Tetrahedron Letters No. 17, pp 1655 - 1658, 1972. Pergamon Press. Printed in Great Britain.

A NOVEL ROUTE TO TETRACYCLIC HYDROXYQUINONES

F. Fariña and J. C. Vega

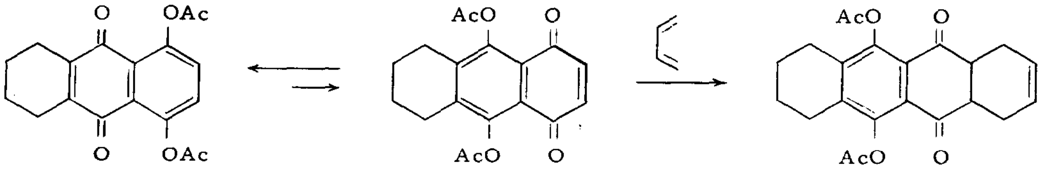
Instituto de Química Orgánica General (CSIC). Madrid-6, Spain

(Received in UK 23 February 1972; accepted for publication 17 March 1972)

The polyhydroxyderivatives of 7, 8, 9, 10-tetrahydro-5, 12-naphthacenequinone are of special interest due to their occurrence as natural pigments, forming the group of anthracyclinones (1). These are Streptomycete metabolites and possess a tetracyclic system related to that present in the tetracycline antibiotics.

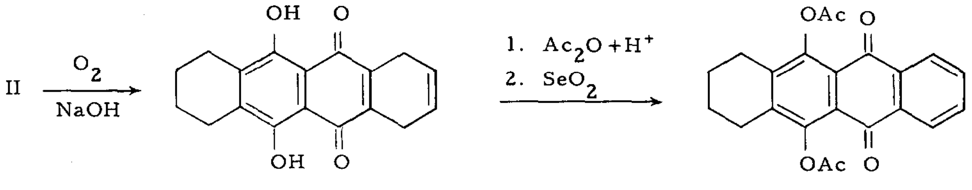
The synthesis of tetracyclic hydroxyquinone systems has generally been accomplished starting with a Friedel-Crafts reaction and few approaches based on a Diels-Alder reaction have been proposed (2).

In a recent publication (3) we have described that diacetates of substituted naphthazarins may react in a Diels-Alder addition through the energetically less favourable form, as a result of a previous transacylation. We wish now to report studies on the application of this reaction to the synthesis of tetracyclic systems closely related to the anthracyclinones. The behaviour of 2, 3-dimethylnaphthazarin diacetate, which reacts through the less stable isomer (6, 7-dimethylnaphthazarin diacetate) (3), suggested that it might be possible a similar Diels-Alder reaction using 5, 6, 7, 8-tetrahydroquinizarin diacetate as dienophile. This diacetate usually exists as Ia, and this structure is supported by the n.m.r. spectrum showing two low-field

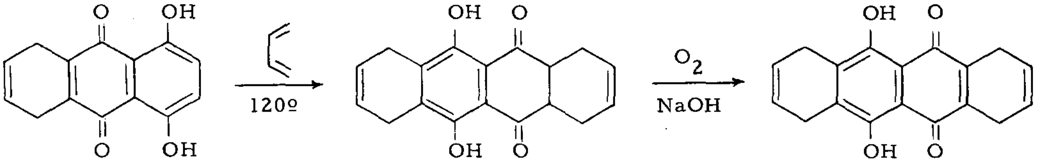


Ia Ib II

protons at τ 2.68 (aromatic and not quinonoid protons). We have found, however, that the reaction with butadiene (or substituted butadienes) takes place with previous transacylation Ia ⟶ Ib, giving the tetracyclic non-angularly substituted adduct II (4). The addition product II, m.p. 158° (5) is obtained in 95% yield, on heating in sealed tube at 150°, using benzene as solvent. The structure II was confirmed by the n.m.r. spectrum [τ 4.30 (2H, CH=CH); 6.70 (2H, CH-CO); 7.31 (4H, CH_2 in 7 and 10); 7.60 (6H, AcO); ~7.6 (4H, CH_2 in 1 and 4); 8.22 (4H, CH_2-CH_2).] Moreover, II may be easily converted into partially hydrogenated derivatives of 6,11-dihydroxy-5,12-naphthacenequinone. Thus, air oxidation of II in dilute alkali affords, with concomitant hydrolysis, 6,11-dihydroxy-1,4,7,8,9,10-hexahydro-5,12-naphthacenequinone (III), m.p. > 300° (subl.), the electronic spectrum of which is consistent with a naphthazarin chromophore [$\lambda_{max}^{CHCl_3}$: 287, 480, 508, 547]. The diacetate of III (6), m.p. 212-213° (dec.) is easily aromatised to the tetrahydroderivative IV, m.p. 235-236° (dec.); its structure was confirmed by the n.m.r. spectrum showing the aromatic protons as a typical A_2B_2 splitting pattern with centers at τ 1.83 and 2.30.



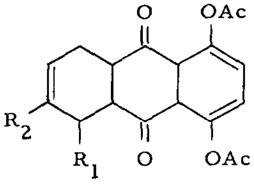
III IV



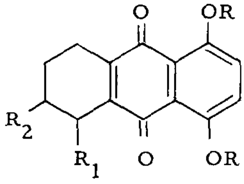
V VI VII

Similar studies have been conducted with free 5,8-dihydroquinizarin (V), which adds to butadiene through the less stable tautomeric form (7), yielding the tetracyclic adduct VI, m.p. 145-146°, which on mild air oxidation under alkaline conditions, affords the 6,11-dihydroxy-1,4,7,10-tetrahydro-5,12-naphthacenequinone (VII), m.p. >300° (subl.), the electronic spectrum of which agreed well with the presence of a naphthazarin chromophore [$\lambda_{max}^{CHCl_3}$: 276, 480, 510, 548].

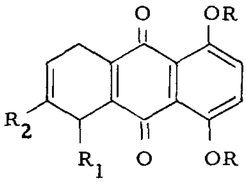
As starting materials for the synthesis of tetracyclic systems not only tetrahydro or dihydroquinizarins (or diacetates) can be used, but also their substituted derivatives (IX or X). In Table I are summarized representative compounds, all of which can be synthesised starting with a Diels-Alder reaction using naphthazarin diacetate and the appropriate diene. The adducts (VIII) are directly oxidised to the dihydroquinizarin derivative (X) or hydrogenated and then oxidised to the tetrahydroquinizarin (IX), using suitable conditions. All these compounds exist in the form IX or X, as is evidenced by n.m.r.; however, Diels-Alder reaction takes place through the less stable tautomeric or isomeric form.



VIII



IX a : R=H
b : R=Ac

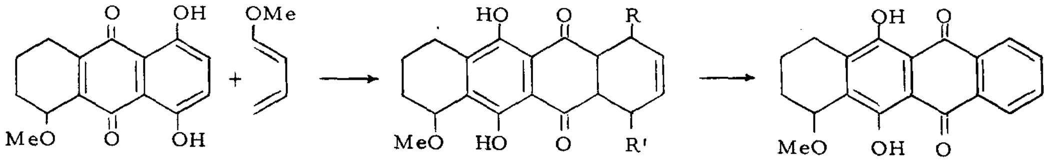


X a : R=H
b : R=Ac

TABLE I

	R$_1$	R$_2$	m.p.	n.m.r. signals, τ (aromatic protons)
IXa	H OMe	H H	159° 116-117°	2.73 2.80
IXb	H OAc	H H	205-206° (dec.) 146-147° (subl.)	2.68 2.61
Xa	H	H	183° (subl.)	2.81
Xb	H	OAc	167-169° (subl.)	2.62

On the other hand, the use of trans-1-methoxybutadiene (or 1-acetoxybutadiene) in a Diels-Alder reaction with IX or X leads to a tetracyclic adduct, which is readily aromatised with methanol elimination. Thus, 5-methoxy-5,6,7,8-tetrahydroquinizarin (IXa : R$_1$ = OMe, R$_2$ = H) reacts with trans-1-methoxybutadiene giving a mixture of the two expected adducts (XIa + XIb). These, on air oxidation under alkaline conditions (3 % NaOH), are readily aromatised, with methanol elimination, giving the 6, 11-dihydroxy-7-methoxy-



XI a : R=OMe, R'=H
b : R=H, R'=OMe

XII

-7,8,9,10-tetrahydro-5,12-naphthacenequinone (XII), m.p. 173-175° (subl.), the n.m.r. data of which [τ -3.16, -2.96 (2H, chel. OH); 1.66, 2.19 (4 arom. H, A_2B_2 mult.); 5.36 (1H, CH-OMe); 6.44 (3H, OMe); 6.7 - 8.8 (6H, CH_2)] are entirely consistent with the proposed structure. Derivatives as XII, related to daunomycinone, have only recently been synthesised (8) by a multi-step procedure starting with a Friedel-Crafts reaction.

Further work in this area is in progress.

Acknowledgements. - We wish to acknowledge partial support of this work by a grant from the Merck Sharp & Dohme de España S.A.E. Thanks are expressed to the Instituto de Cultura Hispánica (Madrid) for a postgraduate fellowship (to J.C.V.) and to the Bayer Hispania for a gift of naphthazarin.

REFERENCES AND FOOTNOTES

1. a) H. Brockmann, Progr. Chem. Org. Nat. Prod., 21, 121 (1963);
   b) R.H. Thomson, "Naturally Occurring Quinones", Academic Press, London and New York, 1971, p. 536.
2. R. Winkler, Chimia, 20, 122 (1966) and references therein.
3. S. Alvarado, F. Fariña and J.L. Martín, Tetrahedron Letters, 3377 (1970).
4. Cycloaddition of diazomethane to Ia, with acyl migration, has recently been reported by H. Brockmann, H. Greve and A. Zeeck, Tetrahedron Letters, 1929 (1971).
5. All new compounds gave satisfactory elemental analysis.
6. Diacetates were obtained due to the insolubility of free hydroxyquinones in most solvents.
7. The presence of a singlet for 2 aromatic protons at 2.81 in the n.m.r. spectrum indicates that the predominant tautomer is V.
8. J.P. Marsh, Jr., R.H. Iwamoto and L. Goodman, Chem. Comm., 589 (1968).