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SEMI-SYNTHETIC PENICILLINS AND CEPHALOSPORINS INCORPORATING A HYDRAZINO GROUP

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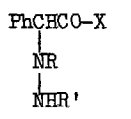
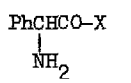
A recent communication by Achiwa and Yamada[1] describing an elegant synthesis of optically active α-hydrazino acids, prompts us to record our own work on the use of α-hydrazinophenyl acetic acid derivatives as acylating agents in the preparation of semi-synthetic penicillins and cephalosporins of type 1a. The unsubstituted hydrazines 1b and 1c bear an obvious close structural relationship to the marketed broad spectrum antibiotics ampicillin, 2a and cephaloglycin, 2b.



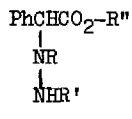
1 a X = APA or ACA ; R,R' = H, acyl
b X = ACA ; R = R' = H
c X = APA ; R = R' = H



2 a X = APA
b X = ACA

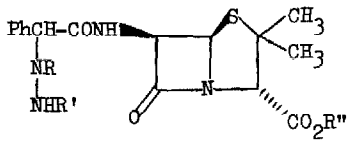
Our general comments should be applicable to the synthesis of peptides incorporating the α-hydrazino group, eminantly studied by Niedrich and co-workers.[2]

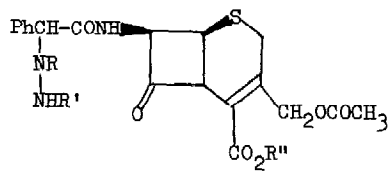
Acylation of DL-α-hydrazinophenylacetic acid, 3a (prepared from DL-α-bromophenyl acetic acid and hydrazine in ethanol, 63% yield, m.p. 191°) with 2.2 equivalents of benzyl chloroformate under Schotten-Baumann conditions provided the bis-protected derivative 3b.[3,4]



3 a R = R' = R" = H
b R = R' = CO_2CH_2Ph, R" = H
c R = R" = H, R' = CO_2Bu^t
d R = R" = H, R' = CO_2CH_2-  -NO_2
e R = R' = CO_2CH_2-  -NO_2, R" = H
f R = CO_2CH_2-  -NO_2, R' = R" = H
g R = H, R' = CO_2CH_2-  -NO_2; R" = Et
h R = R" = H ; R' = COPh

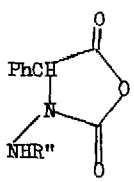
Although activation of the carboxyl group of 3b through the use of dicylohexylcarbodiimide or by mixed anhydride techniques ($ClCO_2Et$) allowed the synthesis of the fully protected β-lactams 4a and 5a, difficulties were encountered in the removal of the protecting benzyl groups in 4a and the acid 5b (prepared from 5a by brief treatment with trifluoroacetic acid).

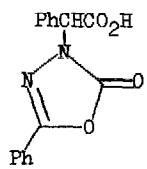




4 a R = R' = CO_2CH_2Ph; R" = CH_2Ph
b R = H, R' = CO_2CH_2-C6H4-NO_2, R" = Na

5 a R = R' = CO_2CH_2Ph; R" = Bu^t
b R = R' = CO_2CH_2Ph; R" = H
c R = R" = H, R' = CO_2Bu^t





6 a R" = CO_2Bu^t
b R" = CO_2CH_2-C6H4-NO_2
c R" = COPh

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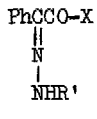
Under the conditions to cleave the benzylic C-O bond, hydrogenolysis of the N-N bond also takes place to some extent. Therefore an alternative means of protecting 3a was sought. Acylation of the hydrazino acid 3a with t-butyl azidoformate at pH 12 in aq. dioxan over 53 hours led to the mono Nβ-derivative 3c in 80% yield (Oil, dicyclohexylamine salt has m.p. 156-8°) even with excess azidoformate. Activation of the carboxyl in 3c by DCCI or by mixed anhydride and subsequent reaction with ACA-t-butyl ester led to several components, clearly indicating that for successful couplings both NH groups of 3a required protection. This was achieved by conversion of the mono-(Nβ-)-derivatives (e.g. 3c and 3d) to their corresponding N-carboxy anhydrides, 6a and 6b respectively.[6] Protection of the α-NH and activation of the carboxyl were thus achieved simultaneously. Thus treatment of 3c with phosgene in THF containing suspended silver carbonate over 1hr. provided 6a, which reacted with the triethylammonium salt (or better the trimethylsilyl ester) of ACA in methylene chloride to provide the desired cephem derivative 5c. Brief treatment of the latter with TFA-anisole led to DL-α-hydrazinophenylacetamidocephalosporanic acid 1b as its TFA salt.[7]

For the synthesis of the corresponding penicillin derivative 1c, the easily hydrogenolysable p-nitrobenzyloxycarbonyl group was chosen to protect the β-nitrogen as in 3d. Initially reaction of 3a with p-nitrobenzylchloroformate (1 equivalent) at pH 11 in aq. dioxan provided low yields of the desired compound 3d (m.p. 126-130°) owing to contamination with both the bis-protected and the Nα-mono protected derivatives 3e and 3f respectively. However reaction of the corresponding ethyl ester of 3a with the chloroformate in the presence of pyridine enabled 3g to be isolated in 95% yield. Saponification of the latter to 3d was however complicated, a set-back which was overcome by replacing the ethyl ester of 3a by the trimethylsilyl ester. Following the reaction with the chloroformate and aqueous work up 3d was isolated in 65% yield.[8] Conversion of the latter to the NCA-derivative 6b proceeded as for 6a and reaction of 6b with the silyl ester of APA together with aqueous work up provided the penicillin derivative 4b in 65% yield. Finally hydrogenolysis of the latter over $Pd/CaCO_3$ proceeded smoothly to give sodium DL-α-hydrazino phenylacetamidopenicillanate 1c.

A limiting factor to the use of N-carboxy anhydrides of type 6 was uncovered when the Nβ-benzoyl derivative 3h was treated with phosgene-silver carbonate. Instead of 6c the oxadiazolone, 7 was isolated[9] in 86% yield, m.p. 128-130°.



8 a X = APA or ACA ; R' = acyl
b X = APA ; R' = $CONH_2$
c X = ACA ; R' = $CONH_2$

Another approach to penicillins and cephalosporins to type (R = H, R' = acyl) would involve reduction of the corresponding hydrazones 8a. To test this approach, the semicarbazones 8b and 8c were prepared, in good yield, by reaction of the appropriate ketones with semicarbazide in aqueous ethanol. Preliminary attempts at reducing these semicarbazones using sodium bromohydride in pH 7 phosphate buffer/THF or by hydrogenation over 10% palladium-on-charcoal or platinium at 50 p.s.i. in aqueous ethanol were without success. These reductions were not however exhaustively studied because of the success of the other route described.

The penicillin and cephalosporin derivatives 1b, 1c, 4b 5b and 5c were without useful microbiological activity.

The authors thank Mr. J. Newman, Mr. P.D. Berry and Mr. N. Henderson for skilful technical assistance.

References

1. K. Achiwa and S. Yamada : Tetrahedron Letters, 1975, 2701.
2. See e.g. R. Grupe, B. Baeck and H. Niedrich, J. Prakt. Chem. 1972, 314, 751 and references cited therein.
   See also P.H. Bentley and J.S. Morley, J. Chem. Soc., 1966, C, 60.
3. The Na salt m.p. 157-8° of 3b precipitates from the medium in 40% yield, acidification of this and processing of the liquors gives a total 80% yield.
4. Structures of all new compounds reported herein were confirmed by spectroscopic and analytical data.
5. cf R. Grupe and H. Niedrich, Chem. Ber. 1966, 99, 3914 who report the synthesis of the corresponding 3-phenyl 2-hydrazinopropionic acid derivative.
6. The use of N-carboxy anhydrides in this form is the first to our knowledge, although of course it is a well-known peptide coupling method.
7. Ratio of epimers is ca 1:1 as judged by h.p.l.c.
8. This contrast between predominantly Nβ-acylation in esters of 3a and mixed Nα- and Nβ-acylation in 3a itself is worthy of further comment. Molecular models indicate that in esters of 3a there is real steric hindrance to approach at the α-nitrogen by the acylating agent, whereas in 3a and its amides, including 1b and 1c, the two nitrogens appear equally exposed. Bulky acylating agents also clearly favour Nβ-acylation with 3a viz 3c.
9. This result is perhaps not too surprising in view of the known reaction of hydrazides with phosgene to give oxadiazolones. In contrast alkoxycarbonylhydrazines yield the corresponding carbonyl chlorides. See Houben-Weyl "Methoden der Organischen Chemie" (ed. E. Müller), Verlag, Stuttgart, 1967, 10/2, 386.