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SYNTHESIS OF ANTHRACYCLINONES VIA o-QUINODIMETHANES

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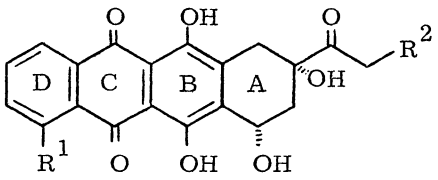
The preparation of several key intermediates in the synthesis of anthracyclinones is described. The key step in the construction of the C ring of the tetracyclic system involves a Diels-Alder reaction with an appropriate o-quinodimethane.

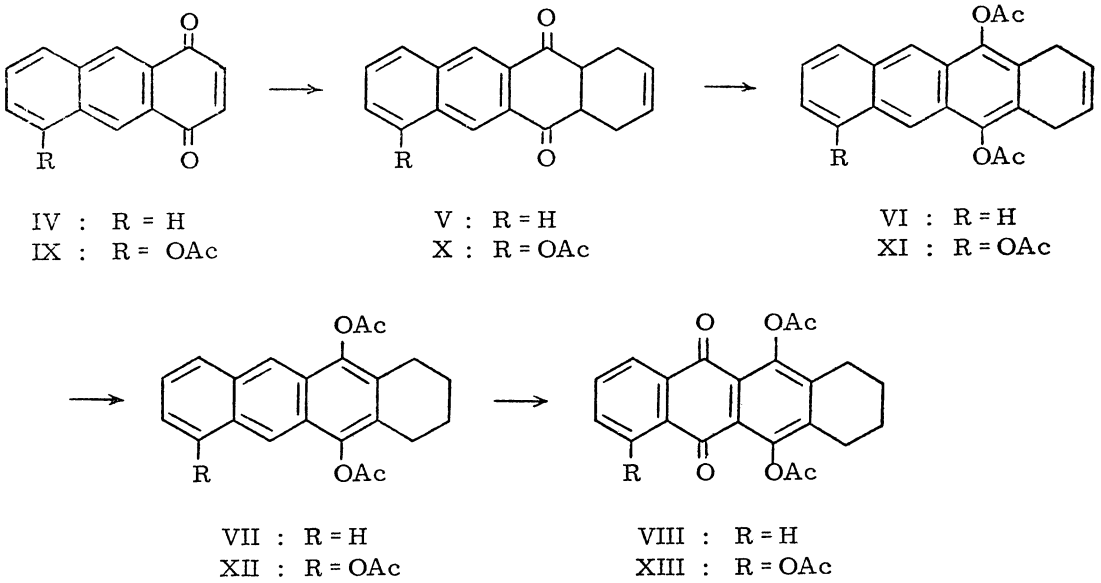
The synthesis of anthracycline antibiotics is of considerable current interest because of their potent activity against various types of human cancer. Several synthetic approaches of the anthracyclinones I and II, the aglycones of daunomycin and adriamycin, and their derivatives have been reported[1].



I : R^1 = OMe; R^2 = H
II : R^1 = OMe; R^2 = OH
III : R^1 = H ; R^2 = H

Previously[2], we have also developed a route to the tetracyclic anthracyclinone ring system starting from a Diels-Alder reaction with naphthazarin and in a preceding paper[3] we have reported the functionalization of the A ring in order to allow the conversion in 4-demethoxy daunomycinone (III). However, all the attempts of extending this approach to the functionalization of the D ring were unsuccessful.

In view of the above results, in a model study[4], we have developed a novel alternative route to the tetracyclic system of the anthracyclinones starting from the Diels-Alder adduct V of butadiene and 1,4-anthraquinone (IV, prepared *vía* an o-quinodimethane by the procedure of Cava and coworkers[5]). Acetylation of V to the diacetate VI, catalytic hydrogenation and subsequent chromic acid oxidation led to the tetracyclic diacetoxyquinone VIII. This approach could be extended to the synthesis of daunomycinone (I) and related anthracyclinones, starting from a 1,4-anthraquinone with an OR group in 5-position.



IV : R = H
IX : R = OAc

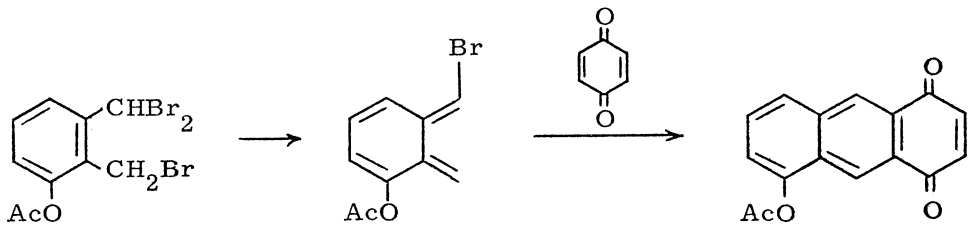
V : R = H
X : R = OAc

VI : R = H
XI : R = OAc

VII : R = H
XII : R = OAc

VIII : R = H
XIII : R = OAc

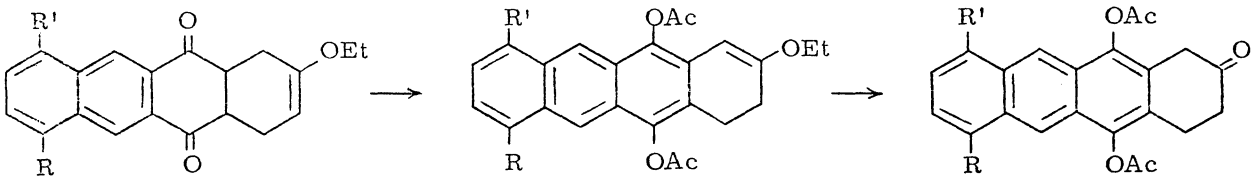
Thus, the synthesis of 5-acetoxy-1,4-anthraquinone (IX) was achieved by Diels-Alder reaction between the o-quinodimethane XVa (generated in situ from the tribromo-derivative XIV[6] + NaI in DMF, 70°C) and p-benzoquinone with HBr elimination and simultaneous aromatization (54% yield); m.p. 160-161° C). Diels-Alder reaction of quinone IX and butadiene (benzene, sealed tube, 100°C) gave adduct X (80-100%; m.p. 147°C) easily acetylated to XI (97%; m.p. 216-217°C), which by catalytic hydrogenation (Pd/C in EtOAc, 25°C) yielded XII (84%; m.p. 207° C). Upon chromic acid oxidation (CrO_3 in AcOH-H_2O, 0°C) a 38% of the tetracyclic quinone XIII (m.p. 222-223°C) was obtained.



XIV XVa IX

In order to achieve the functionalization of ring A, the quinone IX was allowed to react with 2-ethoxy-1,3-butadiene by refluxing in benzene 24 hr, yielding a mixture of the regioisomers XVIa+XVIb (85%; m.p. 163-167°C). Acetylation (Ac_2O, Py, 10 min, reflux) gave the mixture of triacetates XVIIa +XVIIb (89%; m.p. 193-197°C)[7]. Upon hydrolysis of the mixture of vinyl ethers XVIIa +XVIIb (HOAc-H_2O, reflux, 10 min), the tetracyclic ketones XVIIIa + XVIIIb were obtained (81%; m.p. 160-164°C dec.). After conversion into the corresponding dithioacetals XIXa + XIXb (1,3-propanedithiol, BF_3 etherate, room temp., 15 min.; 74% yield) the mixture

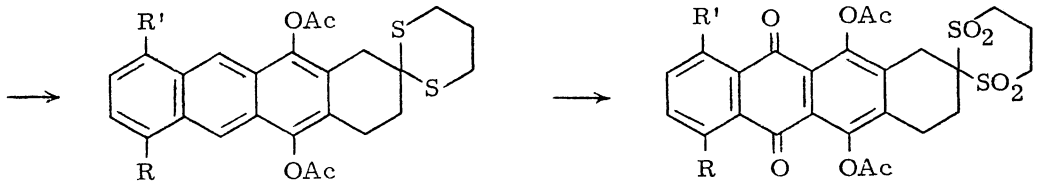
of the triacetoxyquinones XXa + XXb [m.p. 253-258°C (dec.); n.m.r. ($CDCl_3$): δ 8.10-7.75 (m, 3H); 3.53 (s, 2H); 3.37-2.91 (m, 6H); 2.51, 2.47, 2.43, 2.39 (4s, 9H)] was obtained in 36% yield by chromic acid oxidation (CrO_3 in HOAc-H_2O, room temp., 50 min.).



XVIa : R = H; R' = OAc
XVIb : R = OAc; R' = H

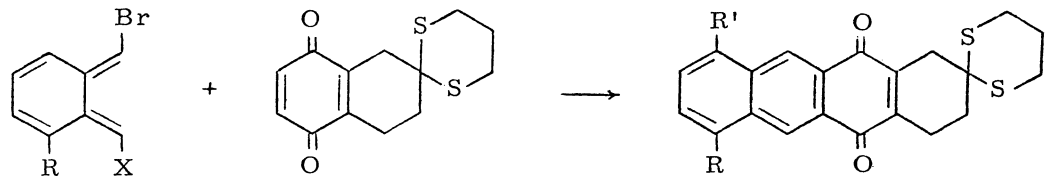
XVIIa : R = H; R' = OAc
XVIIb : R = OAc; R' = H

XVIIIa : R = H; R' = OAc
XVIIIb : R = OAc; R = H



XIXa : R = H; R' = OAc
XIXb : R = OAc; R' = H
XIXc : R = R' = H

XXa : R = H; R' = OAc
XXb : R = OAc; R' = H
XXc : R = R' = H



XVa : R = OAc; X = H
XVb : R = H; X = Br

XXIc

XXIIa : R = H; R' = OAc
XXIIb : R = OAc; R' = H
XXIIc : R = R' = H

We have developed an alternative route to compounds of the type XX starting from a Diels-Alder reaction with an o-quinodimethane XV, generated from an appropriate o-xylene derivative, and 6-oxo-5,6,7,8-tetrahydronaphthoquinone 6-trimethylenedithioacetal (XXIc)[8,9]. Thus the o-quinodimethane XVb, generated from tetrabromo-o-xylene (NaI in DMF, 70°C), was trapped by the quinone XXIc, yielding the quinone XXIIc (76%, m.p. 263-264°C) with simultaneous HBr elimination. Reductive acetylation of XXIIc (Ac_2O, NaOAc, Zn, reflux, 30 min) gave diacetate XIXc (94%; m.p. 251-252°C). Chromic acid oxidation (CrO_3 in HOAc-H_2O, room temperature, 90 min) of XIXc afforded XXc [67%; m.p. 239-241°C (dec.); n.m.r. ($CDCl_3$): δ 7.90 (m, 4H); 3.57 (s, 2H); 3.39-2.97 (m, 6H); 2.81-2.31 (m, 4H); 2.54 (s, 3H); 2.49 (s, 3H)].

The possibility of extending this route to compounds of the type XX with the D ring adequately functionalized has been proved starting from the Diels-Alder adduct of the o-quinodimethane XVa and quinone XXIc (70%; m.p. 180-182°C). The mixture of quinones XXIIa + XXIIb by reductive acetylation (Zn, Ac_2O, NaOAc, reflux, 30 min.) afforded a mixture of triacetates

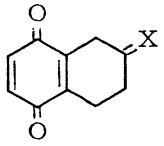
XIXa + XIXb (90%; m.p. 225-230°C) similar to that obtained by the above mentioned procedure.

The tetracyclic compounds of type XX obtained in this work are interesting key intermediates in the synthesis of anthracyclinones[10].

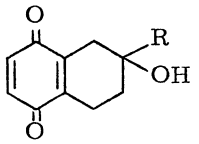
Acknowledgments. We wish to thank the Comisión Asesora de Investigación Científica y Técnica for financial support and the Ministerio de Educación y Ciencia for two postgraduate fellowships (to J.P. and T.T.).

REFERENCES AND NOTES

1. See our preceding paper[3] for references.
2. F. Fariña and J.C. Vega, Tetrahedron Letters, 1655 (1972).
3. F. Fariña and P. Prados, Tetrahedron Letters, 477 (1979).
4. F. Fariña, C. Garranzo and M.V. Martín, XVI Reunión Bienal de la Real Sociedad Española de Física y Química, Oviedo, 24-29 September 1973. Abstracts p. 212; C. Garranzo, Sc. D. Thesis, Facultad de Ciencias, Universidad de Madrid, July 1975.
5. M.P. Cava, A.A. Deana and K. Muth, J. Am. Chem. Soc., 81, 6458 (1959). Also available by $NaBH_4$ reduction of quinizarin according to A.N. Grinev, I.S. Protopopov and A.A. Cherkasova, Zh. Org. Khim., 8, 215 (1972).
6. M.p. 68°C; prepared in 96% yield by NBS bromination of 2,3-dimethylphenyl acetate. The more appropriate tetrabromoderivative (m.p. 135°C) was obtained only as a minor product.
7. Simultaneous isomerization of the double bond was evidenced by the n.m.r. spectrum in which the olefinic proton appeared as a singlet at δ 5.70.
8. We have synthesized the quinones XXIa-c and XXIIIa-c by Ag_2O oxidation of the respective hydroquinone or by oxidative demethylation of the corresponding dimethyl ethers prepared



XXIa : X = O
b : X = $O(CH_2)_2O$
c : X = $S(CH_2)_3S$



XXIIIa : R = $-CH_2CH_3$
b : R = $-C\equiv CH$
c : R = $-COCH_3$

from the well known Diels-Alder adducts of 2-alkoxybutadiene and p-benzoquinone. The detailed results will be reported elsewhere.
9. After these results were presented by us[11,12,13], J.R. Wiseman, N.I. French, R.K. Hallmark and K.G. Chiong [Tetrahedron Letters, 3765 (1978)], described a similar approach starting with an o-quinodimethane and the functionalized quinone XXIIIc[8].
10. Cleavage of the disulfonyl protecting group [S.J. Daum and R.L. Clarke, Tetrahedron Letters, 165 (1967)] in XX could lead to intermediates used in previous synthesis of anthracyclinones.
11. J. Primo, Sc. D. Thesis, Facultad de Ciencias, Universidad Autónoma, Madrid, June 1977.
12. T. Torres, Sc. D. Thesis, Facultad de Ciencias, Universidad Autónoma, Madrid, April 1978.
13. F. Fariña, P. Prados, J. Primo and T. Torres, Symposium on Organic Synthesis, 75° Aniversario de la Real Sociedad Española de Física y Química, Madrid, 2-7 October 1978. Abstracts of scientific papers, Symp. 31, p. 69.
14. All new compounds gave satisfactory combustion and/or mass spectrometric analysis and spectroscopic data consistent with the assigned structures.

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