Experimental Section

Melting points were determined in capillary tubes with Thomas-Hoover apparatus and are uncorrected. Column chromatography was performed on a medium-pressure system which included a Milton Roy D pump and LDC chromatography columns. Columns were packed with Merck 230–400 mesh silica gel 60. Preparations of representative compounds are given below. Reaction data for all products are summarized in Table I and supplementary material.

***N*-Ethyl-3-(cyanimino)-3-ethoxypropanamide (3a).** Dry HCl gas was bubbled into a solution of 17.03 g (0.152 mol) of *N*-ethyl-2-cyanoacetamide and 6.98 g (0.152 mol) of dry ethanol in 300 mL of dry THF at 0 °C for 10 min. After being stirred for 2 h, the mixture was concentrated in vacuo. The residue was crystallized from ethyl acetate to yield 15.52 g (0.0798 mol, 52%) of iminium ester hydrochloride **2**. This material was stirred for 16 h in 600 mL of toluene with 3.35 g (0.0798 mol) of cyanamide which had been purified by ether extraction. The toluene was filtered through cotton. The filtrate was concentrated in vacuo to yield 6.24 g (43%) of crystalline *N*-ethyl-3-(cyanimino)-3-ethoxypropanamide. This was recrystallized from EtOAc/cyclohexane, mp 68.5–70.0 °C, and used without further purification.

Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.44; H, 7.15; N, 22.94. Found: C, 52.46; H, 7.24; N, 22.22.

***N*-*n*-Butyl-3-(cyanimino)-3-ethoxypropanamide (3b).** The basic procedure for the *N*-ethyl compound (vide supra) was followed. Thus, 36 g (0.257 mol) of 2-cyano-*N*-*n*-butylacetamide and 11.82 g (0.257 mol) of ethanol were converted to the iminium ester hydrochloride, which was dissolved in 500 mL of methylene chloride and reacted with 10.8 g (0.26 mol) of cyanamide. After 20 h, the solution was filtered. The filtrate was partitioned with aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated in vacuo to give 38.21 g (70% overall) of a yellow oil which was *N*-*n*-butyl-3-(cyanimino)-3-ethoxypropanamide. This was clean by TLC. Spectral data were consistent with the assigned structure. This material was used without further purification.

***N*-Ethyl-3-morpholino-3-(cyanimino)propanamide (4b).** A 2.60-g (0.0142-mol) sample of *N*-ethyl-3-ethoxy-3-(cyanimino)propanamide was stirred with 2.94 g (0.034 mol) of morpholine in 250 mL of toluene. After 3 h, the resultant white crystalline product was filtered to yield 2.66 g (84%) of pure *N*-ethyl-3-morpholino-3-(cyanimino)propanamide, mp 188–189.5 °C.

Anal. Calcd for $C_{10}H_{16}N_4O_2$: C, 53.55; H, 7.19; N, 24.98. Found: C, 53.54; H, 7.52; N, 25.01.

2-Amino-3-ethyl-6-piperidino-4-pyrimidinone (5a). A solution of 1.21 g (0.00545 mol) of *N*-ethyl-3-(cyanimino)-3-piperidinopropanamide (**4a**) in 40 mL of tetrahydrofuran and 5 mL of dimethylformamide was stirred with 2.42 g (0.022 mol) of potassium *tert*-butoxide for 2 h. The mixture was partitioned between methylene chloride and aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed (4% methanol/methylene chloride on silica gel) to yield 1.05 g (87%) of crystalline product. This was recrystallized from ethyl acetate to yield 0.95 g of pyrimidinone **5a**, mp 276–277 °C.

Anal. Calcd for $C_{11}H_{18}N_4O$: C, 59.43; H, 8.16; N, 25.21. Found: C, 59.48; H, 8.26; N, 25.47.

2-Amino-3-*n*-butyl-6-ethoxy-4-pyrimidinone (6). A solution of 7.60 g (0.036 mol) of *N*-*n*-butyl-3-(cyanimino)-3-ethoxypropanamide in 100 mL of tetrahydrofuran was treated with 8.07 g (0.072 mol) of potassium *tert*-butoxide. After 10 h, the mixture was partitioned between aqueous sodium bicarbonate and methylene chloride. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was chromatographed (4% ethanol in methylene chloride on silica gel) and crystallized from ethyl acetate and cyclohexane to yield 1.22 g (17%) of white crystalline **6**, mp 109–111 °C.

Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.92; H, 8.69; N, 20.32.

***N*-Ethyl-3-[(aminocarbonyl)imino]-3-morpholinopropanamide (7b).** A solution of 1.00 g (0.00446 mol) of *N*-ethyl-3-(cyanimino)-3-morpholinopropanamide (**4b**) in 10 mL of acetic acid and 1 mL of concentrated hydrochloric acid was stirred for 6.5 h. The mixture was partitioned between sodium carbonate and methylene chloride. The organic phase was dried over sodium sulfate and concentrated in vacuo to give 0.56 g (52%) of crystalline **7b**. This was recrystallized from methylene chloride/cyclohexane to yield 0.54 g of **7b**, mp 115–115.5 °C.

Anal. Calcd for $C_{10}H_{18}N_4O_3$: C, 49.57; H, 7.49; N, 23.13. Found: C, 49.59; H, 7.39; N, 22.94.

Registry No.—**1** (R = Et), 15029-36-4; **1** (R = *n*-Bu), 39581-21-0; **2** (R = Et), 69309-04-2; **2** (R = *n*-Bu), 69309-05-3; **3a**, 69309-06-4; **3b**, 69309-07-5; **4a**, 69308-94-7; **4b**, 69308-95-8; **4c**, 69352-31-4; **4d**, 69352-32-5; **4e**, 69331-25-5; **5a**, 69308-96-9; **5b**, 69308-97-0; **5c**, 69308-98-1; **5d**, 69308-99-2; **5e**, 69331-24-4; **6**, 69309-08-6; **7a**, 69331-23-3; **7b**, 69309-00-8; **7c**, 69309-01-9; **7d**, 69309-02-0; **7e**, 69309-03-1; cyanamide, 420-04-2; pyrrolidine, 123-75-1; morpholine, 110-91-8; diethylamine, 109-89-1.

Supplementary Material Available: Full NMR data for the above compounds (1 page). Ordering information is given on any current masthead page.

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Hydrolysis of Model Compounds for α-Hydroxylation of the Carcinogens *N*-Nitrosopyrrolidine and *N'*-Nitrosonornicotine

Stephen S. Hecht* and Chi-hong B. Chen

Division of Environmental Carcinogenesis, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York 10595

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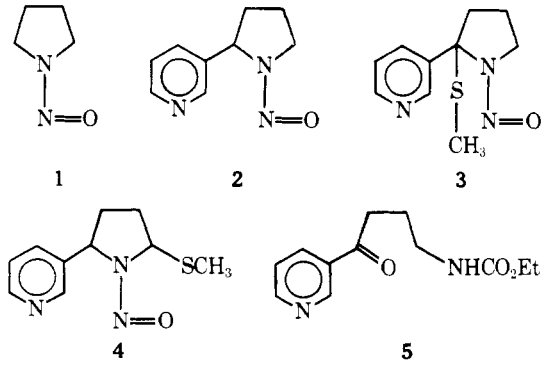
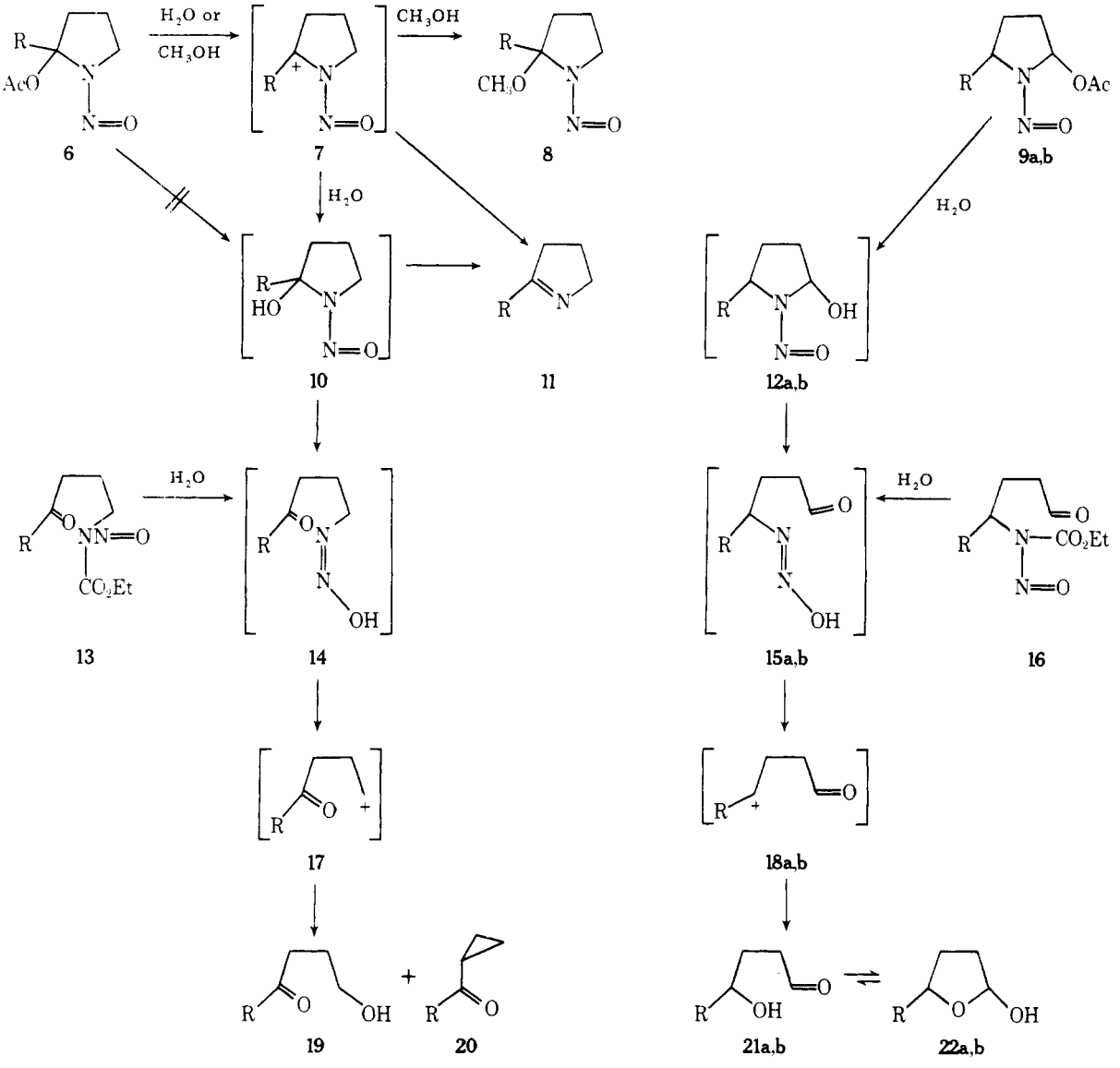
The environmental carcinogens *N*-nitrosopyrrolidine (**1**) and *N'*-nitrosonornicotine (**2**) are most likely converted to their ultimate carcinogenic forms by metabolic α-hydroxylation.[2-5] Since the resulting α-hydroxynitrosamines (**10**, **12a,b**, Scheme I) are unstable, the chemistry of α-hydroxylation is best studied by the use of model compounds. α-Acetoxynitrosamines have been proven to be useful compounds in studying the chemical and biological properties of α-hydroxynitrosamines.[3,6-12] In order to determine the nature of the products of α-hydroxylation of **1** and **2**, the hydrolyses of 2-acetoxy-*N*-nitrosopyrrolidine (**9b**), 2'-acetoxy-*N'*-nitrosonornicotine (**6**), and 5'-acetoxy-*N'*-nitrosonornicotine (**9a**) were studied. To further clarify the chemistry of these α-oxidized cyclic nitrosamines, the hydrolyses of nitrosourethanes **13** and **16** were also studied.

The syntheses of 2-acetoxy-*N*-nitrosopyrrolidine (**9b**) and 4-(*N*-carbethoxy-*N*-nitrosamino)butanal (**16**) have been described.[3,4] For the preparation of **6** and **9a**, **2** was converted to a mixture of α-carbanions with lithium diisopropylamide. Reaction with dimethyl disulfide[13] gave a mixture of 2'-thiomethyl-*N'*-nitrosonornicotine (**3**) and 5'-thiomethyl-*N'*-nitrosonornicotine (**4**) in which the former predominated. The



Scheme I



6, 7, 8, 9a, 10, 11, 12a, 13, 14, 15a, 17, 18a, 19, 20, 21a, 22a, R = 3-Pyr
9b, 12b, 15b, 16, 18b, 21b, 22b, R = H

preferential formation of **3** presumably resulted from the charge-stabilizing ability of the 3-pyridyl group. The thioethers **3** and **4** were separated and each was allowed to react with chlorine and triethylammonium acetate.[3] The acetates **6** and **9a** were obtained in 10–20% yield; however, the 2′-acetate **6** was contaminated with 10–20% myosmine (**11**) which formed during purification of **6**. Yields of pure **6** were only 1–2%. The nitrosourethane **13** was prepared by reaction of myosmine (**11**) with ethyl chloroformate to give urethane **5**, which was nitrosated with N_2O_4. This scheme was feasible because **11** was in equilibrium with the corresponding amino ketone under the conditions used for reaction with ethyl chloroformate.

The hydrolyses of **6**, **9a**, and **9b** were studied. In the case of **9b**, the hydrolysis was done with catalysis by hog liver esterase and its half-life was 30 min. The major product (60–70%) from hydrolysis of **9b**, as reported previously,[4] was the cyclic hemiacetal 2-hydroxytetrahydrofuran (**22b**). Minor amounts of butenals were also observed. 5′-Acetoxy-*N*′-nitrosonornicotine (**9a**) underwent hydrolysis without catalysis ($t_{1/2} \simeq 180$ min) or in the presence of esterase to give 5-(3-pyridyl)-2-hydroxytetrahydrofuran (**22a**) as the major product isolated (60–70%); 3-pyridylbutenals were not observed. The uncatalyzed hydrolysis of 2′-acetoxy-*N*′-nitrosonornicotine (**6**) was more rapid ($t_{1/2} \simeq 10$ min) and gave myosmine (**11**) (50%) and 4-hydroxy-1-(3-pyridyl)-1-butanone (**19**, 10%). The same products and yields were observed in the presence of esterase. When **6** was allowed to decompose in methanol, myosmine (**11**) and 2′-methoxy-*N*′-nitrosonornicotine (**8**) were formed. When 5′-acetoxy-*N*′-nitrosonornicotine (**9a**) was heated in methanol, it was recovered unchanged. Nitrosourethanes **13** and **16** gave the keto alcohol **19** and 2-hydroxytetrahydrofuran (**22b**),[4] respectively, as the major products (40–50% yield) when hydrolyzed with catalysis by esterase or base. Hydrolysis of **13** also gave minor amounts (1–2%) of **11** and cyclopropyl 3-pyridyl ketone (**20**).[14]

The results are most readily interpreted according to Scheme I. Both **9a** and **9b** were hydrolyzed to the α-hydroxynitrosamines **12a,b**. These unstable intermediates opened to diazohydroxides **15a,b**, which decomposed to carbonium ions **18a,b**.[15,16] The latter reacted with H_2O to give hydroxyaldehydes **21a,b** which exist predominantly as the cyclic hemiacetals **22a,b**. The intermediacy of **15b** as a decomposition product of **12b** is supported by the high yields of **22b** from both **9b** and **16**.[17]

The lower stability of **6** compared to **9a,b** under the conditions studied and the products formed in the solvolyses with H_2O and methanol indicate that **6** dissociated predominantly

by cleavage of the 2′-oxygen bond to give carbonium ion **7**. Loss of NO^+ from **7** yielded myosmine (**11**). Reaction of **7** with H_2O gave **10** which opened to diazohydroxide **14** resulting in formation of keto alcohol **19**. The preferential formation of carbonium ion **7** from **6** was also supported by observation of 2′-methoxy-*N*′-nitrosonornicotine (**8**) as a product of the decomposition of **6** in methanol; 4-methoxy-1-(3-pyridyl)-1-butanone, which would have resulted from formation of **10** in the methanolysis of **6**, was not detected. Decomposition of α-acetoxynitrosamines by loss of acetate has also been observed in the solvolysis of (1-acetoxy-1-phenylmethyl)-methylnitrosamine.[12]

The results suggest that **6** is a poor model compound for **10** since formation of **10** from **6** is apparently only a minor pathway. The nitrosourethane **13** is a more satisfactory model with respect to electrophilic intermediates which may be formed by 2′-hydroxylation of *N*′-nitrosonornicotine. However, for **9a** and **9b**, the results support the intermediacy of α-hydroxynitrosamines **12a** and **12b**.

Experimental Section

Infrared spectra were run on a Perkin-Elmer Model 267 grating infrared spectrophotometer in $CHCl_3$ solution or as liquid films. NMR spectra were determined with a Hitachi Perkin-Elmer Model R-24 spectrometer in $CDCl_3$ solution and are reported as parts per million downfield from Me_4Si as internal reference. UV spectra were determined with a Cary Model 118 instrument. Mass spectra and combined GLC–MS were run with a Hewlett Packard Model 5982A dual source instrument using a membrane separator. GLC analysis was done on a Hewlett Packard Model 5711 instrument equipped with a flame ionization detector and a 6 ft × 1/8 in. 10% Carbowax 20M-TPA on gas Chromosorb Q column with helium as carrier gas at a flow rate of 60 mL/min. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

2′-Thiomethyl-*N*′-nitrosonornicotine (3) and 5′-Thiomethyl-*N*′-nitrosonornicotine (4). A solution of lithium diisopropylamide (103 mmol) was prepared in anhydrous THF (250 mL) from 15 mL of freshly distilled diisopropylamine and 43 mL of 2.4 M *n*-BuLi at −78 °C. To this was added 17.7 g (100 mmol) of *N*′-nitrosonornicotine (**2**)[18] in 20 mL of THF while the temperature was maintained at −78 °C. After 10 min, 44 mL of dimethyl disulfide was added. Stirring was continued for 3 h at −78 °C. After being warmed to 20 °C, the mixture was extracted with CH_2Cl_2 and the CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to give a residue which was chromatographed on silica gel with elution by benzene, benzene–$CHCl_3$, $CHCl_3$, and $CHCl_3$–MeOH. This gave 8.2 g (40%) of 2′-thiomethyl-*N*′-nitrosonornicotine (**3**) as an oil. The 5′-isomer **4** coeluted with some **3** and unreacted **2**. It was purified by column chromatography on activity II–III alumina with elution by benzene–Et_2O and Et_2O followed by preparative TLC (alumina, Et_2O). The yield of the oil **4** was 1–2%.

Spectral properties (**3**): IR (film) 1590, 1580, 1480, 1430, 1290, 1230, 1210, 1160, 1130, 1060, 1020 cm^{-1}; NMR δ 8.8–7.2 (4 H, m, pyridyl H), 3.81 (2 H, t, 5′-CH_2), 2.45 (4 H, m, CH_2CH_2), 2.00 (3 H, s, CH_3); MS *m/e* (rel intensity) 193 (44.3), 176 (100), 118 (92.0), 105 (28.7). Anal. Calcd for $C_{10}H_{13}N_3OS$: C, 53.79; H, 5.87; N, 18.82. Found: C, 53.65; H, 5.99; N, 18.68.

Spectral properties (**4**): IR (film) 1590, 1580, 1480, 1425, 1320, 1285, 1230, 1210, 1160, 1130, 1060, 1020 cm^{-1}; NMR δ 8.8–7.1 (4 H, m, pyridyl H), 6.2–4.8 (2 H, m, 2′-CH and 5′-CH), 2.80–1.80 (7 H, m + s at 2.30, CH_2CH_2 + SCH_3); MS (*m/e*, rel intensity) 223 (M^+, 0.9), 193 (20.6), 176 (39.9), 145 (24.0), 118 (100). Anal. Calcd for $C_{10}H_{13}N_3OS$: C, 53.79; H, 5.87; N, 18.82. Found: C, 53.59; H, 5.99; N, 18.50.

2′-Acetoxy-*N*′-nitrosonornicotine (6) and 5′-Acetoxy-*N*′-nitrosonornicotine (9a). To a solution of 2′-thiomethyl-*N*′-nitrosonornicotine (**3**) (940 mg, 4.0 mmol) in 4 mL of CH_2Cl_2 at −78 °C was added 1.76 mL (4.0 mmol) of a 5% vol–vol solution of Cl_2 in CH_2Cl_2. Immediately following addition of the Cl_2, 20 mL of a 1.0 M solution of triethylammonium acetate (from 7.0 mL of redistilled Et_3N and 3.0 mL of HAc in a total volume of 50 mL) in CH_2Cl_2 was added in one portion. Stirring was continued at −78 °C for 1 h, followed by stirring at 20 °C for 1 h. The resulting mixture was diluted to 25 mL with CH_2Cl_2 and washed quickly with 2 × 25 mL of H_2O, dried (Na_2SO_4), and concentrated. The residue was purified in two portions by rapid elution with $CHCl_3$ through 10 g of Florisil. Some decomposition to myosmine (**11**) took place during this purification. The fractions eluting first (10 mg) were free of **11** but the later fractions (170 mg) contained up to 20% **11**. The 2′-acetate **6** was a yellow oil: IR ($CHCl_3$) 1748, 1440, 1420, 1170, 1079, 1010, 951 cm^{-1}; NMR δ 9.0–7.0 (4 H, m, pyridyl H), 3.82 (2 H, t, 5′-CH_2), 3.3–1.7 (7 H, m, CH_3COO, CH_2CH_2); MS (*m/e*, rel intensity) 193 (25), 176 (37), 145 (17), 118 (100), 91 (18), 74 (11).

The 5′-acetate **9a** was prepared the same way except that the triethylammonium acetate was added 10 min after addition of Cl_2. The crude product was chromatographed on Silicar CC-7 with elution by $CHCl_3$. The chromatography was followed by TLC (silica gel 9/1 Et_2O–CH_3OH or 1/1 $CHCl_3$–CH_3CN) to give pure **9a** (10–20%) as a yellow oil: IR ($CHCl_3$) 1745, 1580, 1470, 1140, 1022, 950 cm^{-1}; NMR δ 8.0–6.9 (5 H, m, pyridyl H + 5′-CH), 5.5–4.8 (1 H, m, 2′-CH), 3.0–1.5 (7 H, m, CH_3COO + CH_2CH_2); MS *m/e* (rel intensity) 235 (M^+, 9), 193 (10), 191 (11), 176 (10), 118 (75), 106 (100), 93 (37), 78 (15).

The 5′-acetate **9a** was stable indefinitely in $CHCl_3$ at 10 °C but the 2′-acetate **6** decomposed after several days under these conditions.

4-(*N*-Carbethoxyamino)-1-(3-pyridyl)-1-butanone (5). To a mixture of myosmine (**11**)[18] (1 g, 6.9 mmol), benzene (1 mL), H_2O (3 mL) and K_2CO_3 (1 g) was added ethyl chloroformate (1 g, 9.2 mmol) with cooling and stirring. After the addition was complete, the mixture was stirred at 20 °C for 5 h and then stored in the cold for 3 days. The mixture was extracted with $CHCl_3$ and the $CHCl_3$ layers were dried (Na_2SO_4) and concentrated to give a residue which was purified by column chromatography on silica gel with elution by benzene, benzene–$CHCl_3$, and $CHCl_3$–MeOH to give **5**: mp 88–89 °C (0.5 g, 30%); IR (Nujol) 3450, 1705, 1690, 1590, 1530, 1300 cm^{-1}; NMR δ 9.0–7.0 (4 H, m, pyridyl H), 4.85 (1 H, br s, NH), 4.00 (2 H, q, CH_2OCO), 3.05 (4 H, m, CH_2N and pyr-$COCH_2$), 1.90 (2 H, q, CCH_2C), 1.15 (3 H, m, CH_3); MS *m/e* (rel intensity) 236 (M^+, 0.7), 122 (100), 121 (68), 106 (81), 78 (70). Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.01; H, 6.83; N, 11.86. Found: C, 61.05; H, 7.01; N, 11.81.

4-(*N*-Carbethoxy-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone (13). The urethane **5** (74 mg, 0.3 mmol) was dissolved in 3 mL of CH_2Cl_2 in which 50 mg of $NaHCO_3$ was suspended. The suspension was stirred at −30 °C under N_2 and a solution of 50 mg of N_2O_4 in 0.1 mL of CH_2Cl_2 was added slowly. After addition was complete, stirring was continued for 1 h with cooling. The resulting mixture was added to 5 mL of 10% aqueous $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC (silica, $CHCl_3$–CH_3CN 2/1): IR (film) 1750, 1690, 1590, 1510, 1470, 1380, 1280, 1140, 990 cm^{-1}; NMR δ 9.3–7.2 (4 H, m, pyridyl H), 4.55 (2 H, q, CH_2O), 3.92 (2 H, t, CH_2N), 2.95 (2 H, t, pyr-$COCH_2$), 2.00 (2 H, q, CCH_2C), 1.50 (3 H, t, CH_3); MS *m/e* (rel intensity) 235 (22), 148 (31), 121 (35), 106 (100), 78 (47).

Solvolyses of Model Compounds. (a) Determination of Half-Lives. The half-lives of **6** and **9a** in H_2O at 37 °C were determined by extracting aliquots with $CHCl_3$ and measuring the intensity of the carbonyl absorption at 1750 cm^{-1}. The decomposition of **9b** was followed by disappearance of its UV absorption at 348 nm.

(b) Product Studies. The acetate **6** (free of **11**) or **9b** (0.102 mmol) was incubated at 37 °C in 15 mL of pH 7 phosphate buffer with 130 units of esterase [EC 3.1.1.1. hog liver esterase (Sigma): 1 unit hydrolyzes 1 μmol of butyrate per min at pH 8.0 and 25 °C] or without esterase for 10 half-lives. The nitrosourethane **13** (5.6 mg, 0.021 mmol) in 3 mL of pH 7 buffer was incubated for 72 h with esterase (65 units); **13** was also allowed to decompose in 1 N aqueous NaOH.

The aqueous solutions were extracted five times with equal volumes of $CHCl_3$ and the combined $CHCl_3$ layers dried (Na_2SO_4) and concentrated. The residues were analyzed by GC and GC–MS using a temperature program of 150 °C for 8 min, then 8 °C/min to 200 °C. Relative retention times of products: **20**,[19] 0.78; **11**, 1.00; **22a**,[5] 2.10; **19**,[20] 2.15. Absolute retention time of **11**, 12 min.

Solvolyses of **6** (1 h, 37 °C) and **9a** (24 h, 37 °C) in MeOH were done similarly except that the MeOH was evaporated and the products analyzed directly by GC as above. Compound **8** (relative retention time, 2.19) gave MS, *m/e* (rel intensity) 207 (M^+, 6), 176 (2), 163 (11), 148 (20), 135 (76), 134 (100), 118 (23), 105 (32), 78 (24) and NMR δ 3.2 (s, CH_3O), consistent with the assigned structure. The same compound was isolated from reaction of **3** with Cl_2 followed by Et_3N and MeOH under conditions as described for synthesis of **6** and **9a**. The mixture resulting from solvolysis of **6** in MeOH was also analyzed by GC–MS with specific ion monitoring at *m/e* 106 for detection of any 4-methoxy-1-(3-pyridyl)-1-butanone.

Registry No.—**2**, 53759-22-1; **3**, 69204-75-7; **4**, 69204-76-8; **5**, 69204-77-9; **6**, 68743-64-6; **8**, 69204-78-0; **9a**, 68743-65-7; **9b**, 59435-85-7; **11**, 532-12-7; **13**, 68743-68-0; **19**, 59578-62-0; **20**, 24966-13-0; **22a**, 53798-73-5; dimethyl disulfide, 624-92-0; ethyl chloroformate, 541-41-3; *N*-nitrosopyrrolidine, 930-55-2.

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(16) Alternatively, **15a,b** may be converted to the corresponding diazo compounds. The carbonium ions **17** and **18a,b** may be cyclic oxonium ions.
(17) The sterochemistry of diazo hydroxides **14** and **15a,b** is not known. NMR showed that the acetate and nitroso groups of **6** and **9b** were anti and that **9a** was a mixture of syn and anti isomers.
(18) M. W. Hu, W. E. Bondinell, and D. Hoffmann, *J. Labelled Compd.*, **10**, 79 (1974).
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(20) S. S. Hecht, C-h. B. Chen, M. Dong, R. M. Ornaf, D. Hoffmann, and T. C. Tso, *Beitr. Tabakforsch.*, **9**, 1 (1977).

An Abbreviated Stereorational Synthesis of [10.10]Betweenanene

James A. Marshall* and Kyoo-Hyun Chung

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

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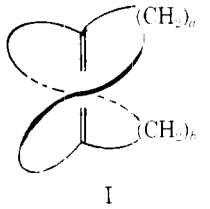
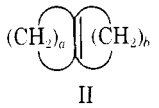
[*a.b*]Betweenanenes (I) are a novel class of fused bicyclic *trans*-cycloalkenes in which the double bond is common to



I

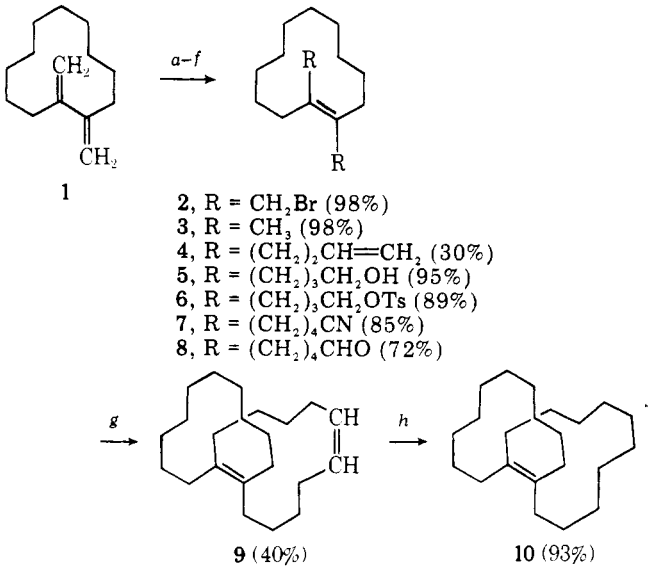


II

both rings.[1] This unique geometric arrangement requires the bridging chains to crisscross above and below the double bond, at least for smaller values of *a* and *b*, thereby effectively burying it and sharply diminishing its reactivity. Cahn, Ingold, and Prelog, in their treatise on molecular chirality,[2] appear to have been the first to recognize these types of structures [they called them "bis(*trans*-polymethylene)ethylenes"] and pictured [6.6]betweenanene[3] as a hypothetical example of a molecule possessing planar chirality.

We independently perceived the betweenanene structure (I) some ten years ago in connection with studies involving photoinitiated ionic additions to cycloalkenes.[4] Recently, we completed a stereochemically definitive synthesis of [10.10]betweenanene (I, $a = b = 10$), the first known bis(*trans*-polymethylene)ethylene, and its cis isomer II ($a = b = 10$).[1] At about the same time, Nakazaki and co-workers reported the photoisomerization of bicyclo[10.8.0]eicos-1(12)-ene (II; $a = 10$, $b = 8$) to [10.8]betweenanene (I; $a = 10$, $b = 8$), thus demonstrating an alternative approach to betweenanenes.[5] More recent efforts in our laboratory have been aimed at developing efficient stereocontrolled routes to functionalized betweenanenes for planned studies of the chemical and physical properties of selected members of this unique class of cycloalkenes. This note describes a recent step in this direction.

Scheme I



[a] Br_2, $CHCl_3$. [b] CH_2=$CHCH_2MgCl$, THF, HMPA. [c] $(SiAm)_2BH$, THF; H_2O_2, NaOH. [d] *p*-TsCl, C_5H_5N. [e] NaCN, Me_2SO. [f] $(i\text{-}Bu)_2AlH$, ether; H_2O, NH_4Cl. [g] $TiCl_3$, Zn(Cu), DME. [h] H_2/Pt–C, EtOAc.

The synthesis, outlined in Scheme I, originates with 1,2-dimethylenecyclododecane (1), available in quantity from cyclododecanone via aminomethylation, Wittig condensation, quaternization, and Hoffman elimination.[6] Bromination of diene 1 afforded the *trans*-dibromide **2** as a solid in 98% yield. Analogous bromination of 2,3-dimethyl-1,3-butadiene has been shown to yield *trans*-2,3-dimethyl-1,4-dibromo-2-butene.[7] Proof for the stereochemistry of dibromide **2** was secured through its reduction with K-selectride[8] in 98% yield to *trans*-1,2-dimethylcyclododecene.[9]

After numerous trials with Grignard and organolithium reagents, as well as organocuprates, in various solvents, we found that allylmagnesium chloride in tetrahydrofuran–hexamethylphosphoramide gave the highest yield of triene **4** (30%). In all cases reduction–elimination to diene **1** predominated. This behavior stands in sharp contrast to that of the aforementioned 1,4-dibromo-2,3-dimethyl-2-butene, which couples almost quantitatively with allylmagnesium chloride.[10]

Further elaboration of the butenyl side chains of triene **4** was effected along standard lines by hydroboration–oxidation to diol **5** and cyanide displacement of the tosylate derivative **6**. The dinitrile **7**, thus obtained in over 80% overall yield, was reduced with diisobutylaluminum hydride to the dialdehyde **8** in 72% yield. Cyclization was effected by the recently reported titanium reagent of McMurry[11] to afford the [10.10]-betweenadiene **9** in 40% yield. While no attempt was made to ascertain the stereochemistry of the disubstituted double bond in this diene, a prominent peak at 970 cm^{-1} in its infrared spectrum suggests a predominance of the trans isomer.[11,12] Hydrogenation over platinum yielded [10.10]betweenanene (**10**), identical with material previously synthesized.[1] While further improvements are expected, the sequence described above represents a sixfold improvement in overall yield compared with our original route.[1]

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