Tetrahedron Letters,Vol.28,No.35,pp 4109-4112,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHESIS, STRUCTURE AND REACTIVITY OF 4-ACETYLAMINO-9a-ACETOXY-1,9,10-ANTHRACENETRIONE

Francisco Fariña*[a], M. Carmen Paredes[a] and Valter Stefani[b]

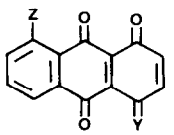
[a]*Instituto de Química Orgánica General, C.S.I.C., Juan de la Cierva 3, 28006 Madrid, Spain*

and

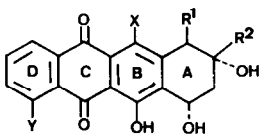
[b]*Instituto de Química, U.F.R.G.S., Av. Bento Gonçalves, 9.500, 90.000 Porto Alegre (RS), Brasil*

Summary: The anthracenetrione **8** undergoes a [1,5]-acetoxy shift and reacts with nucleophiles to give 3-substituted 1-acetylamino-4-hydroxy-9,10-anthraquinones. Cycloaddition of cyclopentadiene to **8** affords compounds related to anthracyclinones.

Quinizarinquinone (**1**) and derivatives have been used as BCD synthons for the elaboration of the aglycones of several anthracycline antitumor agents, such as daunomycinone (**4**) and demethoxy-daunomycinone (**5**), *via* a Diels-Alder reaction[1,2,3,4].



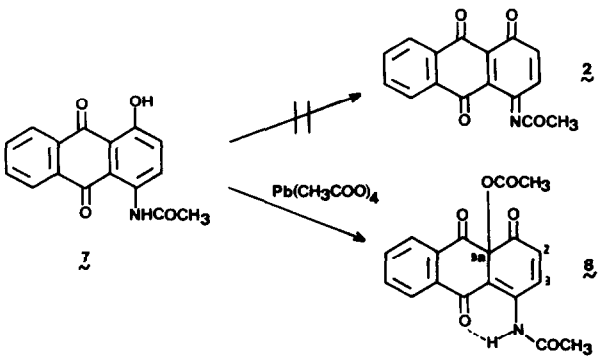
1 , Y = O , Z = H
2 , Y = $NCOCH_3$, Z = H
3 , Y = $NCOCH_3$, Z = OCH_3



4 , X = OH , Y = OCH_3 , R^1 = H , R^2 = $COCH_3$
5 , X = OH , Y = H , R^1 = H , R^2 = $COCH_3$
6 X = H , Y = OH , R^1 = CO_2CH_3 , R^2 = CH_2CH_3

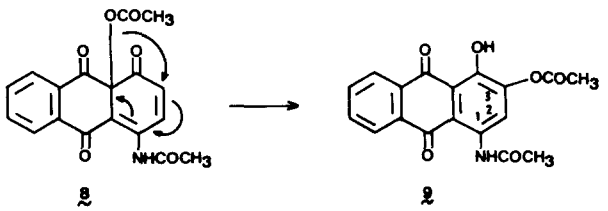
We were interested in the quinizarinquinone monoimine **2**, and substituted derivatives thereof such as **3**, because it offered the possibility of using a Diels-Alder strategy and removing the $NHCOCH_3$ group after the elaboration of the tetracyclic system, to afford derivatives of aklavinone (**6**), the aglycone of aclacinomycin A, one of the most promising anthracyclines[5].

However, attempts to oxidize the monoacetate **7** with lead tetraacetate failed to give the desired diquinone imine **2**[6]. Instead, oxidation of **7** led to the anthracenetrione **8**, which shows synthetic interest because of its unusual pattern of reactivity. This letter reports the obtention of **8**, its rearrangement under mild conditions, the reaction with cyclopentadiene and the behaviour towards several nucleophiles.



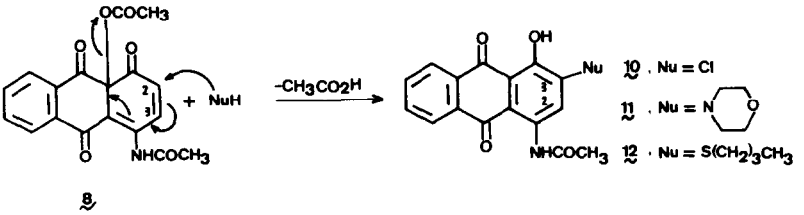
Oxidation of monoacetate **7** with lead tetraacetate at room temperature, in glacial acetic acid, led to a new compound as yellow-orange crystals, m.p. 148°C. The structural determination of the new compound **8** was made on the basis of the spectral data. The ^{1}H n.m.r. spectrum showed $NHCOCH_3$ and $OCOCH_3$ singlets (δ 1.93 and 2.27) and a signal at δ 11.66 assignable to a chelated NH proton; there was also an AB system (δ 6.59 and 8.67, J = 9.9 Hz) attributed to the H-2 and H-3 protons of a conjugated enone. Examination of the ^{13}C n.m.r. spectrum revealed three carbonyl carbons (δ 185.5, 187.5 and 188.7) and a quaternary carbon signal at δ 80.0 (assignable to the C-9a with an acetoxy group occupying the angular position), in a total of 18 carbons. This information is consistent with the 4-acetylamino-9a-acetoxy-1,9,10-anthracenetrione structure for **8**.

The anthracenetrione **8** presumably arose from the addition of acetic acid to the internal double bond of the expected diquinone imine **2**. A very recent report of Kanematsu[7] describes a related conjugate addition to the internal double bond of quinizarinquinone (**1**).



On heating the anthracenetrione **8** at 90-100°C in glacial acetic acid, a smooth rearrangement occurred to afford **9** as red crystals m.p. 247-249°C (71 %) (Lit. ref[8], m.p. 245°C). Its structure was confirmed by the ^{1}H n.m.r. spectrum which showed two sharp singlets at δ 2.26 ($NHCOCH_3$) and 2.36 ($OCOCH_3$) and signals assignable to chelated OH and NH protons. The spectrum lacked the AB system of the H-2 and H-3 protons but contained a low-field singlet (δ 9.00) consistent with an aromatic proton in *ortho* position to the $NHCOCH_3$ group. This rearrangement may most simply interpreted on the basis of an intramolecular [1,5]-acetoxy shift, similar to those previously observed in other related systems with substituents occupying angular positions[7,9,10].

Anthracenetrione **8** reacted readily at C-2 with hydrogen chloride and with *N*- and *S*-nucleophiles, such as morpholine and butane-1-thiol, with elimination of acetic acid to afford the 3-substituted 1-acetylamino-4-hydroxy-9,10-anthraquinone (**10-12**, Table). The 3-substitution of the new



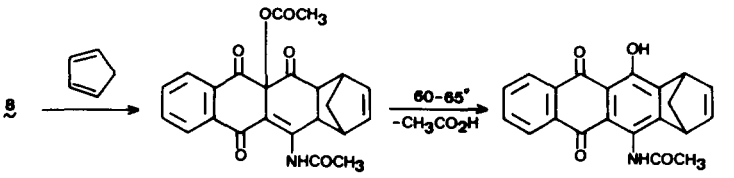
8

anthraquinones was deduced from the presence of a characteristic low-field signal in the ^{1}H n.m.r. spectra as indicated above for compound **9**.

TABLE. 1-Acetylamino-4-hydroxy-9,10-anthraquinones obtained from **8**

Compound	M.p. (°C)	Yield (%)	H-2	OH	NH
9	247-249	71	9.00	13.42	12.50
10	262-263	50	9.30	13.82	12.33
11	227-233 (d)	45	8.61	14.62	12.73
12	162	25	9.00	14.03	12.56

Anthracenetrione **8** reacts as a mild dienophile towards cyclopentadiene (7 days at 0°C in diethyl ether) to afford the expected Diels-Alder adduct **13**, m.p. 144-145°C (77 %). The structure **13** is consistent with the presence of $OCOCH_3$ (δ 2.33), $NHCOCH_3$ (δ 2.05) and chelated NH (δ 12.86) signals in the ^{1}H n.m.r. spectrum[11] and three carbonyl carbons (δ 184.9, 188.4 and 198.9) and a quaternary carbon (δ 81.0) in the ^{13}C n.m.r. spectrum.



13 14

The cycloadduct **13**, by heating at 60-65° C in glacial acetic acid, lost acetic acid to produce **14**, m.p. 218-220°C (95 %)[12]. The ^{1}H n.m.r. spectrum of **14** confirmed the dissapearance of the $OCOCH_3$ and *exo* protons and showed two low-field singlets (δ 10.90 and 12.99) for chelated NH and OH protons.

The new anthracenetrione **8** may be a valuable synthon in organic chemistry. We are currently investigating further applications in organic synthesis as well as the potential of cycloaddition reactions with this new synthon in the construction of anthracyclinones.

Acknowledgments. We thank the Comisión Asesora de Investigación Cientffica y Tecnica (Spain) and the PROPESP-UFRGS (Brasil) for financial support and the CAPES (Brasil) for a postgraduate fellowship (to V.S.).

REFERENCES AND NOTES

1. A. S. Kende, Y. Tsay and J. E. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976).
2. R. B. Garland, J. R. Palmer, J. A. Schulz, P. B. Sollman and R. Pappo, *Tetrahedron Lett.*, 3669 (1978).
3. R. C. Gupta, D. A. Jackson and R. J. Stoodley, *J. Chem. Soc. Perkin 1*, 525 (1985).
4. P. C. Bullman-Page and S. V. Levy, *J. Chem. Soc. Perkin 1*, 1847 (1984).
5. H. S. El Khadem Ed., "Anthracycline Antibiotics", Academic Press, New York, 1982.
6. We have found (V. Stefani, Sc. D. Thesis, Facultad de Ciencias, Universidad Autónoma de Madrid, 1983), however, that lead tetraacetate oxidation of compounds of type **7** ($CH_3C_6H_4SO_2$ instead of CH_3CO) affords the expected anthradiquinone monosulfonimides. These results will be reported elsewhere.
7. K. Hayakawa, M. Aso and K. Kanematsu, *J. Chem. Soc. Chem. Comm.*, 102 (1987).
8. G. Schultz and J. Erber, *Ber.*, **35**, 906 (1920).
9. S. C. Cooper and P. G. Sammes, *J. Chem. Soc. Chem. Comm.*, 633 (1980).
10. (a) F. B. H. Ahmad, J. M. Bruce, J. Khalafy, V. Pejanovic, K. Sabetian and I. Watt, *J. Chem. Soc. Chem. Comm.*, 166 (1981); (b) F. B. H. Ahmad, J. M. Bruce, J. Khalafy and K. Sabetian, *id.*, 169 (1981); (c) R. Al-Hamdany, J. M. Bruce, R. T. Pardasany and I. Watt, *id.*, 171 (1981).
11. The *endo* configuration of the adduct **13** was deduced from the presence of two *exo* protons (δ 3.62 and 4.57), which showed appreciable coupling (J = 3.6 Hz) to the bridgehead protons.
12. All new compounds gave satisfactory combustion analysis.

(Received in UK 17 June 1987)