**) [R′=PNB] then affords the C(3)-amino compound (**8**)§ (>95%). Other *N*-cephem acylamine derivatives (ureas, thiocarbamates, and amides) are available from the C(3)-isocyanate (**10**) [ν_{max} ($CHCl_3$) 2260 cm^{-1}] obtained from the Curtius reaction on the mixed anhydride (**9**).



SCHEME 2

R^2 = Δ^2-C(3)-substituted benzhydryl 7-(2-thienyl)acetamido-cephem-4-carboxylate
R^3 = Δ^3-C(3)-substituted benzhydryl 7-(2-thienyl)acetamido-cephem-4-carboxylate

Catalytic reduction of the Δ^2-acylazide [ν_{max} ($CHCl_3$) 2143 cm^{-1}] gave the Δ^2-primary-amide (67%), while secondary and tertiary amides are available from the acid chloride or mixed anhydride.

C(3)-Ketones were prepared from the Grignard (MeMgBr) reaction on the mixed anhydride (**9**) to give 46—49% of the Δ^2-C(3)-acetyl (**11**) [m.p. 139—140°] plus 40—50% of (**4**). It is, however, more convenient to prepare such C(3)-ketone derivatives *via* the Grignard¶ reaction on the Δ^2-C(3)-formyl derivative (**1**) [Yields R″ = Me (45—65%), Et, or Ph (30—35%)] to give diastereoisomeric carbinols (separated in the case of R″ = Me,†† Et.‡‡). Oxidation to the corresponding ketones followed by double-bond isomerization then gave (**12**) [ν_{max} ($CHCl_3$) 1795—1800 cm^{-1}] R″ = Me (m.p. 201° decomp.), Et (m.p. 220° decomp.), Ph (m.p. 209° decomp.). The corresponding C(4)-acids were then obtained by TFA cleavage.

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‡ The C(3)-PNB carbamate-C(4)-acid has m.p. 149—150°.

§ Identical i.r. and n.m.r. to the product obtained by W. Spitzer *et al.* from an independent synthesis, personal communication.

¶ Optimum yields are obtained using 3 equiv. of Grignard reagent. Apparently two equiv. are tied up with the amide and the C(4)-proton.

†† One of the methyl diastereomeric carbinols is crystalline (m.p. 133—134°).

‡‡ Secondary acetates are readily prepared from the diastereoisomeric carbinols.

[1] R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *J. Amer. Chem. Soc.*, **1966**, **88**, 852.
[2] For Δ^3-C(3)-formyl cephalosporins see J. W. Chamberlin and J. B. Campbell, *J. Medicin. Chem.*, 1967, **10**, 966.
[3] J. E. Shaw, D. C. Kunerth, and J. J. Sherry, *Tetrahedron Letters*, **1973**, 689.
[4] T. Shioiri, K. Ninomiya, and S. Yamada, *J. Amer. Chem. Soc.*, **1972**, **94**, 6203.