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SEMI-SYNTHETIC PENICILLINS AND CEPHALOSPORINS INCORPORATING A HYDROXYAMINO GROUP

Peter H. Bentley* and Gerald Brooks
Beecham Pharmaceuticals Research Division, Brockham Park,
Betchworth, Surrey, England.

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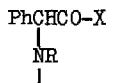
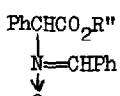
A previous note[1] describes the synthesis of semi-synthetic penicillins and cephalosporins incorporating a hydrazino grouping in the side-chain. This paper describes experiments designed to provide the analogous compounds, e.g. 1a, containing the α-hydroxyamino grouping. We also offer some observations on the synthesis of several α-hydroxyamino phenylacetic acid derivatives, which might be applicable elsewhere, in particular to the synthesis of N-hydroxypeptides.[2]

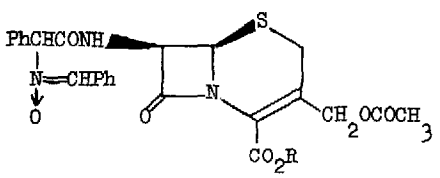


1a X = APA or ACA ; R, R' = H, alkyl or acyl
b X = ACA ; R = R' = H
c X = ACA ; R = COPh, R' = H
d X = APA ; R = R' = H
e X = ACA ; R = COPh, R' = Me
f X = ACA ; R = R' = Me
g X = APA ; R = R' = Me

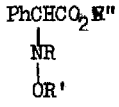
DL-α-hydroxyaminophenylacetic acid 2a (65% yield) was synthesised according to the general method of Buehler[3] in which the nitrone ester 3a is hydrolysed with hot hydrochloric acid. If the ester 3a is saponified, the derived acid 3b[4] (a frothy solid, 62% yield, dicyclohexylamine salt m.p. 131-2°) has the necessary N-O protection to enable coupling to 6-APA and 7-ACA to be achieved following activation of the carboxyl group in the usual way. Thus although carbodiimides were less successful a mixed anhydride of 3b with $ClCO_2Bu^i$ reacted with the t-butyl ester of 7-ACA to provide the cephalosporin derivative, 4a (77% yield).

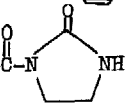
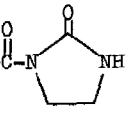


3a R" = Et
b R" = H
c R" = Bu^t



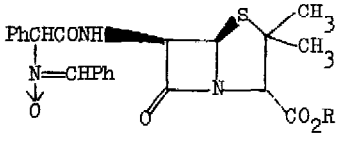
4a R = Bu^t
b R = H



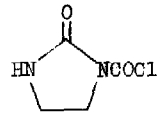
2a R = R' = R" = H
b R = R' = H ; R" = Et
c R = R' = H ; R" = Bu^t
d R = PhCO ; R' = H ; R" = Et
e R = PhCO ; R' = H ; R" = Bu^t
f R = PhCO ; R = R" = H
g R = CO_2CH_2-(4-NO_2)-Ph ; R' = H ; R" = Bu^t
h R = CO_2CH_2-(4-NO_2)-Ph ; R' = R" = H
i R =  ; R' = H ; R" = Bu^t
j R =  ; R' = R" = H
k R = PhCO ; R' = Me ; R" = Bu^t
l R = PhCO ; R' = Me ; R" = H
m R = CO_2CH_2-(4-NO_2)-Ph ; R' = Me ; R" = Bu^t
n R = CO_2CH_2-(4-NO_2)-Ph ; R' = Me ; R" = H
p R = H ; R' = R" = Et
q R = R" = H ; R' = Et
r R = R' = Me ; R" = H

Treatment of the latter with TFA provided the acid 4b and this with p-toluene sulphonic acid (ethanol, 4hrs.) led to the desired DL-α-hydroxyaminophenylacetamido cephalosporanic acid 1b (59% overall yield). When 4a was treated with p-toluene sulphonic acid (1 equivalent, chloroform, 30 mins), the nitrone grouping was selectively cleaved. Although attempts to isolate the t-butyl ester of 1b led only to recombination with the liberated benzaldehyde, this ester was found to undergo in situ N-acylation e.g. with benzoyl chloride, and following TFA treatment, the N-benzoyl derivative 1c was isolated.

In a similar fashion the mixed anhydride of 3b ($ClCO_2Bu^i$, THF) was used to acylate the 2,2,2-trichloroethyl ester of 6-APA. Following chromatography the ester 5a was isolated in 73%, but attempts to remove either protecting group failed. More successfully the same mixed anhydride of 3b reacted with the triethylammonium salt of 6-APA and following work-up the Na salt 5b was obtained. Careful treatment of 5b with acetone : 2N-HCl (1:1) (1 hr, 25°) provided a 59% yield of the desired DL-α-hydroxyaminophenylacetamido penicillanic acid, 1d.

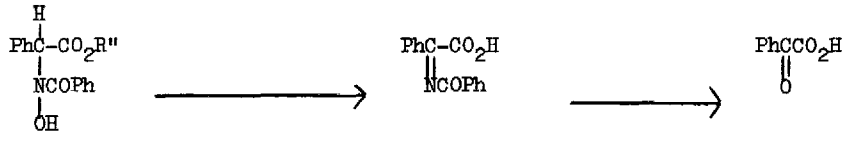


5a R = CH_2CCl_3
b R = Na



6

Whilst attempted N-acylations of 2a proved fruitless, the esters 2b and 2c[5] were benzoylated in a two-phase system of CH_2Cl_2- sodium bicarbonate (aq.) to provide 2d (70%, oil) and 2e (81%, m.p. 146-9°) respectively.[6] Saponification of 2d led only to the isolation of phenylglyoxylic acid (62% yield) presumably arising via base abstraction of the Cα-proton (Scheme 1). However the acid 2f (82% as the dicyclohexylamine salt, m.p. 147-9°) was readily obtained on treating 2e with TFA.



R" = H or Et

Scheme 1

In the same way p-nitrobenzylchloroformate reacted with 2c in the 2-phase system to provide 2g (77%, m.p. 102-4°) and TFA treatment gave the acid 2h (94% of the dicyclohexylamine salt, m.p. 134-6°). Similarly the allophanamide derivative 2i (75%, m.p. 175-8°) was isolated from the reaction of 2c with the carbonyl chloride 6. TFA treatment again provided the corresponding acid 2j (85%, m.p. 158-160°). Compounds 2d - 2j all gave a positive $FeCl_3$ test indicating the presence of the hydroxamic acid unit. Attempts to couple the acids 2f, 2h or 2j to APA or ACA, however were largely unsuccessful, in view of the presence of the unprotected N-hydroxy group. Thus although 2f, DCCI and the t-butyl ester of ACA gave a 91% yield of the ester of 1c after chromatography, these and other conditions failed with 2h. To overcome this difficulty the N-hydroxy group was O-alkylated. Attempted alkylation of 2e with Meerwein's reagent, or with MeI/NaOH were unsuccessful, whilst dimethylsulphate (acetone, K_2CO_3) gave 2k in 20% yield. More success was obtained using dimethylsulphate under phase transfer conditions (aq. NaOH, CH_2Cl_2, $PhCH_2\overset{+}{N}Et_3Br^-$) when the yield of 2k rose to 69% following chromatography. TFA treatment of the latter gave the acid 2l (60% as the DCHA salt). Similarly 2g was methylated to give 2m (48% after chromatography) and TFA treatment provided the acid 2n (81%). Acid 2l reacted with the t-butyl ester of ACA satisfactorily using DCCI to give the t-butyl ester of 1e (30% yield following chromatography) and the latter after treatment with TFA provided the desired DL-α-N-benzoyl-N-methoxy aminophenylacetamidocephalosporanic acid 1e (91% yield). Synthesis of the corresponding penicillin analogue, however, was abandoned owing to the lack of a suitable nuclear-carboxyl protecting group.

An alternative and less successful route to compounds of type 2 (R = acyl, R' = R" = alkyl) was also investigated. Thus the nitrone 3a on treatment with Meerwein's reagent (1.15 equivalents in CH_2Cl_2) followed by hydrogen chloride in ether precipitated the hydrochloride salt of 2p (76%, m.p. 115-7°). Attempted N-acylations of 2p under a variety of conditions were without success. Of some interest was the acid 2q corresponding to 2p. Saponification of the latter yielded only phenylglyoxylic acid (91% yield) by a process assumed to be analogous to that of scheme 1. The hydrochloride salt of 2q (40%, m.p. 221-3°) was however

obtained by brief refluxing of 2p with concentrated HCl. All attempts to acylate APA or ACA with the latter were unsuccessful.

For entry into the series 1a with R = R' = alkyl, DL-α-bromophenyl acetic acid was reacted with O,N-dimethylhydroxylamine (ethanol, reflux 3 hrs, 18 hrs, at 20°) to provide the hydrochloride salt of the desired derivative 2r (38%, m.p. 139-141°). A mixed anhydride of the latter prepared from $ClCO_2Bu^i$ and N-methylmorpholine (2 equivalents) was reacted with the t-butyl ester of ACA to give the ester of 1f (85% after chromatography). Following TFA treatment DL-α-N-methoxyphenylacetamido cephalosporanic acid 1f was isolated in (82% yield). The same mixed anhydride reacted also with the triethylamine salt of APA in aq. THF and provided the corresponding penicillin analogue 1g (80% isolated as its Na salt).

The β-lactam derivatives 1b - 1g, 4b and 5b were without useful microbiological activity.

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References and Notes:

1. P.H. Bentley and E. Hunt, Tetrahedron Letters submitted for publication.
2. See G. Zvilichovsky and L. Heller, Tetrahedron Letters, 1969, 1159. and T. Kolasa and A. Chimiak, Tetrahedron 1974, 30, 3591 and references cited.
3. E. Buehler and G.B. Brown, J. Org. Chem. 1967, 32, 265.
4. All new compounds herein reported gave satisfactory analytical and spectroscopic data.
5. 2b and 2c were obtained by treating the corresponding nitrones 3a and 3c with aq. ethanolic HCl (18 hrs, 20°) and ethanolic hydrazine (1.1 equivalents, 3 hrs, 45°) respectively or by esterifying 2a.
6. This procedure follows that described by T. La Noce, E. Bellasio and E. Testa, Ann. Chim. (Rome) 1968, 58, 393.