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STUDIES DIRECTED TOWARD THE SYNTHESIS OF ADRIAMYCIN: DIELS-ALDER REACTIONS OF ANTHRADIQUINONES AND VARIOUS DIENES

T. Ross Kelly[1]*, Richard N. Goerner, Jr., John W. Gillard and Barbara K. Prazak
Department of Chemistry, Boston College
Chestnut Hill, Mass. 02167 USA

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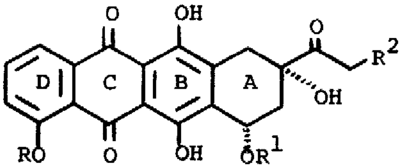
Adriamycin and its analogs[2] are among the most promising anticancer agents under investigatio This fact, coupled with a need to prepare new analogs of 1 with lower toxicity, has stimulated

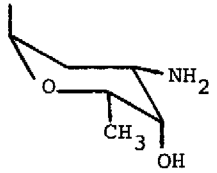


1: Adriamycin
$R=CH_3$, $R^1=S$, $R^2=OH$

2: Daunorubicin
$R=CH_3$, $R^1=S$, $R^2=H$

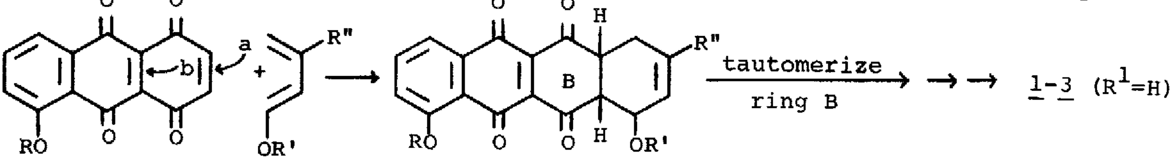
3: Carminomycin[2b]
$R=R^2=H$, $R^1=S$

S=



intense activity directed toward the development of practical and versatile syntheses of 1-3 and their derivatives. Particular attention has focused on the synthesis of the aglycones 1-3 (R^1=H).[3,4a]

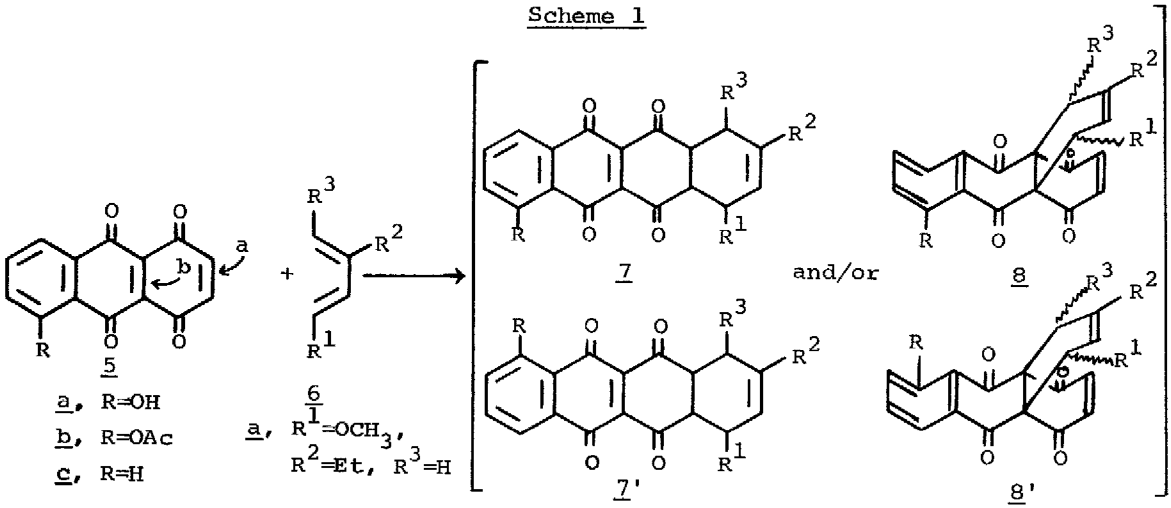
(Eq.1)



One of the potentially most direct and flexible approaches to the aglycones is outlined in Equation 1, where R" can be either a partially or fully elaborated sidechain. Consideration of the initial Diels-Alder reaction evokes, however, two immediate questions (Scheme 1): 1) will the reaction between 5 and 6 produce the desired, terminally annulated products 7, 7' (addition at bond a), or the internally annulated adducts 8, 8' (addition at bond b), and 2) if linear annulation occurs, will regioselectivity also be obtained to give 7, or will 7' be produced concurrently in substantial amounts? In this communication we address the first question; the adjoining paper provides a partial answer to the second question.

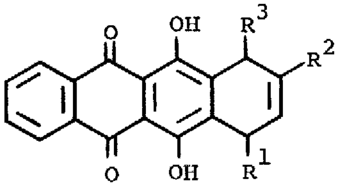
Previous workers[4] have shown that the Diels-Alder reaction between quinizarin diquinone (5c)[5] and butadiene or terminally substituted butadienes usually-but not always[4b]-proceeds to give adducts analogous to 7 or 7' (R^2=H) as the principal products. However, when 5a[6] was reacted with 6a[7] at 25°C in methylene chloride, only the internal adduct corresponding to 8 or 8' was produced. Analogous adducts were obtained upon reaction of 6a with 5b[9] and with 5c. As a consequence of

Scheme 1

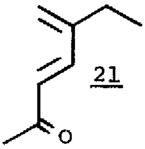


these untoward results, we have examined the reaction of 5a as well as of 5c with a wide variety of dienes.[11] The results are outlined in Table 1.[12]

The results delineated in Table 1 are characterized by few general trends and are perhaps most remarkable for their inconsistency. The stark contrast in regioselectivity in the cases of 10 and 13 and 9 and 12, and the difference between the site of reaction of 17 and other 1,4,-disubstituted dienes are particularly noteworthy. While there is some correlation between diene substitution pattern and site of reaction, this may be due simply to the nature of the dienes examined; i.e., only one of the dienes listed in Table 1 (11) contains an electron withdrawing group. In this context, results (at 25° C) with two additional dienes, 21[13] and 22[14], are noteworthy. Reaction of 21 with 5c produces no significant amount of Diels-Alder adduct of any type, while reaction of 22 with 5c gives little if any of the 8 adduct. In the latter case, however, a small amount (10%) of the tautomerized terminal adduct 20 is produced. Whether this result can be improved upon and extended has yet to be determined.



18, R^1=CH_2OH, R^2=H, R^3=CH_3. mp 219-21°
19, R^1=$COOCH_3$, R^2=H, R^3=CH_3. mp 199-200°
20, R^1=$COOCH_3$, R^2=CH_3, R^3=H. mp 208° (dec)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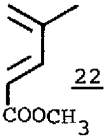
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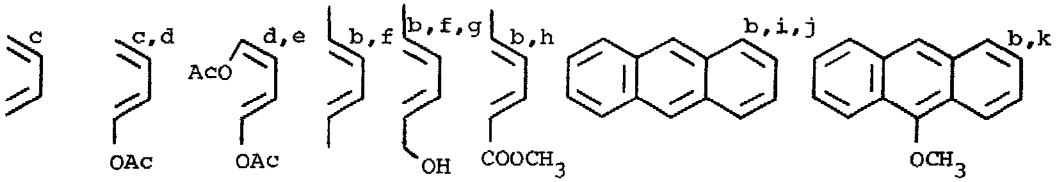
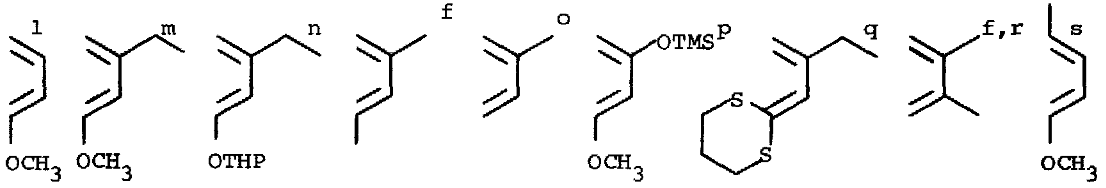
Table 1[a]

I. Dienes Which Add Primarily at the Terminal Double Bond of 5a and/or 5c to Give 7 or 7'[b].



9 10 11 12 13 14

II. Dienes Which Add Primarily at the Internal Double Bond of 5a and/or 5c to Give 8 or 8'[12b].



15 6a 16 17

13[i,j,t]

III. Dienes Which Give Substantial Amounts of Both Terminal and Internal Adducts.

trans-1,3-pentadiene[f,u] *trans*-1,3-hexadiene[f,v]

[a] With the exception of reactions reported by others[c,d,e,i], all reactions recorded in this Table were carried out at room temperature in CH_2Cl_2 or $CDCl_3$ with excess diene. [b] The initial adducts of 11, 12, 13, and 14 with 5c underwent substantial tautomerization to the corresponding orange-to-red anthraquinones (e.g. 18 and 19) and were characterized as such. The adduct of 5c and 10 was isolated as 7 ($R=R^2=H$, $R^1=R^3=CH_3$), mp 213-215°. [c] Reaction carried out at 45-50° in benzene (ref. 4a). [d] See ref. 4b; these authors report that reaction of 5c with 9 gives a double adduct. [e] Reaction carried out at 50° in benzene.[4b] [f] Purchased from Chemical Samples Co. [g] Used as a mixture of geometrical isomers. It was assumed that the *trans*-*trans* isomer would react preferentially.[10] [h] Prepared from sorbic acid (Aldrich) and diazomethane. [i] The internal adduct is obtained at 25°. When this adduct is heated at 100° in $CDCl_3$ it isomerizes to the terminal adduct. No other adducts were observed to undergo similar rearrangements. [j] The tautomerized adduct from 13 + 5c at 100° darkens at 240° and melts at 258-60° (rapid heating); compare note t. [k] Tautomerized adduct from 14 + 5c: mp 212-216° (decomp). [l] Reaction run in benzene.[4b] [m] See ref. 7. [n] Prepared in ca. 30% yield (unoptimized) as a *cis*-*trans* mixture from α-ethylacrolein[8] and tetrahydropyranyloxytriphenylphosphorane in ether: H. Schlude, *Tetrahedron*, 31, 89 (1975); bp. ~80-120°/2mm (Kugelrohr). [o] Adduct with 5c (i.e., 8, $R=R^1=R^3=H$, $R^2=CH_3$): mp 154.5-157°. [p] S. Danishefsky and T. Kitihara, *J. Amer. Chem. Soc.*, 96, 7807 (1974). We thank Prof. Danishefsky and Mr. P.F. Schuda for a generous sample of this diene. [q] Prepared from α-ethylacrolein[8] and 2-lithio-2-trimethylsilyl-1,3-dithiane: D. Seebach, M. Kolb and B-T. Grobel, *Ber.*, 106, 2277 (1973). [r] Adduct with 5c: mp 200-202°. [s] Prepared as a 1:1 *cis*-*trans*:*trans*-*trans* mixture from crotonaldehyde and $Ø_3P=CHOCH_3$, bp. 100°/760mm. It was assumed that the *trans*-*trans* isomer reacted preferentially. This reaction was carried out twice with identical results. Adducts with 5c: mp 183.5-185°. [t] When the pale yellow adduct obtained from 5c + 13 at 25° is placed in a capillary tube and inserted in a melting point apparatus preheated to 210°, it melts to give a transiently dark green liquid which turns red and solidifies as red crystals. Continued heating (rapid) causes darkening at 240° followed by melting at 260-61° (compare note j). [u] Reaction of 5c gives substantial amounts of both possible adducts, reaction with 5a gives predominantly type-8, 8' adducts. [v] Used as a mixture of *cis*-*trans* isomers; it was assumed that the *trans*-isomer would react preferentially.[10] Only reaction with 5c was investigated.

References and Notes

1. Recipient of NIH Research Career Development Award 1975-80.

2. a) For a leading reference see F. Arcamone, S. Penco and A. Vigevani, Cancer Chemother. Rep., Part 3, Vol. 6, #2, 123 (1975). We thank Profs. Leon Goodman and Wm. Rosen (Univ. of Rhode Island) for bringing this reference to out attention. b) M.C. Wani, H.L. Taylor, M.E. Wall, A.T. McPhail and K.D. Onan, J. Amer. Chem. Soc., 97 5955 (1975); G.R. Pettit, J.J. Einck, C.L. Herlad, R.H. Ode, R.B. VonDreele, P. Brown, M.G. Brazhnikova and G.F. Gause, ibid., 97, 7388 (1975) and references therein.

3. C.M. Wong, R. Schwerk, D. Popien and T-L. Ho, Can. J. Chem., 51, 466 (1973); A.S. Kende, J. Belletire, T.J. Bentley, E. Hume and J. Airey, J. Amer. Chem. Soc., 97 4425 (1975). We thank Professor Kende for a preprint of this paper. After this manuscript was submitted A.S. Kende, Y. Tsay and J. Mills reported [J. Amer. Chem. Soc., 98, 1967 (1976)] the synthesis of 2 (R^1=H) using an approach somewhat similar to that in Eq. 1. Their route gave a 1:1 mixture of 7/7'-type adducts.

4. a) W.W. Lee, A.P. Martinez and D.W. Henry, "Abstracts of the 167th National Meeting of the American Chemical Society", March 31-April 5, 1974, Abstract MEDI 58. W.W. Lee, A.P. Martinez, T.H. Smith and D.W. Henry, J. Org. Chem. 41, 2296 (1976). b) H.H. Inhoffen, H. Muxfeldt, V. Koppe and J. Hermann-Trosien, Ber., 90, 1448 (1957).

5. L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967, p. 538.

6. O. Dimroth and V. Helcken, Ber., 54B, 3050 (1921); O. Dimroth, L. Kraft and K. Aichinger, Ann. 545, 138 (1940). The hydroxydiquinone used in this work was prepared using the following modified procedure: To a nearly complete solution of 2g 1,4,5-trihydroxyanthraquinone (See Acknowledgements) in 600cc glacial acetic acid was added 4.8g lead tetraacetate. The reaction was stirred at room temperature for ca. 2 hr and glycerol was added to destroy excess $Pb(OAc)_4$. The reaction mixture was poured into water and extracted with $CHCl_3$ (3 x 200cc). The $CHCl_3$ extracts were washed with water, dried and evaporated in vacuo: crude yield 80-100%. The major impurity (ca. 20%) was starting material. Crude 5a was usually used without further purification.

7. Prepared in 40% yield (unoptimized) as a 40:60 cis:trans mixture from α-ethyl-acrolein[8] and methoxymethylenetriphenylphosphorane [G. Wittig and M. Schlosser, Ber. 94, 1373 (1961)] (reaction conducted in ether), bp. ca. 40°/12mm (Kugelrohr). The trans isomer reacts preferentially.

8. M.B. Green and W.J. Hickinbottom, J. Chem. Soc. 3262 (1957). Preparations of this material by Messrs. James Potter, Daryl Douglas and Rich Theriault are gratefully acknowledged.

9. Prepared from 5a by acetylation with Ac_2O/H_2SO_4: L.F. Fieser and J.T. Dunn, J. Amer. Chem. Soc., 59, 1016 (1937).

10. See A.S. Onishchenko, "Diene Syntheses", Israel Program for Scientific Translations, Jerusalem, 1964, p. 8.

11. With the exception of borderline dienes (Table 1, Part III), 5a and 5c react in a virtually identical fashion. For reasons of availability and greater symmetry, 5c was used in most cases, but the results were reconfirmed with 5a in several instances.

12. a) Differentiation between internal and external adducts was made primarily by examining the olefinic region of the NMR spectrum of the adducts. Olefinic protons derived from the dienes appeared at δ5-6, while olefinic protons derived from the diquinone (present only in Type-8 adducts) appeared at δ6.5-7 as singlets or AB quartets. b) In general adducts of Type-8, such as that formed from 5c and 6a, contain both possible stereoisomers (at the methoxyl-bearing carbon) in similar amounts. In such cases no attempt was made to separate the mixtures or to characterize the adducts beyond establishing the site of addition (by NMR). No attempt was made to determine the regiochemical relationship between diene substituents and the OH group in adducts derived from 5a.

13. Prepared as essentially pure trans isomer from α-ethylacrolein[8] and $\phi_3P{=}CHOCH_3$ (bp. 75°/ 20 mm).

14. Prepared as essentially pure trans isomer from methacrolein and trimethylphosphonoacetate: R.J. Sundberg, P.A. Bukowick and F.O. Holcombe, J. Org. Chem., 32, 2938 (1967).