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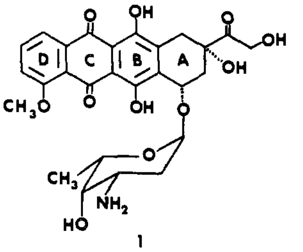
Regiochemical Control in the Diels-Alder Reactions of Substituted Naphthoquinones. Model Studies on a Regiospecific Approach to Adriamycinone

Sir:

Adriamycin (**1**) and its analogues are dramatically efficacious in the treatment of a broad spectrum of human cancers.[1]



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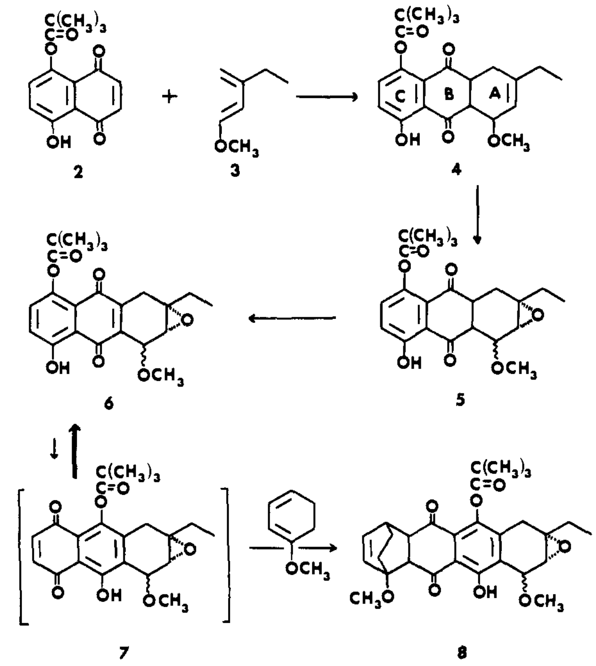
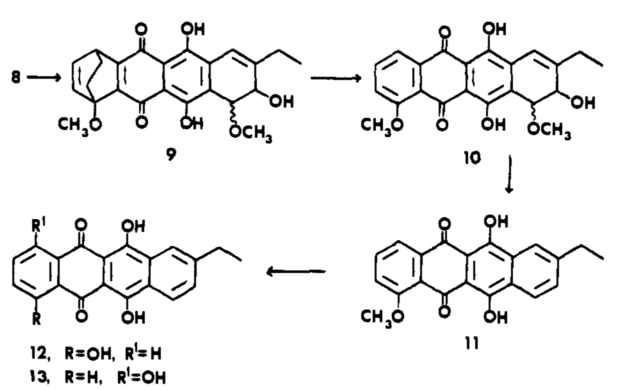
This fact, coupled with the intriguing structural and regiochemical challenges presented by these drugs, has stimulated intense efforts directed toward their total synthesis. To date practical solutions exist for the synthesis of the sugar portion of the molecule (daunosamine)[2] as well as for the coupling of daunosamine to the appropriate aglycones.[3] However, existing solutions[4,5] to the preparation of the aglycones, while noteworthy synthetic achievements, do not provide a method for controlling the relative orientation of the A- and D-ring substituents. We now wish to report the results of model studies which offer a potential solution to this regiochemical problem (Scheme I).

Scheme I



Scheme II

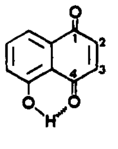


Reaction of naphthazarin monopivalate (**2**, orange crystals, mp 140.5-41 °C, prepared in 60-70% yield by treatment of naphthazarin with ∼4 equiv of pivalic anhydride in benzene at 50-70 °C) with excess **3**[5a] in benzene or dichloromethane for 24 h at 25 °C gives **4** (mp 125-127 °C) in 92-99% yield. Attempts to oxidize the A-B ring junction of **4** were frustrated by concurrent aromatization of the A ring, but oxidation of epoxide **5** (off-white crystals, mp 119-120 °C, prepared from **4** in 90-95% yield by reaction with 2-3 equiv of *m*-chloroperbenzoic acid in CH_2Cl_2 for 2-5 days) with excess active lead dioxide[6] for 5-8 days at 60-70 °C in 1:1 dichloromethane-tetrachloroethylene (vigorous stirring) gives **6** (amber-orange crystals, mp 129-132 °C) in 50-65% yield. The stereochemistry of the A ring is not yet rigorously established. Reaction of **6** with 1.5-2 equiv of 1-methoxycyclohexa-1,3-diene[7] at 25 °C for 24 h in benzene or CH_2Cl_2 affords **8** (mp 157-159 °C) in 85-95% yield. The average overall yield of **8** from **2** is approximately 45%.

The key step **6** ⇆ [**7**] → **8** takes advantage of the unfavorable but facile equilibrium **6** ⇆ **7** which allows for the intramolecular transfer of the two directing (vide infra) groups. The minor[8] tautomer **7** is the more reactive dienophile and is trapped selectively, thereby providing a means of converting **6** to **8** through the intermediacy of **7**.[10]

Adduct **8** is obtained as a mixture of stereoisomers (the eventual elimination of the asymmetry introduced in the reaction **6** → **8** renders this lack of stereoselectivity inconsequential) but the regiochemical homogeneity of **8** was established unambiguously by conversion to **12** (Scheme II). Treatment of **8** with 0.5% aqueous KOH in ethanol-tetrahydrofuran for 4 h at 0 °C in the presence of oxygen gives **9**,[11] which yields **10** (red crystals, mp 212-214 °C) upon pyrolysis at 150-160 °C in ∼90% overall yield. Hydrogenation of **10** (5% Pd/C, EtOAc) gives **11** (mp 202 °C) which affords **12** (mp 203-205 °C, lit.[12] 206 °C) upon treatment with excess BBr_3 in CH_2Cl_2 at −60 °C. Comparison[12] of spectra of the **12** so obtained with spectra[12] of authentic samples of **12** and the spectrally distinguishable alternative regioisomer **13** totally support the structure assigned to **12**. None of the regioisomer **13** could be detected. The regiospecific formation of **8** is thereby demonstrated.

The expectation that the Diels-Alder reactions of **2** and **7** would lead to the regiochemical consequences observed emerged from a consideration of the results and rationales of ourselves[5b] and others. Inhoffen, Muxfeldt, and coworkers[13] have reported that juglone (**14**) and its acetate (**15**) give opposite regiochemical results in their Diels-Alder reactions with 1-acetoxybutadiene, affording, as principal products, **16** and **17**, respectively. More recently, Powell and Birch have reported[14] that reaction of **14** with 1-methoxycyclohexa-1,3-diene gives exclusively **18**, explained[14] as being, in effect, a



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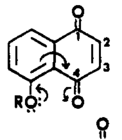
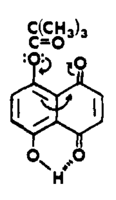


15, $\mathrm{R{=}CH_3\overset{O}{\overset{\|}{C}}-}$
20, $\mathrm{R{=}CH_3}$



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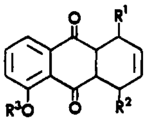
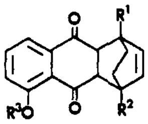


16, $\mathrm{R^1{=}R^3{=}H,\ R^2{=}OCOCH_3}$
17, $\mathrm{R^1{=}OCOCH_3,\ R^2{=}H,\ R^3{=}COCH_3}$



18, $\mathrm{R^1{=}R^3{=}H,\ R^2{=}OCH_3}$
21, $\mathrm{R^1{=}OCH_3,\ R^2{=}H,\ R^3{=}CH_3}$
22, $\mathrm{R^1{=}H,\ R^2{=}OCH_3\ R^3{=}CH_3}$

consequence of activation of the C-4 carbonyl by intramolecular hydrogen bonding (see **14**). The C-4 carbonyl in **14** would thus[14] be the most electron-withdrawing substituent on the C-2,C-3 double bond and would determine the regiochemical outcome of the reaction.[15] To our knowledge Inhoffen, Muxfeldt, and coworkers have not offered a rationale for the regiochemical dichotomy embodied in the formation of **16** and **17**, but extension of the Birch-Powell thesis[14] suggests that the regiochemical reversal observed in the formation of **17** might result from selective electron feeding from the *peri*-acetoxy group (**15**, arrows)[16] to the C-4 carbonyl. Such resonance donation[18] into the C-4 carbonyl would render the C-1 carbonyl the most electron-withdrawing substituent on the C-2,C-3 double bond and thus the regiochemical director by default. Further extension of this hypothesis suggests that incorporation of both *peri*-acyloxy (or alkoxy)[16] and hydroxy groups into the same molecule so that their conflicting influences could operate in a complementary fashion (see **19**) would permit a high degree of orientational control in the Diels-Alder reaction of molecules such as **2** and **7**. The above results confirm this expectation and demonstrate the effectiveness of such long-range regiochemical control in the Diels-Alder reactions of naphthazarin derivatives.

Extension of this work is in progress and will be reported in due course.

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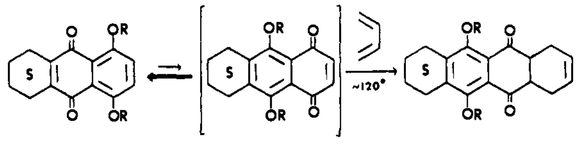
(10) The expectation that the **6** ⇄ **7** equilibrium might exist and that **7** could be trapped selectively was suggested by the observations of Fariña and Vega[9c] that the *symmetrical* naphthazarin derivatives i and ii react in a similar fashion to give iii and iv, respectively. For additional examples of *acylwanderung*, see H. Brockmann, H. Greve, and A. Zeeck, *Tetrahedron Lett.*, *1929* (1971); and ref 9b.



i, R=H
ii, R=COCH$_3$
iii, R=H
iv, R=COCH$_3$

(11) Use of other oxidizing agents permits preservation of the epoxide ring.

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(16) Further support for this rationale is found in the observation (T. R. Kelly, unpublished results) that reaction (benzene, 80 °C) of juglone methyl ether (**20**) with 1-methoxycyclohexa-1,3-diene affords **21** and **22** in a 2.5:1 ratio. The regiochemistry of this reaction was demonstrated by conversion—tautomerization[17] (KO-t-Bu, THF; HCl), oxidation (Pb(OAc)$_4$), and pyrolysis (145°)—of the crude adduct to a mixture of 1,5- and 1,8-dimethoxyanthraquinone and comparison (NMR) with reference mixtures of authentic samples. The overall yield from **20** to the mixture of dimethoxyanthraquinones is ~80% after chromatography. This hypothesis is also supported by the fact that **14** is a significantly more reactive dienophile than **20** in competition experiments with 1-methoxycyclohexa-1,3-diene (reaction conducted in CDCl$_3$, monitored by NMR).

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(19) Recipient of NIH Research Career Development Award, 1975–1980.

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Monoisopinocampheylborane— a New Chiral Hydroborating Agent for Relatively Hindered (Trisubstituted) Olefins

Sir:

Optically active monoisopinocampheylborane-triethylamine ($\mathrm{IPCBH_2{\cdot}NEt_3}$), readily available via the reaction of optically active α-pinene with thexylborane-triethylamine, undergoes a rapid reaction with borane to yield free, optically active monoisopinocampheylborane in nearly quantitative yield. This new chiral monoalkylborane was successfully utilized for the asymmetric hydroboration of 1-methylcyclopentene to give after oxidation *trans*-2-methylcyclopentanol in an optical purity of 55.4%. Other hindered (trisubstituted) olefins, such as 2-methyl-2-butene and 1-methylcyclohexene, which resist hydroboration with diisopinocampheylborane, undergo facile