this acetate ester of the adduct **4**. A molecular ion at *m/e* 495 in agreement with a molecular formula of $C_{20}H_{25}N_5O_{10}$ and a UV maximum at 263 nm (ϵ 14 610) in ethanol in accordance with monoalkyl substitution[9] on N^6 support the above structure assignment.

Further confirmation of the *N*-(hydroxymethoxy)methyl structure for the adduct **4** was provided by the off-resonance decoupled ^{13}C NMR spectrum of the pivalate ester **6**, which showed methylene triplets at δ 70.32 and 86.34.

Prolonging reaction at 0 °C or conducting the reaction at room temperature resulted in the conversion of this initially formed mono *N*-(hydroxymethoxy)methyl derivative to another product, presumably a diadduct. Proper characterization of this adduct proved to be difficult because of its instability.

Stable monomethylol derivatives[15] are formed in the reaction of formaldehyde with amides, imides, and pyrimidine bases, where intramolecular hydrogen bonding to the carbonyl oxygen stabilize such adducts. The formation of a *N*-(hydroxymethoxy)methyl adduct in the present case may, likewise, be attributed to the stabilization by intramolecular hydrogen bonding involving either the amino or hydroxyl hydrogen in a six-membered cyclic arrangement.

Experimental Section

The following spectrometers were used: IR, Beckman AccuLab 4; ^1H NMR, Varian T-60; ^{13}C NMR, Varian FT-80A; UV, Cary 14; mass spectrum, Riber R10-10 interphased with PDP-8A computer. Chemical shifts are reported in parts per million relative to tetramethylsilane as internal reference. Column chromatography was performed on silica gel 60 (E. Merck). Precoated silica gel 60 F254 (E. Merck) or Analtech GHLF plates were used for thin-layer chromatography.

2′,3′,5′-Triacetyl 6-[[(Hydroxymethoxy)methyl]amino]purine-9-β-D-arabinoside (4). 2′,3′,5′-Triacetyl arabinosyladenine[13] (200 mg) was dissolved in ice-cold 5 M aqueous formaldehyde (5 mL) and kept stirred at 0–4 °C. The reaction was monitored by TLC [silica gel, dichloromethane–acetone (1:1)]. When most of the starting material had disappeared (after 28 h), the reaction mixture was extracted with dichloromethane and the extract was washed twice with water. After the extract was dried (Na_2SO_4), the solvent was removed to furnish a thick glue (0.28 g). The product was contaminated with some polymeric formaldehyde. Attempted purification by chromatography resulted in its decomposition: ^1H NMR ($CDCl_3$) δ 1.96 (s, 3 H), 2.13 and 2.16 (s, 3 H each), 4.2–4.6 (m, 3 H), 5.1–5.7 (m, 6 H, NCH_2OCH_2 and 2′-H and 3′-H), 6.03 (d, J = 4 Hz, 1 H), 8.11 (s, 1 H), 8.46 (s, 1 H). (Polymeric formaldehyde peaks were at 4.8–5.0).

2″,3″,5″-Triacetyl 6-[(3′-Acetoxy-2′-oxapropyl)amino]purine-9-β-D-arabinoside (5). The above (hydroxymethoxy)methyl derivative **4** (280 mg) was dissolved in ice-cold dry pyridine (2.5 mL), and acetic anhydride (2.5 mL) was added with stirring. After 17 h at 0–4 °C, the excess acetylating agent was destroyed with crushed ice. The solvents were distilled off in vacuum at room temperature. The residue was taken in water and washed twice with ether. The ether washings were discarded. The aqueous layer was then extracted with dichloromethane. The dichloromethane extract was washed once with water and then with brine. After drying (Na_2SO_4), the organic extract was evaporated to yield an oily residue (285 mg) which on preparative thin-layer chromatography (silica gel, ethyl acetate) afforded the pure ester **5** (110 mg) as a thick oil: ^1H NMR ($CDCl_3$) δ 1.93 (s, 3 H), 2.08, 2.15, 2.18 (s, 3 H each), 4.2–4.6 (m, 3 H), 5.3–5.7 (m, 6 H), 6.63 (d, 1 H, J = 4 Hz), 7.7 (br t, 1 H, J = 6 Hz), 8.11 (s, 1 H), 8.45 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.42, 21.57, 21.83, 22.13, 64.13, 72.23, 75.95, 77.0, 81.14, 84.32, 88.03, 120.51, 141.0, 150.86, 154.35, 155.39, 169.77, 170.72, 171.61, 171.84; IR (film) 1738 cm^{-1} (C=O); UV max (EtOH) 263 nm (ϵ 14 610); mass spectrum, *m/e* 495 (M^+), 465, 452, 436, 392 ($M^+ - CH_2OCH_2OCOCH_3$); chemical ionization (NH_3) 496 $(M + 1)^+$.

2″,3″,5″-Triacetyl 6-[(3′-Pivaloxy-2′oxapropyl)amino]purine-9-β-D-arabinoside (6). To an ice-cold solution of the 6-[[(hydroxymethoxy)methyl]amino]purine **4** (1 g) in dichloromethane (40 mL) were added dry pyridine (5 mL) and pivalic anhydride (5 mL), and the reaction mixture was kept stirring at 0–4 °C for 48 h. After stirring with methanol (5 mL) for 1 h, the solvents were evaporated off in vacuum at room temperature. The residue was diluted with water and extracted with dichloromethane. The residue (1.54 g) obtained on washing, drying (Na_2SO_4), and evaporation of the solvent was chromatographed on silica gel. Elution with dichloromethane–ethyl acetate (1:1) furnished the pure pivalate ester **6** (152 mg) as a hygroscopic foam: ^1H NMR ($CDCl_3$) δ 1.23 (s, 9 H), 1.93, 2.15, 2.16 (s, 3 H each) 4.2–4.6 (m, 3 H), 5.4–5.65 (m, 6 H), 6.65 (d, 1 H, J = 4 Hz), 7.4 (br t, 1 H, J = 7 Hz), 8.1 (s, 1 H), 8.46 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.59 (q), 20.0 (q), 26.3 (q), 38.16 (s), 62.39 (t), 70.32 (t), 74.18 (d), 75.27 (d), 79.33 (d), 82.49 (d), 86.34 (t), 118.98 (s), 139.32 (d), 149.19 (s), 152.43 (d), 153.64 (s), 167.9 (s), 168.88 (s), 169.77 (s), 177.47 (s); IR (KBr) 1745 (C=O); UV max (EtOH) 263 nm (ϵ 18 660); mass spectrum, chemical ionization (NH_3) *m/e* 538, $(M + 1)^+$.

Acknowledgment. Helpful discussions with Prof. R. G. Carlson, Department of Chemistry, University of Kansas, is gratefully acknowledged.

Registry No. **3**, 15830-52-1; **4**, 89178-18-7; **5**, 89178-19-8; **6**, 89178-20-1; formaldehyde, 50-00-0.

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[15] (a) Bansal P. C.; Pitman, I. H.; Tam, J. N. S.; Mertes, M.; Kaminski, J. *J. Pharm. Sci.* **1981** *70*, 850 and references cited therein. (b) Pitman, I. H. *Med. Res. Rev.* **1981**, *1*, 189.

Novel Base-Induced Double Epimerization of Ethyl 2-*endo*,3-*exo*-3-Nitro-7-oxabicyclo[2.2.1]heptane-2-carboxylate

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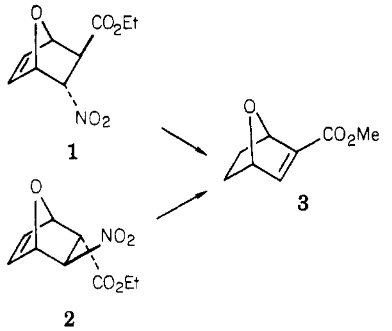
Received October 12, 1983

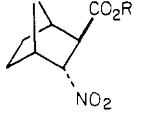
The racemic Diels–Alder adducts **1** and **2** obtained from furan and ethyl β-nitroacrylate[1] represent useful intermediates for the preparation of (+)-methyl (1*R*,4*S*)-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylate (**3**), a key intermediate in our recently completed synthesis of (+)-compactin.[2] In this connection we have shown that ester **4**,



1

3

2



4, R = Et
5, R = H

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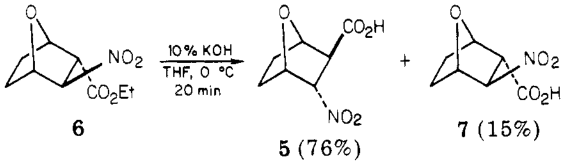
[1] Just, G.; Martel, A. *Tetrahedron Lett.* **1973**, 1517.

obtained by diimide reduction of **1**, upon hydrolysis [10% KOH–THF (3:2), 0 °C, 20 min] gave rise to a 97% yield of racemic acid **5**, mp 166.0–167.5 °C, which was resolved with D(−)-α-phenylglycinol and converted into **3** in a straightforward manner.[2]

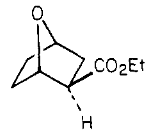
In sharp contrast, when β-nitro ester **6**, obtained by reduction of **2**, was subjected to hydrolysis under conditions identical with those employed above for **4**, there was obtained a 76% yield of **5**, mp 166.0–167.0 °C, along with only 15% of the anticipated acid **7**, mp 119–121 °C.[3] This result is remarkable in that during the course of this double epimerization there exists the possibility of bringing about β-elimination of both the C(3) nitro group and the C(7) bridging oxygen atom. Independent treatment of **4** and **6** with sodium ethoxide in ethanol at 0 °C led to complex mixtures that undoubtedly arise by base-induced β-elimination of the heteroatom bridge. These results are not surprising since it is well established that the 7-oxabicyclo[2.2.1]heptane derivatives **8** and **9** undergo facile β-elimination upon exposure to base.[4] In order to shed some light on the transformation of **6** into **5**, we examined the reaction of the 2-nitro-7-oxabicyclo[2.2.1]heptanes **10** and **11**[5] with 10% potassium hydroxide in tetrahydrofuran at 0 °C.



6

5 (76%)

7 (15%)



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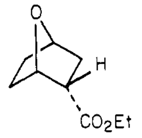

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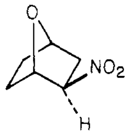
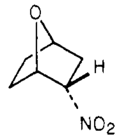
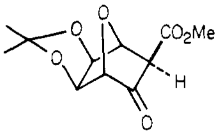


10



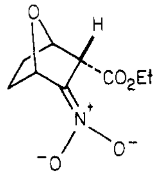
11

In separate experiments both **10** and **11** gave rise upon quenching with 10% oxalic acid to a 1:1 mixture of **10** and **11** as clearly evidenced by NMR analysis. These results establish that deprotonation of either **10** or **11** gives rise to a sufficiently stablized anion such that one observes no β-elimination of the bridging C(7) oxa substituent. Kozikowski[6] has shown that treatment of β-keto ester **12** with potassium *tert*-butoxide in tetrahydrofuran and subsequent C-alkylation with iodoacetonitrile proceeds in excellent yield with no trace of β-elimination.

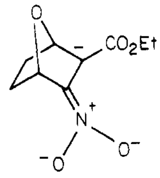


12

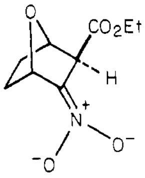
We believe the novel base-induced transformation of **6** into **5** proceeds initially via the intermediacy of the delocalized anion **13**. This is not unreasonable in view of the pK_a of the proton adjacent to the nitro group.[7] Subsequent deprotonation adjacent to the carbethoxy group generates dianion **14**, which upon reprotonation gives rise to anion **15** and eventually **5** by delivery of a proton from the exo face of **15** and saponification. The β-nitro acids **5** and **7** are both stable to 10% potassium hydroxide in tetrahydrofuran at ambient temperature.



13



14



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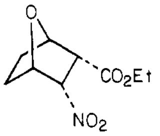
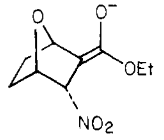
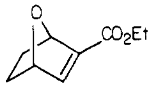
Alternatively it could have been argued that the sequence of events leading to **5** involves initial protonation of **13** from the exo face followed by proton abstraction–reprotonation adjacent to the carbethoxy group in **16** so as to alleviate the severe steric interaction between the nitro and the carbethoxy groups. The major drawback with the latter mechanism is that one would have expected enolate **17** to undergo rapid β-elimination of either the nitro group or the C(7) oxa bridge. Note that treatment of either **4** or **6** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing methylene chloride affords olefin **18** in excellent yield via loss of the β-nitro group.



16

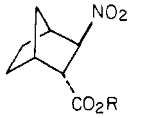


17

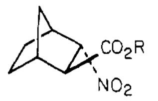


18

In a separate series of experiments norborane derivative **19** (prepared by reduction of the corresponding nor-



19, R = Me
20, R = H



21, R = Me
22, R = H

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(2) Grieco, P. A; Zelle, R. E.; Lis, R.; Finn, J. *J. Am. Chem. Soc.* **1983**, *105*, 1403.

(3) The structures of acids **5** and **7** were readily established by examination of their ^1H NMR spectra (see Experimental Section). In the case of **5** the C(3) exo proton appears at δ 5.41 (ddd) with $J_{3,4}$ = 4.0 Hz. In contrast, the C(3) endo proton in **7** appears as a simple doublet centered at δ 5.16 with $J_{2,3}$ = 6.1 Hz. Note there is no coupling between the C(3) and C(4) protons since the dihedral angle bewteen these protons is ca. 90°.

(4) Cf. Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299. Also see: Guildford, A. J.; Turner, R. W. *J. Chem. Soc., Chem. Commun.* **1983**, 466. Kozikowski, A. P.; Kuniak, M. P. *J. Org. Chem.* **1978**, *43*, 2083. Stork, G.; van Tamelen, E. E.; Friedman, L. J.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1953**, *75*, 384.

(5) Nitro compounds **10** and **11** were prepared from the corresponding 2-nitro-7-oxabicyclo[2.2.1]hept-5-enes [Eggelte, T. A.; deKoning, H.; Huisman, H. O. *Heterocycles* **1976**, *4*, 19] by reduction (H_2, 10% Pd/C, EtOAc).

(6) Kozikowski, A. P.; Ames, A. *J. Am. Chem. Soc.* **1981**, *103*, 3923.

(7) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439.

bornene[8]) upon treatment with 10% potassium hydroxide in tetrahydrofuran at 0 °C gave rise exclusively and in quantitative yield to nitro acid **20**. Similarly exposure of β-nitro ester **21** to base gave rise to nitro acid **22** as the sole product. It remains unclear why the norbornane derivatives behave differently than the 7-oxabicyclo[2.2.1]heptane derivatives **4** and **6**.

Experimental Section

Proton nuclear magnetic resonance (NMR) spectra were taken at 220 MHz (Varian HR-220) or at 360 MHz (Nicolet NT-360) as indicated. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (δ 0.0). Infrared (IR) spectra were taken on a Perkin-Elmer 298 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Melting points were obtained on a Fisher-Johns hot-stage melting point apparatus and are uncorrected.

Ethyl 2-*exo*,3-*endo*-3-Nitro-7-oxabicyclo[2.2.1]heptane-2-carboxylate (4) and Ethyl 2-*endo*,3-*exo*-3-Nitro-7-oxabicyclo[2.2.1]heptane-2-carboxylate (6). To a stirred solution of olefins **1** and **2** (7.21 g, 33.8 mmol, 4:1 mixture, respectively) in 140 mL of absolute methanol containing 59.0 g (304 mmol) of suspended potassium azodicarboxylate cooled to 0 °C was added dropwise, over an 8-h period, a solution of acetic acid (35 mL) in 70 mL of dry methanol. After the addition was complete, the reaction was warmed to room temperature, and stirring was continued for 12 h. The solution was concentrated in vacuo, and the residue was dissolved in 350 mL of water. The aqueous solution was extracted with ether (3 × 175 mL), and the combined ethereal extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in 50 mL of ether and flushed through an alumina plug to afford 6.81 g (95%) of **4** and **6** (4:1 mixture, respectively) as a light yellow oil. Separation was accomplished on a Waters Prep LC/system 500A using two Prep PAK-500/silica gel cartridges (57 mm × 30 cm, ethyl acetate–hexane, 3:16, flow rate 300 mL/min, two recycles).

Compound 4: R_f 0.41 (ether–hexane, 2:3); IR ($CHCl_3$) 3010, 2980, 2960, 2800, 1731, 1551, 1468, 1445, 1374, 1354, 1328, 1312, 1295, 1281, 1243, 1188, 1138, 1113, 1093, 1054, 1033, 1025, 1007, 993, 983, 940, 923, 908, 865, 850, 819, 653 cm^{-1}; NMR (220 MHz, $CDCl_3$) δ 1.30 (t, 3 H, J = 7.0 Hz), 1.49–1.97 (m, 4 H), 3.32 (d, 1 H, J = 4.5 Hz), 4.16 (q, 2 H, J = 7.0 Hz), 4.84 (d, 1 H, J = 5.0 Hz), 4.92 (t, 1 H, J = 5.0 Hz), 5.27 (dd, 1 H, J = 4.5, 5.0 Hz). An analytical sample was prepared by recrystallization from ether–pentane, mp 35.0–36.0 °C. Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.32; H, 6.08; N, 6.40.

Compound 6: R_f 0.37 (ether–hexane, 2:3); IR ($CHCl_3$) 3020, 2980, 2975, 2930, 2900, 2875, 1732, 1554, 1465, 1442, 1377, 1350, 1324, 1318, 1293, 1269, 1250, 1224, 1190, 1068, 1051, 1029, 1018, 1010, 977, 942, 928, 913, 899, 860, 829, 818, 656 cm^{-1}; NMR (220 MHz, $CDCl_3$) δ 1.28 (t, 3 H, J = 7.0 Hz), 1.36–1.91 (m, 4 H), 3.77 (br s, 1 H), 4.15 (q, 2 H, J = 7.0 Hz), 4.80 (m, 2 H), 5.03 (d, 1 H, J = 5.0 Hz). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 49.97; H, 6.00; N, 6.53.

2-*exo*,3-*endo*-3-Nitro-7-oxabicyclo[2.2.1]heptane-2-carboxylic Acid (5). To a stirred solution of β-nitro ester **4** (239 mg, 1.11 mmol) in 1.2 mL of tetrahydrofuran cooled to 0 °C was added 1 mL of a 10% aqueous potassium hydroxide solution. The reaction mixture was stirred for 20 min, diluted with water (5 mL), and washed with ether (10 mL). The aqueous layer was acidified at 0 °C with concentrated hydrochloric acid to pH 3 and was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo, leaving 198 mg (97%) of carboxylic acid **5** as a crystalline solid. Recrystallization from methylene chloride–pentane afforded colorless flakes: mp 166.0–167.5 °C; IR (KBr) 3660–2500, 3000, 2970, 2915, 2580, 1735, 1722, 1544, 1470, 1468, 1452, 1405, 1380, 1343, 1327, 1310, 1278, 1240, 1201, 1185, 1180, 1175, 1136, 1080, 1052, 1026, 1003, 991, 971, 941, 917, 909, 900, 853, 815, 780, 763, 718, 665, 639 cm^{-1}; NMR (220 MHz, acetone-d_6) δ 1.50–2.13 (m, 4 H), 3.49 (d, 1 H, J = 4.0 Hz), 4.98 (d, 1 H, J = 5.0 Hz), 5.06 (t, 1 H, J = 5.0 Hz), 5.41 (ddd, 1 H, J = 2.0, 4.0, 5.0 Hz). Anal. Calcd for $C_7H_9NO_5$: C, 44.93; H, 4.85; N, 7.48. Found: C, 45.05; H, 4.87; N, 7.20.

Preparation of 2-*exo*,3-*endo*-3-Nitro-7-oxabicyclo[2.2.1]heptane-2-carboxylic Acid (5) from Ethyl 2-*endo*,3-*exo*-3-Nitro-7-oxabicyclo[2.2.1]heptane-2-carboxylate (6). A solution of 261 mg (1.21 mmol) of β-nitro ester **6** in 1.5 mL of tetrahydrofuran was treated at 0 °C for 20 min with 2.2 mL of a 10% aqueous potassium hydroxide solution. After 20 min at 0 °C, the reaction was quenched with concentrated hydrochloric acid. The product was isolated by extraction with ether (2 × 25 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure, leaving 220 mg (98%) of a 5.1:1.0 mixture of carboxylic acids **5** and **7** which were separated on Waters μ-Porasil column (7.8 mm × 30 cm; 9:1:0.09 hexane–ethyl acetate–acetic acid; flow rate 8 mL/min; chart speed 1 cm/min), giving rise in order of elution to 170 mg (75%) of carboxylic acid **5**, mp 166.0–167.0 °C (retention time 8.7 min), which was identical in all respects with the sample of **5** prepared above from **4** and 34 mg (15%) of carboxylic acid **7**, mp 119.5–121.0 °C (retention time 12.6 min): IR (KBr) 3600–2500, 1725, 1555, 1460, 1410, 1375, 1300, 1278, 1260, 1190, 1080, 1055, 1025, 1000, 920, 856, 820, 785, 710 cm^{-1}; NMR (360 MHz, acetone-d_6) δ 1.68 (m, 3 H), 1.90 (m, 1 H), 3.84 (br s, 1 H), 4.96 (t, 1 H, J = 4.8 Hz), 5.08 (d, 1 H, J = 4.5 Hz), 5.16 (d, 1 H, J = 6.1 Hz). Anal. Calcd for $C_7H_9NO_5$: C, 44.93; H, 4.85; N, 7.48. Found: C, 45.13; H, 4.89; N, 7.39.

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (CA 28865) from the National Cancer Institute. The 360-MHz NMR instrument (Nicolet) used in the above studies was purchased in part through funds provided by the National Science Foundation (Grant No. CHE-81-05004).

Registry No. **1**, 89299-58-1; **2**, 89299-59-2; **4**, 89299-57-0; **5**, 89299-54-7; **6**, 89299-55-8; **7**, 89299-56-9; **10**, 89210-62-8; **11**, 58564-86-6; **19**, 89210-63-9; **20**, 89210-64-0; **21**, 89299-60-5; **22**, 89299-61-6.

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[8] Blom, N. F.; Edwards, D. M. F.; Field, J. S.; Michael, J. P. *J. Chem. Soc., Chem. Commun.* **1980**, 1240.