15b: IR 3500–3150 (NH, OH), 1955 (>NCO) cm^{-1}; ^1H NMR δ 1.12 (t, 3 H, J = 6.5 Hz, CH_2CH_3), 1.32–2.00 (m, 10 H), 2.46 (t, 2 H, J = 6 Hz, H-3), 2.78 (m, 3 H), 3.54 (m, 2 H, CH_2OH), 4.80 (s, 1 H, H-12b), 5.14 (m, 1 H, H_e-6), 7.04–7.60 (m, 4 H, Ar H), 8.30 (br s, 1 H, NH); MS, m/z (relative intensity) M^+, 326 (27), 223 (50), 205 (47), 195 (60), 170 (100). Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.68; H, 8.04; N, 8.59. Found: C, 73.71; H, 8.01; N, 8.66.

16a: IR 3500–3185 (NH, OH), 2800 and 2755 (Bohlmann band) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40–3.56 (m, 14 H), 4.40 (br s, 1 H, CH_2OH), 6.80–7.48 (m, 4 H, Ar H), 10.72 (br s, 1 H, NH); MS, m/z (relative intensity) M^+, 256 (75), 255 (100), 225 (23), 170 (72), 169 (71). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 75.06; H, 7.88; N, 10.94. Found: C, 75.14; H, 7.91; N, 10.88.

16b: IR 3500–3300 (NH, OH), 2800 and 2750 (Bohlmann band) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.00–3.36 (m, 14 H), 4.48 (br s, 1 H, CH_2OH), 6.68–7.48 (m, 4 H, Ar H), 10.72 (br s, 1 H, NH); MS, m/z (relative intensity) M^+, 256 (67), 255 (100), 225 (26), 170 (61), 169 (58). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 75.06; H, 7.88; N, 10.94. Found: C, 74.98; H. 7.84; N, 10.98.

9b: IR 3320 (NH) cm^{-1}; ^1H NMR δ 1.68–3.52 (m, 10 H), 4.24 (m, 1 H, H-11b), 7.04–7.60 (m, 4 H, Ar H), 7.80 (br s, 1 H, NH); MS, m/z (relative intensity) M^+, 212 (71), 211 (100), 184 (33), 156 (22).

11c: IR 2800 and 2760 (Bohlmann band), 1600 (Ar) cm^{-1}; ^1H NMR δ 2.52–3.40 (m, 6 H), 3.60 (dd, 1 H, J = 4 Hz, H-12b), 3.92 (AB q, 2 H, J = 16 Hz, H-5), 3.86 (s, 3 H, OMe), 5.14 (s, 2 H, OCH_2 Ar), 6.64 and 6.72 (2 s, H-9, H-12), 7.03 (d, 1 H, J = 6 Hz, H-1), 7.20–7.60 (m, 5 H), 8.32 (m, 2 H, H-2, H-4); MS, m/z (relative intensity) M^+, 372 (63), 371 (64), 281 (33), 91 (100). Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.48; H, 6.50; N, 7.53. Found: C, 77.39; H, 6.48; N, 7.48.

8c: IR 3500–3100 (NH, OH) and 1650 (>NCO) cm^{-1}; ^1H NMR δ 0.80 (m, 3 H, CH_2CH_3), 1.02–2.60 (m, 19 H), 3.44–3.88 (m, 2 H, CH_2OH), 6.80–7.44 (m, 4 H, Ar H), 8.20 and 8.60 (NH); MS, m/z (relative intensity) M^+, 330 (25), 184 (100). Anal. Calcd for $C_{20}H_{30}N_2O_2$: C, 72.79; H, 9.16; N, 8.49. Found: C, 72.83; H, 9.20; N, 8.41.

12d: IR 3380 (NH), 2780 and 2730 (Bohlmann band) cm^{-1}; ^1H NMR δ 0.62 (t, 3 H, CH_2CH_3), 0.80–2.40 (m, 16 H), 3.10 (br t, 2 H), 3.50 (dd, 1 H, J = 10, 6.5 Hz), 6.62 (d, 1 H, J = 8 Hz), 6.74 (d, 1 H, J = 8 Hz), 7.02 (dt, 2 H, J = 8, 2 Hz); MS, m/z (relative intensity) M^+, 282 (28), 254 (23), 124 (100).

Acknowledgment. We are indebted to Dr. B. Achari, Medicinal Chemistry Division, for discussion and constructive criticism in the preparation of this manuscript.

Regioselective Hydrogenation and Hydrodechlorination of a Pentachloro-2-azanorbornene[1]

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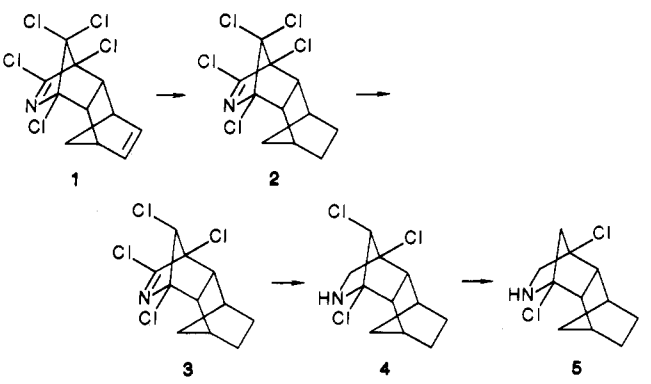
Received March 15, 1988

Regioselective reduction of azaaldrin (**1**), a pentachloro-2-azanorbornenyl derivative, was achieved with sodium hydride complex reducing agents or hydrogen over a rhodium or palladium catalyst. Sodium hydride itself did not react with **1**, but the complex with *t*-AmONa led to saturation of the carbon–carbon double bond in **1** to form only dihydroazaaldrin (**2**). Dechlorination occurred in the presence of the NaH–*t*-AmONa–$Ni(OAc)_2$ complex reducing agent (NiCRA), first reducing the 11-anti chlorine at the methano bridge to yield the tetrachloro derivative **3**. With a larger excess of NiCRA, **3** was reduced further to the trichloro compound **4**, in which the imidoyl chloride was saturated and dechlorinated but the 11-syn chlorine remained. X-ray analysis established the structure of **3**, and **4** was determined accordingly based on IR and NMR spectral comparisons. Treatment of **1** with hydrogen over Rh/C initially produced a mixture of **2**, **3**, and **4**. In no cases were the 11-syn chloro group in **4** reduced to form **5**, except when Pd/C was used as the catalyst. The dichloro derivative **5** was stable to further catalytic reduction.

We have reported[2] that 2-azanorbornenes, particularly azaaldrin (**1**), undergo selective substitutions of the imidoyl halide group by hard and basic nucleophiles. Hydride reagents which are soft bases, e.g., NaH in THF, $LiAlH_4$, or $NaBH_4$ in diethyl ether, do not react with **1** at all. As part of our continuing interest in polycyclic amines,[1] various hydrogenation and hydrodechlorination reactions of **1** have been carried out. Sodium hydride complex reducing agents (CRA) and catalytic hydrogenation conditions using rhodium or palladium as catalyst have been found to reduce **1** in a stepwise, regioselective manner. The sequence of relative reactivity of the chlorines and unsaturations in the 2-azanorbornenyl system is shown in Scheme I.

Scheme I



Results

Sodium Hydride Complex Reducing Agents. When azaaldrin (**1**) was refluxed with NaH in dry THF for 3 days, there was no reaction as evidenced by gas chromatography. Upon refluxing **1** with NaH–*t*-$C_5H_{11}ONa$ (2:1) in THF for 8 h, only the C=C bond was reduced, leading to **2** as a single product. When a 1:1 mixture of **1** and NiCRA (NaH–*t*-AmONa–$Ni(OAc)_2$ 4:2:1) was refluxed in THF for 3 h following Caubere's procedure,[3] two products,

(1) Azadiene Chemistry. 9. Part 8: Rammash, B. Kh.; Atwood, J. L.; Weeks, J. A.; Wong, J. L. *J. Org. Chem.* **1987**, *52*, 2712.
(2) Rammash, B. Kh.; Wong, J. L. *J. Org. Chem.* **1987**, *52*, 64.

0022-3263/88/1953-4241$01.50/0

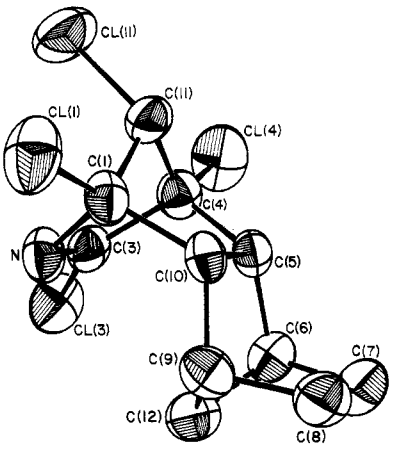


Figure 1. ORTEP structure of 3.

3 and 4, were obtained in about 60% yield in a 3:1 ratio. At 3 equiv of NiCRA, a 1:1 ratio of 3 and 4 was obtained, while 5 equiv of the reducing agent produced 4 exclusively.

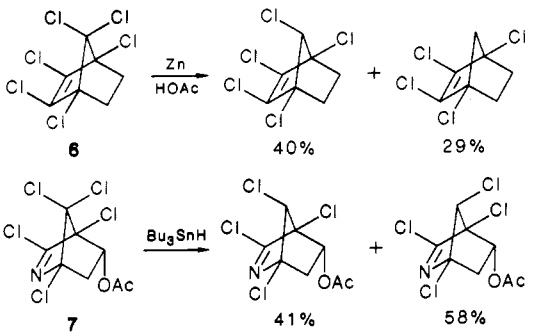
Catalytic Hydrogenation and Hydrogenolysis. Reduction of 1 over 5% rhodium on carbon in ethyl acetate and triethylamine for 14 h at 25 °C, under 1 atm of hydrogen, afforded a 90% yield of a mixture of three products: 2 (40%), 3 (25%), and 4 (25%). With the same conditions but with 10% palladium on carbon instead of the rhodium catalyst, a mixture of two products in 90% yield was obtained: 4 (70%) and 5 (20%). Although 2 and 3 were observed by gas chromatography at the early stages of the reaction, they completely disappeared upon consumption of 1 (14 h).

Structural Assignments. The pivotal compound in this hydrogenation–hydrodechlorination series is the tetrachloro derivative 3. Its structure was established by X-ray crystallographic analysis as shown in Figure 1. This has allowed analysis of the ^1H and ^{13}C NMR spectra of 3 as well as its homologues and hence their assignments as shown in the Experimental Section. Tables of crystallographic experimental details are available as supplementary material. Additionally, the absence of a $\nu_{C=N}$ band, which appeared at 1580 cm^{-1} in 1–3, and the presence of ν_{N-H} 3320–3330 show that reduction of the imidoyl chloride to the saturated amine has taken place in 4 and 5. Also, the dihydro derivative 2 was independently synthesized by reacting 2,3,4,5,5-pentachloro-1-azacyclopentadiene with norbornene according to our previous procedure.[4]

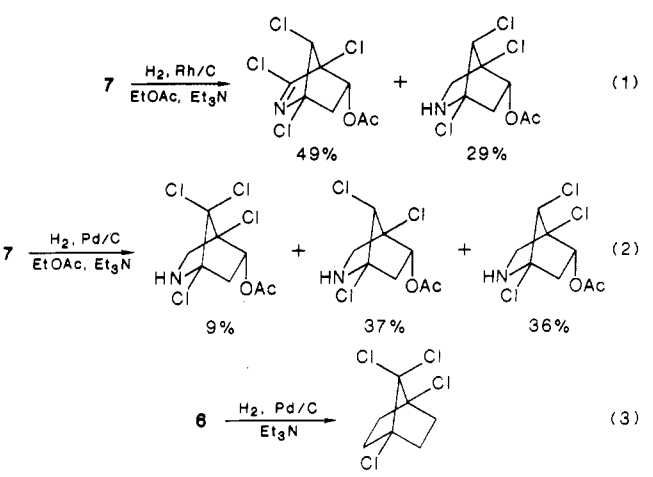
Discussion

Sodium hydride, which has considerable proton affinity, is not a good reducing agent, and the hydride anion itself is too soft a nucleophile to react with the imidoyl chloride in 1.[2] Caubere[3] has introduced the use of complex reducing agents (CRA), NaH–RONa–MX_n, in reducing alkyl halides such as primary, secondary, and tertiary alkyl chlorides to the parent hydrocarbons. The alkoxide aggregates with NaH to increase its solubility in THF, while a MX_n salt such as nickel acetate further activates the reduction potential. The X-ray structure of NiCRA shows a nickel atom center in a cube surrounded by Na^+, H^-, t-AmO^-, and AcO^-. The tendency for electron transfer from the H^- in such a complex is enhanced.[3] These varying H^- reactivities are observed in this work. Whereas NaH itself did not react with 1, the more soluble NaH–t-AmONa (2:1) complex behaved as a selective reducing agent for the carbon–carbon double bond. In the presence of NiCRA, reduction of 1 went further. The 11-anti chlorine (Cl on the methano bridge opposite to C=N) was readily replaced, followed by saturation and dechlorination of the imidoyl chloride. The reaction mixture converged to the trichloro compound 4 as the only product.

Scheme II



Scheme III



There are two surprising features in the above reaction: the clear-cut regioselectivity of 11-anti chlorine over the 11-syn chlorine and the apparent lack of reactivity of the latter in compounds 1–3. In Scheme II are shown two analogous dechlorination reactions for comparison. Wilcox et al.[5] showed that zinc reduction of the hexachloronorbornene 6 occurred first at the 7-anti chlorine followed by replacement of the 7-syn chlorine. If this reduction involves a methano carbanion, the 7-anti negative orbital, being further removed from the π-bond electrons, should be preferred and hence the greater reactivity of the anti over the syn chlorine. On the other hand, Jung et al.[6] found that tri-n-butyltin hydride reduced the methano bridge chlorines in the pentachloro-2-azanorbornene 7 in a ratio of about 4:6, the 7-syn chlorine being more reactive than the anti chlorine. This may be due to the radical nature in this reduction, where the tin hydride reagent is attracted more to the imidoyl side, thereby favoring syn hydrogen transfer.[7] In view of these analogies, the decisive preference of 11-anti over the syn chlorine observed in the dechlorination of 1 by NiCRA provides an interesting contrast. It is all the more unusual that the 11-syn chloro group remains intact in 4 after the imidoyl chloride is reduced to the amine. One may speculate that nonbonding interaction from the imino or amino group either stabilizes

(3) Caubere, P. *Angew Chem., Int. Ed Engl.* **1983**, *22*, 599.
(4) Rammash, B. Kh.; Gladstone, C. M.; Wong, J. L. *J. Org. Chem.* **1981**, *46*, 3036.
(5) Wilcox, C. F., Jr.; Zajacek, J. G. *J. Org. Chem.* **1964**, *29*, 2209.
(6) Jung, M. E.; Sharpiro, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7862.
(7) Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 209.

the 11-syn chlorine or repels electron transfer from the NiCRA from the same side.

Our results from the catalytic hydrogenation/hydrogenolysis of **1** with rhodium and palladium are also different from those reported for similar reactions. Scheme III shows the rhodium- and palladium-catalyzed reduction of **7** reported by Jung et al.[6] and the palladium-catalyzed reduction of **6** by Marchand and Weiman.[8] In eq 1, the rhodium-catalyzed reaction generated the tetrachloro and trichloro products in 49% and 29% yield, respectively, but not sequentially. The major product shows a 7-syn chlorine corresponding to our tetrachloro **3**, however, the minor product in eq 1 is an anomaly, featuring a 7-anti chlorine. The latter is opposite to that found in our trichloro product **4**, which is derived from **3**. Thus, the major product of eq 1 agrees with our notion that the imino group deactivates the syn chlorine on the methano bridge toward reduction by NiCRA or by Rh/C and H_2. The use of palladium, a stronger catalyst than rhodium, allows further hydrogenation and hydrogenolysis. Regarding the literature, both eq 2 and 3 indicate that the π-systems (imidoyl chloride and vinyl dichloride) are the first reduced. Apparently, these π-electrons are more readily attached to the palladium surface than the carbon–chlorine bond. In **1**, however, given the C-12 methylene group crowding the underside of the imine, such is not the case. In both the rhodium and palladium reaction, the 11-anti chlorine is reduced ahead of the imidoyl group. In eq 2, further reduction of the tetrachloro derivative in the presence of Pd/C appears to occur with equal ease at either the 7-anti or 7-syn chlorine. These observations are inconsistent with eq 1, using Rh/C, where hydrodechlorination of the 7-anti chlorine takes precedence. Our present system behaves more orderly: in the Rh/C reaction, the reduction stops at the stage of the trichloro product **4**, but a continuation of the reduction of **4** to the dichloro derivative **5** takes place in the presence of palladium. As for the bridgehead chlorines, they are resistant to palladium-catalyzed hydrogenolysis as shown by previous examples reported above. In conclusion, the sequence of reduction of **1** is summarized in Scheme IV.

Scheme IV

$$\mathbf{1} \xrightarrow{\text{NaH-}t\text{-AmONa}} \mathbf{2} \xrightarrow[\text{or } H_2,\ Rh/C]{\text{NiCRA}} \mathbf{3} \xrightarrow[\text{or } H_2,\ Rh/C]{\text{NiCRA}} \mathbf{4} \xrightarrow[Pd/C]{H_2} \mathbf{5}$$

Experimental Section

NMR spectra were obtained by using a Varian XL-300 spectrometer. NMR samples were prepared in $CDCl_3$ containing 1% tetramethylsilane ($\delta_{TMS} = 0$). Symbols used for proton assignments are as follows: endo (n), exo (x), anti (A), and syn (S). IR spectra were run on a Nicolet 7000 series FT-IR. GLC analyses were performed on a Varian 3700 chromatograph with dual flame-ionization detector using a 6 ft × 0.125 in. aluminum column packed with 10% SE-30 on Chromosorb WAW DMCS and at 30 mL of nitrogen/min: T_i = 240 °C, T_d = 250 °C, T_c = 190 °C. Combustion analyses were performed by MicAnal Organic Microanalysis, Tucson, AZ. Azaaldrin (**1**) was prepared according to the procedure previously described.[2] Reagent grade THF was dried over NaOH and $NaBH_4$ and freshly distilled from CaH_2 under nitrogen. *t*-AmOH was distilled from sodium, and $Ni(OAc)_2$ was dried in vacuo for 8–10 h at 90–110 °C. NaH (60%, in oil) was washed several times with THF under nitrogen, and all reactions involving NaH were carried out under nitrogen.

Dihydroazaaldrin (2) from Reduction of Azaaldrin (1) with NaH-*t*-AmONa. *t*-AmOH (1.76 g, 20 mmol) in 10 mL of freshly distilled THF was added to a vigorously stirred suspension of 2.4 g (60 mmol) of NaH in 10 mL of THF, the mixture was stirred for 2 h at 60–65 °C, and cooled to room temperature, and 3.31 g (10 mmol) of azaaldrin (**1**) in 10 mL of THF was added. The reaction mixture was refluxed for 8 h and filtered, the filtrate concentrated in vacuo, and the residue extracted with Et_2O–H_2O. The ether layer was washed with a saturated solution of NaCl, dried over sodium sulfate, and evaporated to give 2.2 g of a crude product, which after recrystallization from aqueous ethanol gave 1.8 g (54%) of white crystalline **2**: mp 118–120 °C; GLC t_R 15.5 min; IR 1580 (C=N) cm^{-1}; ^1H NMR δ 2.77 (q, H-5), 2.38 (s, H-6), 1.66 (m, H-7n), 1.18 (q, H-7x), 1.66 (m, H-8n), 1.18 (q, H-8x), 2.58 (s, H-9), 2.63 (q, H-10), 0.99 (d, H-12A), 1.84 (d, H-12S); ^{13}C NMR δ 94.94 (s, C-1), 166.92 (s, C-3), 82.89 (s, C-4), 54.54 (d, C-5), 35.42 (d, C-6), 29.97 (t, C-7), 30.84 (t, C-8), 35.71 (d, C-9), 55.55 (d, C-10), 104.42 (s, C-11), 34.73 (t, C-12).

Anal. Calcd. for $C_{11}H_{10}NCl_5$: C, 39.6; H, 3.0; N, 4.2. Found: C, 39.7; H, 2.9; N, 3.9.

Tetrachloro 3 and Trichloro Derivative 4 from Reduction of Azaaldrin (1) with NiCRA. *t*-AmOH (1.76 g, 20 mmol) in 10 mL of freshly distilled THF was added to a vigorously stirred suspension of 2.4 g (60 mmol) of NaH in 10 mL of THF at 60–65 °C, the mixture was stirred for 2 h and cooled to room temperature, and 1.7 g (10 mmol) of $Ni(OAc)_2$ was added, followed by 10 mL of THF. The mixture was refluxed for 4 h, 3.31 g (10 mmol) of azaaldrin (**1**) added, and reflux continued for 1 h. The reaction mixture was filtered, the solvent evaporated in vacuo, and the residue extracted with Et_2O–H_2O. The ether layer was washed with a saturated solution of NaCl, dried over anhydrous sodium sulfate, and evaporated to give 1.9 g of crude product. Column chromatography of the crude material on 100 g silica gel, eluting with hexane, gave products **3** and **4**. Evaporating the eluent from fractions 10–16 gave a residue, which, after recrystallization from aqueous ethanol, afforded 1.3 g (45%) of white crystalline **3**: mp 136–138 °C; IR 1580 (C=N) cm^{-1}; ^1H NMR δ 2.53 (q, H-5), 2.43 (s, H-6), 1.62 (m, H-7n), 1.14 (q, H-7x), 1.62 (m, H-8n), 1.14 (q, H-8x), 2.61 (s, H-9), 2.46 (q, H-10), 4.20 (s, H-11A), 0.97 (d, H-12A), 1.83 (d, H-12S); ^{13}C NMR δ 91.82 (s, C-1), 165.90 (s, C-3), 83.13 (s, C-4), 54.99 (d, C-5), 36.02 (d, C-6), 29.91 (t, C-7), 30.76 (t, C-8), 36.07 (d, C-9), 56.35 (d, C-10), 79.30 (d, C-11), 34.03 (t, C-12).

Anal. Calcd for $C_{11}H_{11}NCl_4$: C, 44.2; H, 3.7; N, 4.7. Found: C, 44.2; H, 3.6; N, 4.4.

Evaporating the eluent from fractions 3–9 gave a residue, which, after recrystallization from aqueous ethanol, afforded 0.4 g (15%) of white crystalline **4**: mp 93–95 °C; IR 3330 (N–H) cm^{-1}; ^1H NMR δ 2.30 (br, N–H), 3.28 (d, H-3n), 3.15 (d, H-3x), 2.48 (q, H-5), 2.23 (s, H-6), 1.60 (m, H-7n), 1.10 (q, H-7x), 1.60 (m, H-8n), 1.10 (q, H-8x), 2.24 (s, H-9), 2.49 (q, H-10), 4.11 (s, H-11A), 1.18 (d, H-12A), 2.20 (d, H-12S); ^{13}C NMR δ 85.87 (s, C-1), 51.70 (t, C-3), 69.64 (s, C-4), 54.44 (d, C-5), 35.39 (d, C-6), 29.44 (t, C-7), 30.50 (t, C-8), 35.88 (d, C-9), 56.30 (d, C-10), 73.25 (d, C-11), 34.67 (t, C-12).

Anal. Calcd. for $C_{11}H_{14}NCl_3$: C, 49.6; H, 5.3; N, 5.3. Found: C, 49.6; H, 5.3; N, 5.1.

Hydrogenation and Hydrogenolysis of Azaaldrin (1) over Rhodium-on-Carbon To Yield 2–4. To 3.31 g (10 mmol) of azaaldrin (**1**) dissolved in 80 mL of ethyl acetate containing 0.84 g of 5% rhodium-on-carbon was added 7 mL (50 mmol) of freshly distilled triethylamine. The mixture was stirred under 1 atm of hydrogen for 14 h at 25 °C. The solvent was evaporated, the mixture stirred for 1 h in anhydrous diethyl ether and filtered, the ether layer evaporated, and the crude residue separated by column chromatography on silica gel, eluting with hexane. Evaporation of the eluent from fractions 2–8, 9–15, and 16–24 gave residues, which, afte recrystallization from aqueous ethanol, afforded 0.6 g (25%), 0.7 g (25%), and 1.3 g (40%) of **4**, **3**, and **2**, respectively.

Hydrogenation and Hydrogenolysis of Azaaldrin (1) over Palladium-on-Carbon To Yield 4 and 5. To 3.31 g (10 mmol) of azaaldrin (**1**) dissolved in 180 mL of ethyl acetate containing 0.84 g of 10% palladium-on-carbon was added 7 mL (50 mmol) of freshly distilled triethylamine. The mixture was stirred under 1 atm of hydrogen for 14 h at 25 °C, evaporated, stirred for 1 h in anhydrous diethyl ether, and filtered, the ether layer evaporated, and the residue separated by column chromatography on silica gel, eluting with hexane. Evaporation of the eluent from fractions 8–15 gave a residue, which, after crystallization from aqueous ethanol, afforded 1.8 g (70%) of **4**. Evaporation of the eluent from fractions 2–7 gave 0.4 g (20%) of a thick oil **5**: GLC t_R 7.5 min; IR 3320 (N–H) cm^{-1}; ^1H NMR δ 2.55 (s, N–H), 3.35 (q, H-3n),

(8) Marchand, A. P.; Weiman, W. R., Jr. *J. Org. Chem.* **1969**, *34*, 1109.

3.16 (d, H-3x), 2.43 (q, H-5), 2.29 (s, H-6), 1.60 (m, H-7n), 1.07 (q, H-7x), 1.60 (m, H-8n), 1.07 (q, H-8x), 2.32 (s, H-9), 2.47 (q, H-10), 2.38 (q, H-11A), 2.28 (d, H-11S), 1.18 (d, H-12A), 1.88 (d, H-12S); ^{13}C NMR δ 84.88 (s, C-1), 56.63 (t, C-3), 66.59 (s, C-4), 57.93 (d, C-5), 34.22 (d, C-6), 29.69 (t, C-7), 30.02 (t, C-8), 35.04 (d, C-9), 60.71 (d, C-10), 54.61 (t, C-11), 30.29 (t, C-12).

Anal. Calcd for $C_{19}H_{15}NCl_2$: C, 56.9; H, 6.5; N, 6.0. Found: C, 57.0; H, 6.5; N, 5.6.

X-ray Crystallography. Crystal data: $C_{11}H_{11}Cl_4N$, M_r 299.03; crystal size 0.40 × 0.37 × 0.30 mm; orthorhombic, space group *Pbca* (No. 61), with a = 10.872 (3) Å, b = 15.074 (3) Å, c = 15.571 (3) Å; U = 2551.8 Å^3; Z = 8, D_{calcd} = 1.56 g cm^{-3}; μ(Mo Kα) = 9.0 cm^{-1}; Mo Kα radiation (λ = 0.71073 Å); Enraf-Nonius CAD4 diffractometer. The data were corrected for *Lp*, decay (average −10% due to X-ray damage), and absorption (program DIFABS). The structure was solved by direct methods and Fourier techniques and refined to a conventional R = 0.036 (R_w = 0.045). The refinements were carried out by full-matrix least-squares on the basis of 1035 unique observed [$I > 3\sigma(I)$] data and 146 parameters; all calculations were made with SDP/VAX; H atoms included as fixed contribution to the structure factor.

Supplementary Material Available: Tables of crystallographic experimental details, positional and thermal parameters, and bond lengths and angles (5 pages). Ordering information is given on any current masthead page.

A Stereospecific Total Synthesis of the Anthracyclinones (±)-Daunomycinone and (±)-Isodaunomycinone

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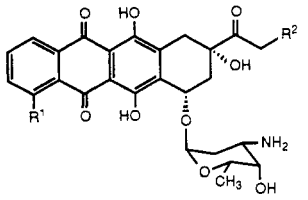
Received May 6, 1987

The complete synthesis of the anthracyclinones (±)-daunomycinone (**5**) and (±)-isodaunomycinone (**6**) is described. The construction of ring A was accomplished through a Diels–Alder cycloaddition using *trans*-4-(trimethylsilyl)-2-acetoxy-1,3-butadiene (**31**) as the diene and 5-methoxy-1,4,9,10-anthracenetetrone (**29**) as the dienophile. The 7-hydroxyl was introduced by the stereospecific replacement of the 7-trimethylsilyl function by acetate through the use of lead tetraacetate.

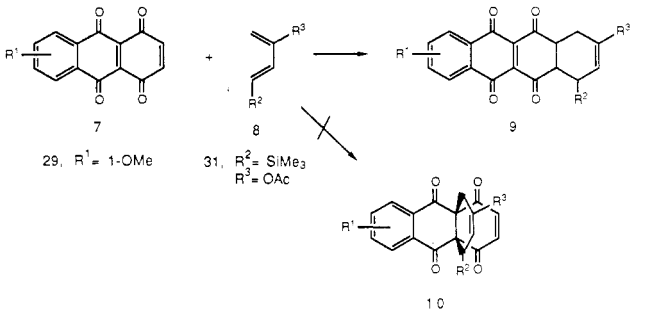
The family of anthracycline antibiotics, of which doxorubicin (adriamycin (**1**)),[1] daunorubicin (daunomycin (**2**)),[2] and carminomycin (**3**)[3,4] are important representative



1, R^1 = OCH_3; R^2 = OH
2, R^1 = OCH_3; R^2 = H
3, R^1 = OH; R^2 = H
4, R^1 = H; R^2 = H

members, has attracted considerable attention because of their remarkable efficacy against a wide variety of human cancers.[5] These cytotoxic agents are also plagued with unwanted side effects, the most serious being their cardiotoxicity.[5,6] A low therapeutic index, and surprising efficacy, has sparked great interest in the development of synthetic pathways to the natural clinically useful anthracyclines as well as analogues with improved activity profiles. This effort has been further stimulated by the fact that small structural differences can produce dramatic activity effects. For example, the synthetic analogue 4-desmethoxydaunorubicin (idarubicin (**4**)) is between 4 and 8 times more active than daunorubicin.[7]

Scheme I



The anthracycline structures are composed of a tetracyclic aglycon attached to the amino sugar L-daunosamine.[8,9] Since a variety of syntheses of this sugar[10] and its coupling to daunomycinone (**5**) have been described,[11]

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