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TRANSACYLATION IN DIACETATES OF NAPHTHAZARINS

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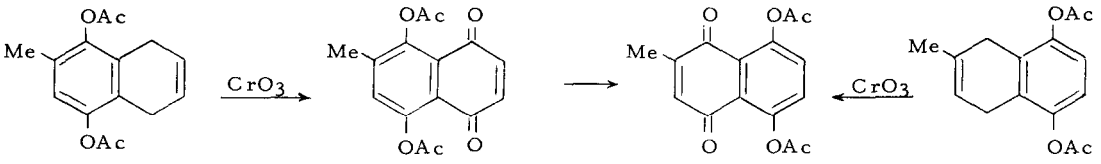
Previously we have reported (1)(2) a new method for the preparation of naphthazarins starting with a Diels-Alder reaction. In the last of these papers we have described the first example, as far as we know, of a transacylation in diacetates of naphthazarins. Thus, when the synthesis of 6-methylnaphthazarin diacetate (II) was attempted by chromic acid oxidation of the diacetate of the butadiene-toluquinone adduct (I), only 2-methylnaphthazarin diacetate (III) was



I II III IV

obtained, identical to that formed directly from the diacetate of the isoprene-benzoquinone adduct (IV). A similar behaviour was observed in the corresponding methylnaphthazarin dibenzoates (2) and in other diacetates of substituted naphthazarins (3). In all these cases, transacylation occurs to give the more stable isomer. The structure III, evidenced by ozonolysis, was now supported by the n.m.r. spectrum in which the ring protons appear as a singlet at τ 2.63 (2 arom. H) and a quartet centred at τ 3.28 (1 quinone H) coupled to the Me protons, as expected

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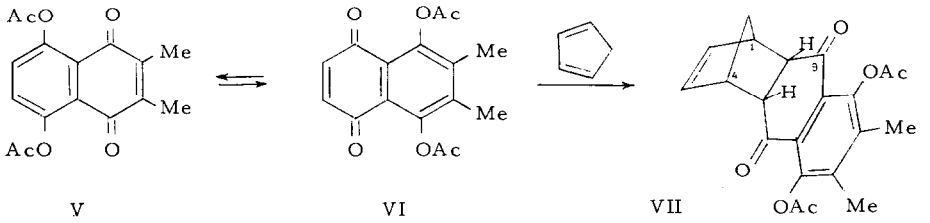
in a quinone ring ($J \simeq 1.3$ Hz).

Recently, Brockmann and Zeeck (4) have revised, on the basis of n.m.r. data, the structure of the predominant tautomer of actinorhodin, a natural binaphthazarin derivative, and in order to explain the reaction of its tetraacetate with diazomethane, they also proposed a previous transacylation to the less stable isomer.

Due to the interest in this rather unusual transacylation, we wish to report several experiments which demonstrate that diacetates of naphthazarins undergo transacylation in very simple experimental conditions. This enables a Diels-Alder reaction to proceed through the less stable isomer or a simultaneous reaction through the both possible isomers.

In order to demonstrate the possible reaction of a diacetate of substituted naphthazarin through the energetically less favoured form, we have selected 2,3-dimethylnaphthazarin diacetate (V). In this compound the two methyl groups reduce the redox potential of the quinone and will stabilize the isomer V more than the transacylated form VI. The structure V is supported by the n.m.r. spectrum in which the ring protons appear as a singlet at τ 2.67 (2 arom. H). Diels-Alder reaction between cyclopentadiene and V would not be favoured for the steric opposition to the formation of an adduct with two angular methyl groups and the deactivating effect of two methyl groups on the quinone double bond (5).



V VI VII

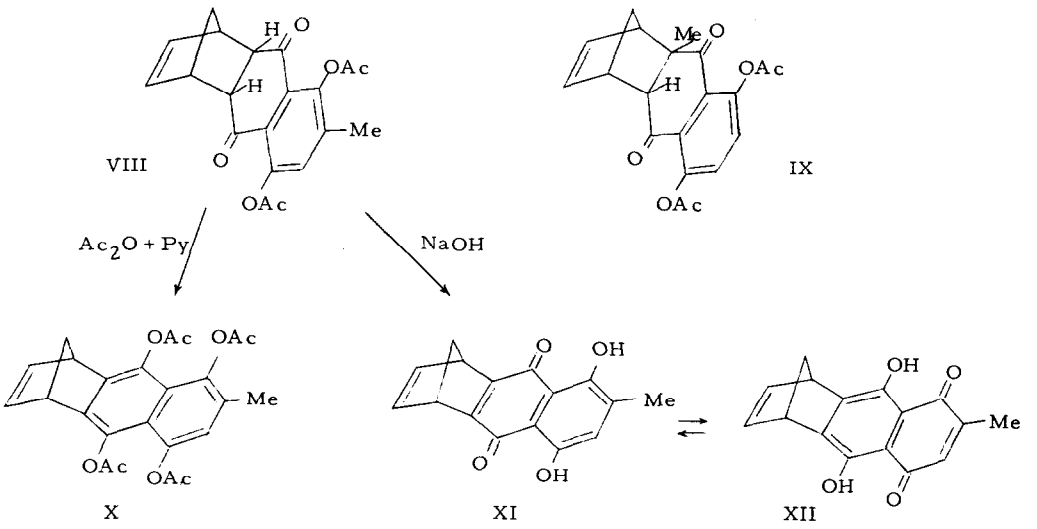
However, an easy formation of the alternative non-angularly substituted adduct by addition to the transacylated form VI would be expected.

In fact, reaction between cyclopentadiene and 2,3-dimethylnaphthazarin diacetate, in boiling benzene, afforded a product VII, m.p. 167° (d). Structure of VII was established on the basis of its n.m.r. spectrum showing the methyl protons as a singlet at τ 7.82 (6H, Me attached to aromatic nucleus) and the C_{4a} and C_{9a} exo protons as a signal at

τ 6.53 (4H, C_1, C_4, C_{4a}, C_{9a}); however, no signals of aromatic protons nor angular methyl groups were present, as would be the case in the adduct between V and cyclopentadiene. The formation of VII demonstrates that cyclopentadiene adds preferentially to 6.7-dimethylnaphthazarin diacetate (VI) with transacylation V ⟶ VI under the reaction conditions.

Reaction between 2,3-dimethylnaphthazarin diacetate and 2,3-dimethylbutadiene also afforded the non-angularly substituted addition product, as expected. Similarly, free 2,3-dimethylnaphthazarin reacted with dienes (butadiene, 2,3-dimethylbutadiene, cyclopentadiene) giving non-angularly substituted adducts.

We have also studied a similar reaction between cyclopentadiene and 2-methylnaphthazarin diacetate. It is interesting that addition in this instance leads to two different compounds, as detected by t.l.c. of the crude reaction mixture. The major product VIII, m.p. 129°, was isolated by recrystallization from ethanol. The structure VIII for this adduct was assigned on the basis of its n.m.r. spectrum which shows only one aromatic proton at τ 2.77, two C_{4a} and C_{9a} exo protons at τ 6.49 (4H, C_1, C_4, C_{4a}, C_{9a}) and the methyl group as a singlet at τ 7.71, as expected for Me attached to an aromatic nucleus. Chemical evidence for VIII was obtained by treatment with Ac_2O in pyridine, at room temperature,



to yield tetraacetate X, m.p. 218° [n.m.r.: τ 3.05 (1 arom. H); 3.28 (2H, CH = CH); 6.10 (2H, CH); 7.62 (12H, AcO); 7.79 (3H, Me); 7.5 - 7.8 (2H, CH_2)] and by mild basic hydrolysis giving, with simultaneous oxidation, XI which isomerizes to the more stable tautomer XII (6), m.p. 137°. The structure XII was assigned on the basis of the electronic spectrum (λ_{max}^{EtOH}: 227, 284, 493, 521, 557) which suggested a naphthazarin system and the n.m.r. spectrum [τ -2.61, -2.51 (2H, chel. OH); 3.11 (2H, CH=CH); 3.23 (1 quinone H); 5.62 (2H, CH); 7.63 (2H, CH_2); 7.79 (3H, Me)] in which the proton at τ 3.23 is long-range coupled with the Me group.

From the mother liquors of recrystallization of VIII, by preparative t.l.c., the minor component, m.p. 107°, was isolated and its n.m.r. spectrum gave conclusive evidence for structure IX. It shows two aromatic protons at τ 2.71, a singlet at τ 8.48 (3H) assignable to an angular methyl group and a signal centred at τ 6.57 for one exo proton (C_{9a}).

These results indicate that, although III is the more stable isomer of methylnaphthazarin diacetate, Diels-Alder addition occurs preferentially to the less stable isomer II, with previous transacylation III ⟶ II. However, as steric opposition to the formation of an adduct with only an angular methyl group is now smaller than in the disubstituted derivative V, some of the angularly substituted adduct IX is formed, by addition of cyclopentadiene to the more stable isomer III.

Consequently, transacylation in diacetates of naphthazarins is a very easy process and these may react through anyone of the two isomers.

Systematic studies are in progress on the Diels-Alder reaction in diacetates of differently substituted naphthazarins.

References and notes

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4. H. Brockmann and A. Zeeck, Chem. Ber., 101, 4221 (1968).
5. M.F. Ansell, B.W. Nash and D.A. Wilson, J. Chem. Soc., 1963, 3012.
6. The tension caused by the presence of the bicyclic system attached to the quinone ring probably reduces the stability of XI more than that of XII. See R.T. Arnold and H.E. Zaugg, J. Am. Chem. Soc., 68, 1317 (1941).

All new compounds gave satisfactory elemental analysis.