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REACTION OF PYRROLO[2,1-c][1,4]BENZODIAZEPINE-2,5,11-TRIONES WITH PHOSPHORUS OXYCHLORIDE

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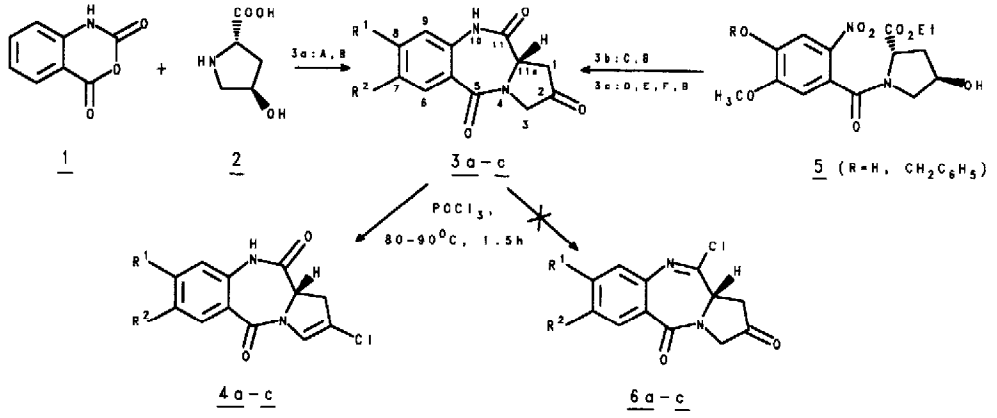
Abstract: Reaction of pyrrolo[2,1-c][1,4]benzodiazepine-2,5,11-triones of type 3a-c with phosphorus oxychloride affords chloroalkenes of type 4a-c instead of the expected chloroimidates (6a-c).

The pyrrolo[2,1-c][1,4]benzodiazepine (PBD) family of antitumor antibiotics[1] includes members such as anthramycin, tomaymycin, sibiromycin, the neothramycins A and B, and chicamycin. These compounds are thought to exert their biological activity through covalent binding in the minor groove of DNA, via an aminal linkage from the electrophilic carbinolamine-bearing C11-position to an N2 of guanine[2]. In view of the importance of the carbinolamine functionality, we became interested in developing new strategies for its synthesis. During the course of these efforts, we attempted to synthesize the 11-chloroimidate 6a by reaction of the pyrrolo[2,1-c][1,4]benzodiazepine-2,5,11-trione (3a) with phosphorus oxychloride. Our intention was to convert 6a to the corresponding imine (a carbinolamine equivalent) using $LiAl(tBuO)_3H$[3], however, the 2-chloropyrrolo[2,1-c]-[1,4]benzodiazepine-5,11-dione (4a) was formed in high yield instead of the desired 11-chloroimidate.



1 2 3a-c 5 (R=H, $CH_2C_6H_5$)

4a-c 6a-c

a, $R^1 = R^2 = H$; b, $R^1 = OCH_2C_6H_5$, $R^2 = OCH_3$; c, $R^1 = OCOC_6H_5$, $R^2 = OCH_3$

A. DMF/150-155°C
B. $CrO_3/H_2SO_4/(CH_3)_2CO$
C. $SnCl_2.2H_2O$/EtOH/75-80°C
D. H_2/Pd-C/EtOAc
E. Toluene/110°C
F. NaH/DMF/PhCOCl

The precursor 3a was prepared by Jones oxidation of 2-hydroxypyrrolo[2,1-c][1,4]-benzodiazepine-5,11-dione, which in turn was synthesized by condensation of isatoic anhydride (1) and trans-4-hydroxy-L-proline (2) in dimethyl formamide[4]. In a typical reaction, a suspension of 3a (200mg) in phosphorus oxychloride (10ml) was heated in an oil bath between 80-90°C for 1.5 h. The reaction mixture was then poured into ice water (30ml) and left for 4-6 h. After extraction with ethyl acetate (3x10ml), the combined organic phase was dried (anhydrous $MgSO_4$) and evaporated under vacuum to afford a solid residue. Purification by column chromatography (silica gel, chloroform-methanol 9.8:0.2) afforded 168mg (78% yield, m.p. 237-239°C) of 5,10,11,11a-tetrahydro-2-chloro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione (4a), which was characterized by analytical and spectroscopic data[5]. Furthermore, 3b and 3c[6] with substituents in the benzene ring, gave the corresponding 2-chloro substituted derivatives (4b and 4c) in 75% and 71% yields on reaction with phosphorus oxychloride, thus establishing the generality of the reaction.

It is interesting to note that the pyrrolo[2,1-c][1,4]benzodiazepine-5,10-dione without a carbonyl functionality at C2 did not undergo reaction with $POCl_3$, and only starting material was recovered. Steric effects are the most likely cause of the unreactivity of the N10-C11 amide, as the electronic structure appears normal from spectroscopic data.

In conclusion, this reaction with $POCl_3$ represents a specific conversion of a pyrrolobenzodiazepin-2-one to the corresponding 2-chloroalkene in the presence of a potentially enolizable amide. The reaction is regiospecific for C2-C3, which may reflect the difference in acidity between the C1 and C3 protons. Most of the biologically active natural products in the anthramycin family have C2-C3 unsaturation and C2-substituents, and therefore this reaction may be useful in the preparation of synthetic precursors. Further investigations are in progress on the applications of this work.

Acknowledgements. We thank the British Council and the Cancer Research Campaign for financial support.

References and Notes

1. L.H. Hurley and D.E. Thurston, Pharm. Res. (1984) 52.
2. (a) L.H. Hurley, T. Reck, D.E. Thurston, D.R. Langley, K.G. Holden, R.P. Hertzberg, J.R.E. Hoover, G. Gallagher, Jr., L.F. Faucette, S-M. Mong, R.K. Johnson, Chem. Res. Toxicol. 1 (1988) 258. (b) W.A. Remers, "The Chemistry of Antitumor Antibiotics, Vol.2", John Wiley, New York (1988), pp 28-92.
3. S. Karady, J.S. Amato, L.M. Weinstock and M. Sletzinger, Tet. Lett. 19 (1978) 403.
4. This type of condensation has been previously reported. For example see: W.B. Wright, Jr., H.J. Brabander, E.N. Greenblatt, I.P. Day and R.A. Hardy, Jr., J. Med. Chem. 21 (1978) 1087 and Ref.6. In this case, DMF was found to be a more suitable solvent than DMSO.
5. IR (KBr) 3420, 1700, 1610, 1485, 1450, 1420 cm^{-1}; ^1H NMR (270MHz, $CDCl_3$,δ) 3.10 (dd, 1H, J=17.0, 11.0Hz, with fine coupling), 3.81 (d, 1H, J=17.0Hz, with fine coupling), 4.58 (dd, 1H, J=11.0, 3.9Hz), 7.01 (d, 1H, J=8Hz), 7.06 (s, 1H), 7.33 (t, 1H, J=8.0, 8.0Hz), 7.54 (t, 1H, J=8.0, 8.0Hz), 8.02 (d, 1H, J=8.0Hz), 8.71 (br s, 1H); ^{13}C NMR ($CDCl_3$,δ) 35.1, 56.3, 119.5, 121.5, 124.4, 125.6, 125.7, 131.7, 133.1, 134.7, 162.5, 168.6; EI mass spectrum 250 ($M^{+\cdot}$ +2, 22), 248 ($M^{+\cdot}$, 68), 213 ($M^{+\cdot}$ -Cl, 45); observed mass 248.0350; calcd for $C_{12}H_9O_2N_2Cl$ 248.0353.
6. The starting materials 3b and 3c were prepared using literature methods: T. Kaneko, H. Wong and T.W. Doyle, Tet. Lett. 24 (1983) 5165.

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