Tetrahedron Letters,Vol.27,No.21,pp 2421-2422,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

# AN EXPEDITIOUS SYNTHESIS OF ANTHRACYCLINES

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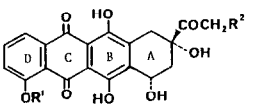
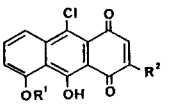
Abstract. Regiospecific cycloaddition of 2-oxybutadienes to derivatives of the 1,4-anthraquinone (6) efficiently leads to the tetracyclic ketones (4) and (5), which previously have been converted into daunomycin, adriamycin and related anticancer agents.

Much recent attention has been directed towards chemical synthesis of anthracyclines used in cancer chemotherapy[1]. Target molecules include the aglycones daunomycinone (1), adriamycinone (2) and carminomycinone (3), which are chemically convertible into the natural antitumor substances daunomycin and adriamycin[2,3]. This communication reports simple, efficient and highly regioselective syntheses of the tetracyclic ketones (4) and (5), established precursors of compounds (1)-(3)[2,4].

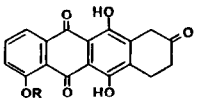
The new procedure is based on the 1,4-anthraquinone (6), a product efficiently obtained from the dyestuff 1,4,5-trihydroxy-9,10-anthraquinone[5]. On being heated with 2-methoxybutadiene as for related cycloadditions[5,6] (6) gave product (7) (68%), m.p. 210° (dec.). Formation of ketal (8) (95%), m.p. 187- 190° (dec.), and subsequent aerial oxidation in the presence of NaOH gave quinone (9) (73%), m.p. 203° (dec.), without significant aromatization of the A-ring. Brief warming of the product in $CF_3CO_2H$ resulted in hydrolysis of the ketal and of the chloride[5], leading to ketone (4) (74%), dec. > 270°. The latter was identical with authentic samples obtained both by synthesis[4] and by degradation of natural daunomycin[2,4].



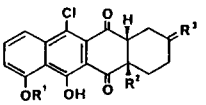
| | $R^1$ | $R^2$ |
|---|---|---|
| 1 | Me | H |
| 2 | Me | OH |
| 3 | H | H |



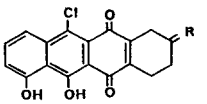
| | $R^1$ | $R^2$ |
|---|---|---|
| 6 | H | H |
| 10 | Ac | H |
| 11 | Ac | Br |
| 14 | Me | H |
| 15 | Me | Br |



4 R = H
5 R = Me



| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| 7 | H | H | O |
| 8 | H | H | $(OCH_2)_2$ |
| 12 | Ac | Br | O |



9 R = $(OCH_2)_2$
13 R = O

The same ketone (4) was obtained more conveniently through selective monoacetylation of (6) in acetic anhydride/pyridine to give (10) [$\delta_{OH}$ ($CDCl_3$) 15.55] (85%), m.p. 196-200°. This product on treatment with bromine in acetic acid[5] led to isolation of a single bromo isomer (11) ($\delta_{OH,H3}$ 15.27, 7.53) (95%), m.p. 197-200°. Cycloaddition of 2-trimethylsilyloxybutadiene to (11) in boiling benzene proceeded regiospecifically under control of the bromo group[5,7]. This gave ketone (12), treatment of which with $CF_3SO_3H$ effected deacetylation and elimination of HBr to form quinone (13) ($\delta_{OH}$ 10.54, 17.49). This was converted to (4) as before. Alternatively boiling (12) in $CF_3CO_2H$ containing NaOAc led directly to (4) (70%). Remarkably no significant aromatization of the A-ring was observed during any of these steps. Nor was the known[8] ketonic regioisomer of (4), corresponding to cycloaddition in the opposite sense detected in the final product. The three-pot operation (6) → (4) proceeded in overall yield of 56%.

While procedures involving the hydroxy ketone (4) lead to derivatives of carminomycinone (3)[9] their extension to daunomycinone (1) and adriamycinone (2) is restricted by the limited selectivity with which (4) and related trihydroxy-9,10-anthraquinones undergo O-mono-methylation[10]. This has been avoided by prior selective O-methylation of the 1,4-anthraquinone (6). Treatment of (6) with methyl iodide in dimethylsulfoxide in the presence of sodium hydride gave (14) ($\delta_{OH,OMe}$ 15.96, 4.07) (88%), m.p. 221-223°. This was elaborated by bromination followed by $BF_3$-catalysed dehydrobromination in EtOH to give the bromide (15) ($\delta_{H3,OMe}$ 7.50, 4.09) (95%) m.p. 222-224.5°. The latter, following successive treatment with 2-trimethylsilyloxybutadiene, $CF_3SO_3H$ and $CF_3CO_2H$, then gave methoxy ketone (5) 45% from (15), m.p. 248-250° (dec.). This was thereby obtained as a single regioisomer in a three-pot operation from (6) (38% overall). It was identical with authentic samples obtained both by synthesis[4] and by degradation of natural daunomycin[2,4]. Compound (5) has been converted into daunomycinone (1) in three further stages[4] and thence into adriamycinone (2)[2].

All new compounds gave satisfactory analyses and spectroscopic data. We thank Professor A.S. Kende and Rhone-Poulenc Santé for samples of (5) and natural daunomycin respectively. This work was carried out with a grant from the Anti-Cancer Council of Victoria.

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(Received in UK 11 March 1986)