(6) is accessible in similar yield. The utility of our synthesis for the preparation of known as well as novel anthracycline antitumor agents is under investigation.

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(14) Cf. J. Sauer, *Angew. Chem. Int. Ed. Engl.*, **6**, 16 (1967).
(15) Cf. R. Sustmann, *Tetrahedron Lett.*, 2717 (1971). We thank Mr. D. Curran for performing these calculations.
(16) See T. Smith, A. Fujiwara, W. Lee, and D. Henry, *J. Am. Chem. Soc.*, following paper in this issue.
(17) R_f values were measured on plates (Analtech) coated with silica gel GF (250 μm) and eluted with 3% (v/v) methanol in methylene chloride; daunomycinone had reference $R_f = 0.14$.
(18) A 100-MHz Fourier transform proton NMR spectrum ($CDCl_3$, δ) showed signals at 13.47, 12.96, 12.17 (s, 1 H ea), 7.94–7.25 (m, 3 H), 5.31 (br s, 1 H, $\nu_{1/2} = 8$ Hz), 3.05 (q, 2 H), 2.43 (s, 3 H), 2.27 (m, 2 H).

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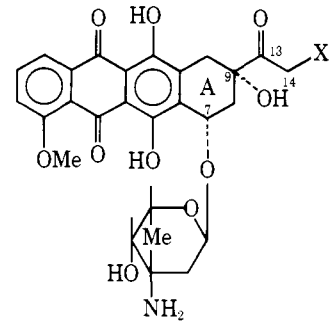
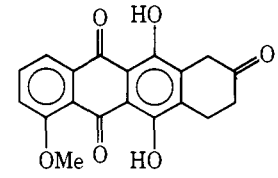
Synthetic Approaches to Adriamycin. Degradation of Daunorubicin to Nonasymmetric Tetracyclic Ketone and Refunctionalization of the A-Ring to Adriamycin

Sir:

The anthracycline antibiotics daunorubicin (**1**) and adriamycin (**2**) are clinically useful antineoplastic agents with adriamycin having an especially broad spectrum of activity.[1] Due to their potent biological activity there is considerable interest in their synthesis.[2] As part of our efforts in developing a practical total synthesis of these agents, we report the preparation of the tetracyclic ketone **3**, a key intermediate in our proposed total synthesis, via a three-step

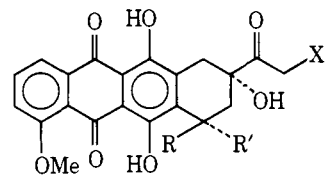


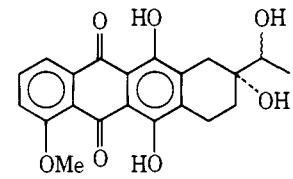
1, X = H
2, X = OH



3

degradation of **1** and its elaboration to adriamycin (**2**) and the new aglycone 7-epidaunomycinone (**4**).





4, X = R′ = H; R = OH
5, X = R′ = R = H
14, X = R = H; R′ = OH
15, X = R′ = OH; R = H
16, X = $OC(C_6H_5)_2$-*p*-$OMeC_6H_4$; R′ = OH; R = H

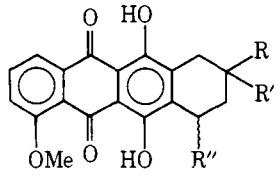
6

Reductive cleavage (2 equiv of $Na_2S_2O_4$, $NaHCO_3$, aqueous THF/MeOH, 23°, 15 min) of **1** afforded the previously reported[3] 7-deoxydaunomycinone (**5**) in quantitative yield. The 9-acetyl group was reduced (4 equiv of LiAlH(O*t*-Bu)$_3$), THF, 23°, 44 h, 80%) to afford the diol **6**.[4] Oxidative cleavage of **6** (2.1 equiv of $NaIO_4$, THF/aqueous MeOH, 16 h, 23°) produced the ketone **3** (ir_{Nujol} 5.82 (C=O), 6.15, 6.35 (chelated quinone) μ; ^1H NMR 100-MHz $CDCl_3$ δ 2.64 (t, 2 H, 8-H_2), 3.25 (t, 2 H, 7-H_2), 3.63 (s, 2 H, 10-H_2), 4.09 (s, 3 H, -OCH_3), 7.38 (dd, 1 H, J = 8 and J = 1 Hz, 3-H), 7.77 (t, 1 H, J = 8 Hz, 2-H), 8.04 (dd, 1 H, J = 8 and J = 1 Hz, 1-H), 13.30 (s, 1 H, phenolic OH), 13.80 (s, 1 H, phenolic OH); MS 12 eV, *m/e* 338 M^+) in 99% yield with 71% conversion of **6**. The product and unreacted starting material could be readily separated and recovered by silica gel chromatography.

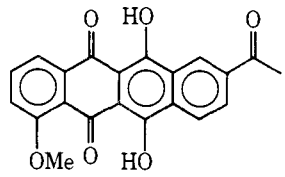
Several synthetic methods for the elaboration of the dihydroxy acetone side chain were investigated during model studies on 5,8-dimethoxy-2-tetralone.[5] The most efficient method in our hands was the addition of methylmagnesium iodide to a protected cyanohydrin followed by acid workup.[6]

Cyanohydrin **7** was prepared in 77% yield by addition of HCN (KCN, HOAc, EtOH/$CHCl_3$, 0–23°, 5 h) to **3**. The tetrahydropyranyl ether **8** (dihydropyran, concentrated HCl (catalyst), THF, reflux, 5 h, 90%) was treated with methylmagnesium iodide (30 equiv, THF, 55°, 14 h) followed by acid hydrolysis (60% HOAc, 90°, 1 h) to afford (±)-7-deoxydaunomycinone (**9**), having spectral (ir, ^1H NMR, MS) properties identical with the degradation product **5** in 45% yield.

Functionalization of the 7-position was achieved by a modification of the procedure developed by Goodman et al.[7] Benzylic bromination of **5** afforded, besides the bromide



7, R = CN; R′ = OH; R″ = H
8, R = CN; R′ = OTHP; R″ = H
9, R = Ac; R′ = OH; R″ = H
10, R = Ac; R′ = OH; R″ = Br
12, R = $COCH_2Br$; R′ = OH; R″ = H
13, R = Ac; R′ = OH; R″ = $OCOCF_3$



11

10, considerable amounts of unreacted **5** and bisanhydrodaunomycinone (**11**), presumably arising from aromatization of **10.** Efforts to achieve complete reaction resulted in increased yields of **11** at the expense of **10.** Although this problem was not fully overcome, the benzylic bromination was achieved most satisfactorily by using Br_2 (1.5 equiv) in refluxing CCl_4 with 2,2′-azobisisobutyronitrile (ABN) as catalyst. Wong[2b] has postulated that steric hindrance about the 10-position allows benzylic bromination to proceed regiospecifically at the 7-position. 14-Bromo-7-deoxydaunomycinone (**12**), arising from ionic bromination of the 14-position, was not observed in the reactions of **5** with Br_2, NMe_4Br_3, or NBS in CCl_4. However, **12** was formed exclusively upon treatment of **5** with Br_2 or NMe_4Br_3 in $CHCl_3$, regardless of the presence of radical initiators.

The unstable bromide **10** was converted to trifluoroacetate **13** with $NaOCOCF_3$ in Me_2SO.[8] To avoid excess handling of the potentially unstable intermediates **10** and **13,** no purification was attempted until after methanolysis at the daunomycinone stage. 7-Deoxydaunomycinone (**5**) was brominated (vide supra) and treated with $NaOCOCF_3$ (Me_2SO, 23°, 16 h) to afford, after aqueous workup and $CHCl_3$ extraction, the crude trifluoroacetate **13,** which was then subjected to methanolysis (MeOH, 23°, 4 h).

Chromatography of the reaction mixture on silica gel afforded, in order of elution, bisanhydrodaunomycinone (**11**), starting material (17%), daunomycinone (**14,** 9%), identical (mp, ir, ^1H NMR, MS, TLC, HPLC, $[\alpha]D$) with an authentic sample, and 7-epidaunomycinone (**4,** 35%), mp 216–218°, $[\alpha]D$ −184° (*c* 0.02, $CHCl_3$).

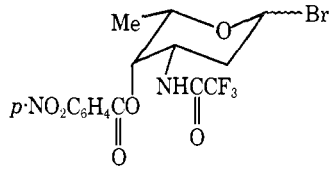
Characterization of **4** was based on its ^1H NMR spectra. The benzylic H-7 proton signal appeared as a multiplet at δ 5.37, $\nu_{1/2}$ = 17 Hz, characteristic of an axial proton.[9] The spectrum of daunomycinone is similar except that the H-7 signal appears as a narrower, $\nu_{1/2}$ = 7 Hz, multiplet due to the equatorial orientation of H-7. The mass spectrum and elemental analysis of **4** showed it to be isomeric with daunomycinone.

Anthracyclinones having an axial proton at C-7 have been epimerized with acid.[9,10] To obtain aglycone possessing the natural stereochemistry, the crude trifluoroacetate **13** was dissolved in TFA (23°, 1.5 h) before methanolysis. Silica gel chromatography of the crude product afforded **11,** starting material (18%), daunomycinone (35%), and 7-epidaunomycinone (6%).

The partial stereospecificity of this sequence can be explained by an SN1 mechanism for the $NaOCOCF_3$ displacement. Approach of the trifluoroacetate anion to the planar benzylic carbonium ion, arising from ionization of the bromide **10,** should be more favorable from the side trans to the axial hydroxyl at C-9. Methanolysis would then result in the observed predominant formation of **4** over **14.**

Daunomycinone was brominated (Br_2, $CHCl_3$, 23°, 16 h),[11] and the crude product was treated with NaOH (1.1 equiv, 80% aqueous acetone, reflux, 5 min) to afford adriamycinone (**15**) identical with an authentic sample in 87% yield. The 14-hydroxyl was protected by conversion of **15** to the monomethoxytrityl ether **16** (10 equiv of *p*-anisyldiphenylchloromethane, pyridine, 5°, 116 h, 94%).

The protected aglycone **16,** with mercuric cyanide, mercuric bromide, and powdered molecular sieve 3A in anhydrous THF, was treated with the bromo sugar **17**[2a] in six 1-molar equiv portions to afford the glycoside **18.** The unpurified crude product was deacylated with 0.1 N NaOH in aqueous THF at 0° to afford **19** which could be separated from the water-soluble sugar by-products of the coupling reaction by partitioning the reaction mixture between $CHCl_3$ and water.



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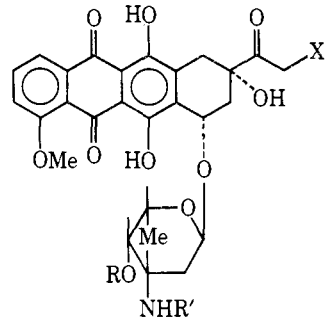

18, X = $OC(C_6H_5)_2$-*p*-$OMeC_6H_4$
R = *p*-$NO_2C_6H_4CO$; R′ = CF_3CO
19, X = $OC(C_6H_5)_2$-*p*-$OMeC_6H_4$
R = R′ = H

Treatment of **19** with 80% HOAc at 23° afforded adriamycin (**2**) which after conversion to the hydrochloride was identical with the natural product in 36% yield from **16.**

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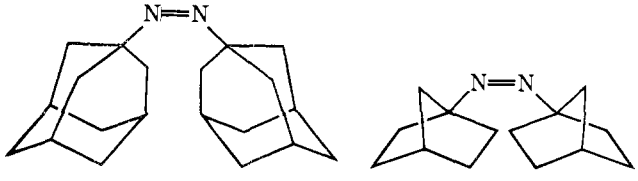
Stable Cis Dialkyldiazenes (Azoalkanes): *cis*-Di-1-adamantyldiazene and *cis*-Di-1-norbornyldiazene

Sir:

Whereas cis aromatic diazenes (*cis*-ArN=NAr) have been known since 1937,[1] their aliphatic counterparts were discovered only in 1964.[2] The cis isomer of diisopropyldiazene is especially well characterized[3] but other cis diazenes which form more stable incipient radicals lose nitrogen rapidly at ambient temperatures.[4,5] In contrast, cis aryldiazenes only isomerize to trans,[6] although both pathways can be found in mixed aryl-alkyl cases.[7]

We were intrigued by the possibility that a properly chosen cis aliphatic diazene might isomerize to trans without losing nitrogen.[8] Trans compounds with considerable steric bulk and high energies of activation for decomposition were selected for study, with the expectation that the corresponding cis forms would be forced to isomerize thermally to trans. *trans*-Di-1-adamantyldiazene (**1t**) and di-1-norbornyldiazene (**2t**, Table I) meet both of these criteria and indeed, cis isomers **1c** and **2c** were found to behave in the anticipated manner, as summarized herein.



1c **2c**

Table I. Activation Parameters for Thermolysis of Trans Diazenes

Compound	$\Delta H_{dec}^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	k_{rel}, 300°
Di-1-adamantyldiazene[9] (**1t**)	60.7	31.4	2×10^{-4}
Di-1-norbornyldiazene[10] (**2t**)	53.8	9.0	1×10^{-6}
Di-*tert*-butyldiazene[11] (**3t**)	42.2	16.2	1.0

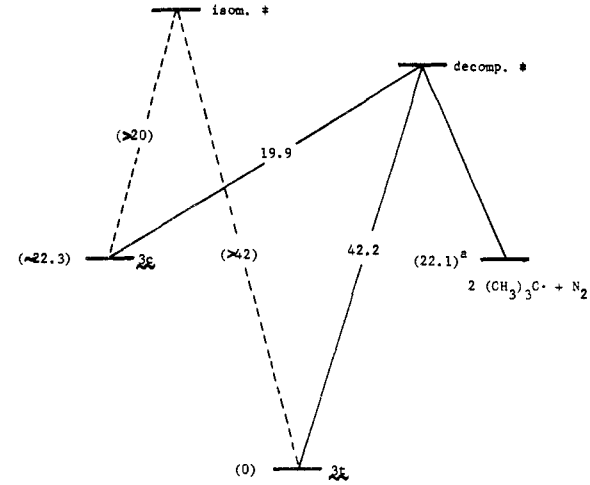


Figure 1. Enthalpy of di-*tert*-butyldiazene (**3**) and the transition states for isomerization and decomposition. Values in parentheses are assumed or calculated. Dashed line indicates a process not observed. [a] $2\Delta H_f[(CH_3)_3C\cdot] - \Delta H_f(\mathbf{3t})$.

Uv irradiation of **1t** in toluene at 0° produced an intense yellow color (**1c**) which faded slowly on warming to room temperature. Its disappearance was monitored at several temperatures on a Cary 17, giving the activation parameters shown in Table II. Compound **2t** behaved similarly except that much higher temperatures were required to cause fading of the color. The greater stability of **2c** allowed its isolation by chromatography on basic alumina, yielding yellow needles which melted at 92.5-93.5°. Further heating (100-115°) in the capillary tube transformed the yellow liquid into a white solid, which remelted at 165-166°. (Authentic **2t** melted at 166-167°.) The sharp melting point implies that little decomposition of **2c** occurs on heating, and is consistent with the extremely low quantum yield for loss of nitrogen (cf. Table II) from **2t.** The quantum yield is higher in the case of **1t,** but still far below the 0.46 reported for **3t.**[12]

Interpretation of the above results is facilitated by first examining the energetics of **3** (cf. Figure 1). The difference between $\Delta H_{dec}^{\ddagger}$ of **3t** and **3c** (22.3 kcal mol^{-1}) is taken as the ground state energy of **3c,** based on the assumption that **3c** and **3t** have transition states of similar energy.[5,13] Since **3c** decomposes rather than isomerizing, the transition state for the latter process must lie above 42 kcal mol^{-1} on the diagram, neglecting possible $\Delta S^{\ddagger}$ differences.

The energy diagram for **2** is shown in Figure 2. A preliminary measurement by differential scanning calorimetry gave a value for the enthalpy of isomerization **2c**(s) → **2t**(s) of approximately 12 kcal mol^{-1},[14] which will be assumed to equal the gas phase value.[15] Despite the slight uncertainty in this measurement, it is clear that isomerization of **2c** is favored over decomposition by ~10 kcal mol^{-1}. In view of the bulky groups in **2c,** its strain energy relative to **2t** (12 kcal mol^{-1}) is intuitively reasonable when compared with *cis*-diisopropyldiazene, which possesses 8 kcal mol^{-1} of

Table II. Data for Diazenes **1**-**3** in Hydrocarbon Solvents

Compound	λ_{max}, nm: Trans	λ_{max}, nm: Cis	ΦN_2[a]	$\Delta H^{\ddagger}$, kcal mol^{-1} [c]	$\Delta S^{\ddagger}$, eu[c]
Di-1-adamantyldiazene (**1**)	368	455	<0.004	25.9 ± 0.5	13.4 ± 1.6
Di-1-norbornyldiazene (**2**)	364	423	0.0008[b]	31.8 ± 0.4	12.8 ± 1.2
Di-*tert*-butyldiazene (**3**)	368	447	0.46	19.9 ± 0.4[d]	4.3 ± 1.5[d]

[a] Quantum yield for nitrogen formation from trans isomers. [b] The irradiated solution was heated for 6 min at 100° before measuring N_2 yield. [c] Activation parameters for disappearance of cis compound. [d] Reference 5.