acetal. This reaction parallels the previously reported acetalization of 2-formylimidazole in acidified ethanol.[13] In all acidified solvents containing exchangeable deuterium (DCl, D_2O), rapid exchange of the methyl protons with deuterium was observed.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded as KBr pellets, on a Perkin-Elmer Model 281 IR spectrometer. Polarimetric measurements were done on a Perkin-Elmer Model 241 polarimeter. The ^1H NMR and ^{13}C NMR spectra were acquired in the FT mode, using a Bruker CXP-300 spectrometer at the frequencies of 300 and 75.46 MHz, respectively. Chemical shifts are given in ppm downfield from Me_4Si. The internal standard for ^1H in Me_2SO-d_6 was tetramethylsilane (Me_4Si). The internal standards used for ^{13}C in various solvents were D_2O (*p*-dioxane, 67.4 ppm), Me_2SO-d_6 (Me_2SO-d_6, 39.5 ppm), CD_3OD (CD_3OD, 49.0 ppm). Abbreviations used are s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; mult, multiplet. Multiplicities for the ^{13}C resonances were determined by off-resonance decoupling. Elementary analyses were done by Atlantic Microlab Inc., Atlanta, GA. Chromatography fractions were analyzed at a wavelength of 250 nm on a Tracer HPLC using a C_{18} μ-Bondapak column, Waters Radial Pak, with MeOH (10%), AcOH (0.5%), H_2O (89.5%) as eluant at a flow rate of 1 mL/min. Compound **6** had a retention time of 20 min and compound 1 5.5 min under these conditions.

D-Glucosone (4). A mixture of 13.4 g (37.4 mmol) of D-glucose phenylosazone,[12] 400 mL of ethanol, 667 mL of H_2O, 16.4 mL of glacial acetic acid, and 21.4 mL (210 mmol) of freshly distilled benzaldehyde was heated at reflux under N_2 until solution was complete (approximately 4.25 h). With continued heating, 400 mL of the solution was distilled off while an equal volume of water was added dropwise. The resulting mixture was allowed to stand under N_2 overnight. The precipitate of benzaldehyde phenylhydrazone was removed by filtration and the filtrate concentrated in vacuo (<40 °C) to 400 mL. This solution was in turn extracted with 4 × 150 mL ether and declorized with charcoal. The resulting yellow solution was evaporated to dryness (<40 °C) and the concentrated syrup was taken up in 100 mL of ethanol. Then, 5 g of mixed bed ion-exchange resin was added and the mixture filtered and again evaporated to dryness to give a thick oil, 4.6 g (25.8 mmol, 69%).

4-(1,2,3,4-Tetrahydroxybutyl)-2-acetylimidazole Ethylene Dithioketal (6). A mixture of the above glucosone (4.6 g, 25.8 mmol), 2-methyl-1,3-dithiolane-2-carboxaldehye[5] (**5**; 15.0 g, 101 mmol), and 125 mL of methanol was stirred at room temperature until solution was complete; then 20.0 g of ammonium acetate was added and the mixture was stirred at room temperature for 18 h.

The entire reaction mixture was poured into 600 mL of H_2O (10 mL of 1 N HCl added) and extracted with 4 × 200 mL of ether. [By redistilling the ether extract, 50% of the original pyruvaldehyde thioketal can be recovered.] The resulting aqueous layer was added to a 40 × 3.5 cm Rexyn (poly(styrenesulfonic acid)) column in the H^+ form and the column washed with 1 L of water. The imidazole fraction was then isolated by washing the column with 1 L of cold 4 M NH_4OH solution.

Evaporation of the ammonia extract gave a thick oil, which was purified by washing through an open 15 × 3.5 cm C_{18} μ-Bondapak column, using 0.5% HOAc–H_2O as eluant. Combining the proper fractions after HPLC analysis and evaporation afforded 2.36 g of **6** as the acetate salt, thick oil (7.7 mmol, 30%). Trituration from EtOH–Et_2O afforded an amorphous solid: mp 148–51 °C; IR (KBr) 3360 (s), 3120 (s), 2920 (s), 1620 (w), 1570 (w), 1470, 1420 (s), 1365, 1305, (w), 1275 (w), 1195, 1110, 1090 (s), 1060 (s), 990 (s), 880 cm^{-1}; NMR (as the acetate salt) ^{13}C (D_2O) 151.99 (C2, s), 136.47 (C4, s), 117.20 (C5, d), 73.73, 71.79, 65.90 (CHOH, d), 63.67 (CH_2OH, t) 60.01 ($-C(S_2)$, s), 41.48 (CH_2S, t), 29.35 (CH_3, q) (acetic acid gave peaks at 22.60 (q) and 179.59 (s)); ^1H (CD_3OD) 1.74 ($CH_3C(S)_2$, s), 3.08–3.09 (SCH_2S, mult), 3.18–3.40 (HCO, H_2CO, mult), 4.51 (IM-α HCO, dd), 6.45 (C5H, d); UV (λ_{max}, log ϵ) 226 nm, 3.92 (H_2O, pH 7.0).

2-Acetyl-4-(1,2,3,4-tetrahydroxybutyl)imidazole (1). To a solution of 2.36 g (7.7 mmol) of **6** acetate salt in 25 mL of H_2O was added 3.0 g (17.6 mmol) $AgNO_3$ in 25 mL of H_2O. The mixture was stirred at room temperature for 18 h in the dark, after which time 1.5 mL of concentrated HCl was added and the solution was stirred for an additional 10 min. The AgCl was removed by filtration through a bed of Celite 540 and the filtrate was then passed through a 15 × 2.5 cm C_{18} μ-Bondapak column. The column was washed with water until all of the product (HPLC analyzed) had eluted.

The combined eluant was then passed through a 15 × 2.5 cm Bio-Rad AG1X2 anion exchange resin in the OAc^- form and the eluate was concentrated to 50 mL in vacuo. After 48 h at 5 °C, the resulting crystals were removed by filtration and dried in vacuo to give 684 mg (two crops, 2.97 mmol, 39%) of **1**; recrystallized from H_2O (charcoal); mp 232–3 °C (soften at 224 °C); $[\alpha]^{25}_D$ −12° (*c* 1.17, 1 N HCl); UV (λ_{max}, log ϵ) 289 nm, 4.11 (H_2O, pH 7.0). IR (KBr) 3450, 3320, 3290, 3020, 1665, 1655, 1455, 1435, 1405, 1380, 1255, 1220, 1090, 1020, 955, 880, 790, 645 cm^{-1}. Anal. Calcd. for $C_9H_{14}N_2O_5$: C, 46.96; H, 6.09; N, 12.17. Found: C, 46.31; H, 6.12; N, 12.05.

NMR: ^{13}C (D_2O, DCl, p.H <2) 27.57 ($CH_3C(O)$–, q), 64.19 (CH_2OH, t), 66.22, 72.08, 74.09 (CHOH, d), 120.62 (C5, d), 139.10 (C4, s), 140.54 (C2, s) and 186.27 (C=O, s); ^{13}C (Me_2SO-d_6, free base) 2 tautomers A and B [A] 25.28 ($CH_3C(O)$, q), 63.49 (CH_2OH, t), 67.10, 71.22, 73.73 (CHOH, d), 119.01 (C5, d), 143.73, 146.72 (C2 and C4, s), 188.26 (C=O, s); [B] 25.05 ($CH_3C(O)$, q), 63.25 (CH_2OH, t), 64.69, 71.22, 73.73 (CHOH, d), 127.92 (C5, d), 139.12, 144.26 (C2, C4, s), 188.15 (C=O, s); ^1H (Me_2SO-d_6, free base) 2-tautomers A and B [A + B] 2.47, 2.48 ($CH_3C(O)$, s), 3.35–3.80 (HCO, H_2 CO, mult), 4.30–4.39, 4.58–4.64, 5.01–5.04 (COH, mult), 4.90–4.92 (IM-α HCO, mult), 7.05, 7.21 (C5H, d); ^{13}C (Me_2SO-d_6, DCl, pH <2) 27.09 ($CH_3C(O)$, mult partially deuterated), 63.57 (CH_2OH, t), 65.14, 71.27, 73.20 (CHOH, d), 119.46 (C5, d), 138.71, 139.55 (C2, C4, s), 183.98 (C=O, s); ^1H (Me_2SO-d_6, DCl, pH <2) one tautomer 2.66 (CH_3CO, s), 3.42–3.56 (HCO, H_2CO, mult), 5.06 (IM-α HCO, dd), 7.67 (C5H, d); ^{13}C (CD_3OD, DCl, pH <2) after standing in CD_3OD, DCl for 12 h 23.21 (CH_3C partially deuterated mult), 64.76 (CH_2OH, t), 66.28, 72.62, 74.69 (CHOH, d), 99.05 ($C(OC)_2$, s), 117.20 (C5, d), 137.88, 147.97 (C2, C4, s); ^1H (CD_3OD, DCl, pH <2) standing in CD_3OD, DCl for 12 h, 1.71 (CH_3CO_2, mult partially deuterated), 3.60–3.83 (HCO, H_2CO, mult), 5.12 (IM-α HCO, dd), 7.39 (C_5H, d).

Acknowledgment. We thank Dr. U. Kröplien, Coca-Cola G.m.b.H., Essen, FRG, for sharing in advance his unpublished results on the isolation of **1** from ammonia caramel. We also extend our appreciation to Dr. Jacob H. Goldstein, Chemistry Department, Emory University, for helpful discussions.

A Convenient Synthesis of 2-Acetyl-4(5)-(1(*R*),2(*S*),3(*R*),4-tetrahydroxybutyl)-imidazole

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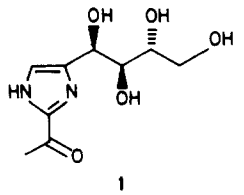
Received October 9, 1984

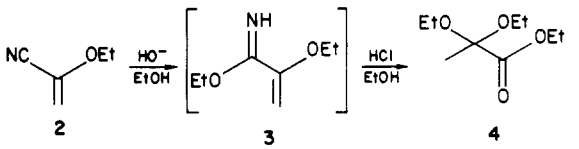
The title compound (**1**), a very minor constituent of Caramel Color III lowers circulating lymphocyte counts when fed to rats.



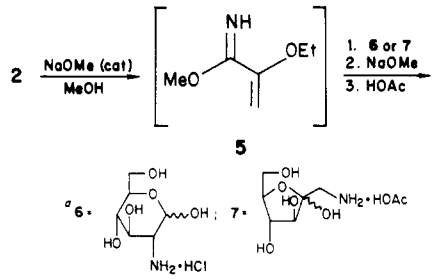
1

0022-3263/85/1950-1134$01.50/0

Scheme I



Scheme II[a]



Kröplien[1] and co-workers who isolated and determined the structure of this imidazole (1) found that it was formed in approximately 1% yield in the reaction of fructosamine acetate, pyruvaldehyde, and aqueous ammonia. This synthesis provided the first evidence that the relative and absolute configuration of the tetrahydroxybutyl side chain was identical with that present in glucose, a finding that did not cause much surprise because caramels are prepared from glucose. This finding was later verified in a second,[2] more efficient synthesis of the factor in which D-glucosone, pyruvaldehyde dithioketal, and ammonia were condensed to yield the dithioketal of the 2-acetylimidazole 1. The capricious hydrolysis of the dithioketal protecting group was best accomplished with excess aqueous silver nitrate. In this paper, we disclose a very simple synthesis of 1.

Cuvigny reported that 2-ethoxyacrylonitrile (2) could be prepared by bromination of ethyl vinyl ether followed by treatment with cuprous cyanide and dehydrobromination with diethylamine.[3] This three-step synthesis proceeded in an overall yield of 49% and did not require isolation of intermediates. Exposure of 2 to ethanol in alkaline media generated an intermediate which upon treatment with acidic ethanol produced ethyl 2,2-diethoxypropionate (4) (Scheme I).[4] This intermediate was tentatively assumed to be ethyl 1-ethoxyvinylimidate (3) on the basis of the structure of its ethanolysis product 4 and the fact that it was shown not to be the 1,4-adduct 2,3-diethoxypropionitrile nor 2,2-diethoxypropionitrile, both of which were prepared by independent syntheses.

We reasoned that imidates such as 3 would be ideal intermediates for the synthesis of 1 since they allow for protection of the acetyl substituent as an enol ether and contain the imidate functionality which is known to generate imidazoles upon treatment with α-amino carbonyls.[5]

It was found that both D-(+)-glucosamine hydrochloride (6), which is commercially available, or 1-amino-1-deoxy-D-fructose acetate (7),[6] prepared from glucose in nearly quantitative yield by treatment with dibenzylamine followed by hydrogenation, can serve as the required α-amino carbonyl component.

A very convenient one-pot synthesis of 1 from readily available starting materials is outlined in Scheme II. A methanolic solution of 2-ethoxyacrylonitrile (2) containing a catalytic amount of sodium methoxide was stirred overnight at room temperature to generate what was assumed to be methyl 1-ethoxyvinylimidate (5).[7] Either glucosamine hydrochloride (6) or fructosamine acetate (7) was added followed by a total of 1 equiv of sodium methoxide. After stirring at room temperature for 2–3 days, the starting amino sugars were consumed. Since the free base of 1 is insoluble in water[2], and strongly acidic conditions are required to form the corresponding imidazolium salt, it was hoped that precipitation of the free base from water would prove to be a convenient workup procedure. Thus, dilution with water, acidification with acetic acid (to hydrolyze the enol ether), and removal of the methanol in vacuo induced precipitation of a light yellow solid. This material was collected by filtration and recrystallized from water to give the desired imidazole 1, identical with the material isolated from ammonia caramel[1] and with that obtained by the alternate synthesis mentioned above.[2]

This reaction sequence (Scheme II) proceeds in a 46% overall yield with fructosamine acetate 7 or 19% yield with the commercially available glucosamine hydrochloride (6). Due to the availability of starting materials and the brevity of this synthesis, 2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole (1) can now easily be prepared in multigram quantities.

Experimental Section

Melting points were determined with a Büchi SMP-20 capillary melting point apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 283B spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra were recorded with a JEOL Model FX 90Q spectrometer. Optical rotations were obtained with a Perkin-Elmer Model 141 polarimeter at the sodium D line at ambient temperature. Ultraviolet spectra were recorded with a Perkin-Elmer Hitachi 200 spectrophotometer.

Reagent-grade anhydrous methanol was purchased from Mallinckrodt and used without purification. 2-ethoxyacrylonitrile[3] and 1-amino-1-deoxy-D-fructose acetate[6] were prepared as reported. D-(+)-Glucosamine hydrochloride was purchased from Aldrich and used directly.

General Procedure for the Preparation of 2-Acetyl-4-(5)-(1(*R*),2(*S*),3(*R*),4-tetrahydroxybutyl)imidazole (1). A 1.93 M solution of sodium methoxide in methanol (0.71 mL, 1.37 mmol) was added to a solution of 2-ethoxyacrylonitrile (2) (1.34 g, 13.80 mmol) in 30 mL of methanol and stirred overnight at room temperature. This solution was diluted with 20 mL of methanol and cooled to −5 °C, and the appropriate amino acid sugar (13.77 mmol) was added in one portion. After 20 min a solution of 1.93 M sodium methoxide in methanol was added (2.14 mL, 4.13 mmol) and the mixture was warmed to room temperature over a 2-h period and stirred overnight. The mixture was cooled to −5 °C and a 1.93 M solution of sodium methoxide in methanol (5.00 mL, 9.65 mmol) was added. The resulting mixture was allowed to warm to room temperature over a 2-h period and stirred for 2–3 days. Filtration of the reaction mixture was followed by dilution with 20 mL of water and addition of glacial acetic acid (0.7 mL, 12.23 mmol). After 30 min the solution was concentrated in vacuo to a volume of approximately 10 mL until precipitation began. The mixture was allowed to stand overnight at room temperature and the solid was collected by filtration. Recrystallization from water gave 1 as a crystalline solid: mp 234–236 °C; $[\alpha]^{25}_D$ −10 °C (*c* 1.00, 1 N HCl); UV_{max} (H_2O) 289 nm (log ϵ 4.14), 215 (3.36) (sh); IR (KBr) 3460, 3290, 3020, 1660, 1380, 1255, 1220, 1090, 1025, 955, 940, 930, 790, 650 cm^{-1}; ^{1}H NMR (D_2O, DCl) δ 2.74 (s, 3 H), 3.64–3.92 (m, 4 H), 4.96 (br s, OH protons and H_2O), 5.29 (br s, 1 H), 7.68 (s, 1 H); ^{13}C NMR (D_2O, DCl) δ 28.26, 64.58, 66.44, 72.38,

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74.33, 120.96, 139.25, 140.59, 186.27.

Preparation of 1 from 2-Amino-2-deoxy-D-(+)-glucose Hydrochloride (6). The general procedure was followed by using 2-amino-2-deoxy-D-(+)-glucose hydrochloride (2.97 g, 13.77 mmol). After the final addition of sodium methoxide stirring was continued for 2 days at room temperature. Typical workup (vide supra) gave 0.60 g (19%) of 1.

Preparation of 1 from 1-Amino-1-deoxy-D-fructose Acetate (7). The general procedure was followed by using 1-amino-1-deoxy-D-fructose acetate (3.30 g, 13.77 mmol). After the final addition of sodium methoxide stirring was continued for 3 days at room temerature. Typical workup (vide supra) gave 1.46 g (46%) of 1.

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Registry No. 1, 94944-70-4; 2, 19479-65-3; 6, 66-84-2; 7, 6333-49-9.

Synthesis and Structure Determination of 3,3,4,4-Tetrafluoro-*N*-methyl-2-(*cis,s-trans*-methyl-*NNO*-azoxy)-*s-cis*-1-cyclobutene-1-amine[1]

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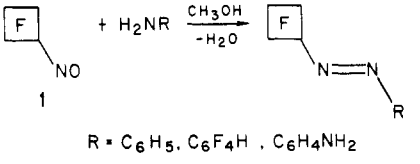
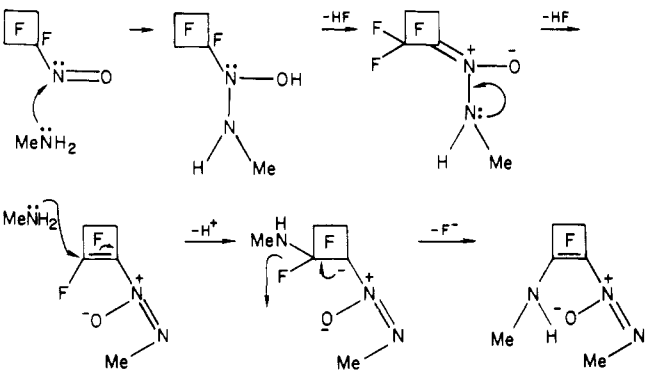
The reactions of nitroso compounds with primary amines normally result in the formation of azo compounds, with concomitant elimination of water.[4,5] Recently there has been renewed interest in the reaction of CF_3NO with aromatic amines as a route to the introduction of trifluoromethyl groups into these molecules via azo intermediates.[6-9] In this context, we studied the reactions of heptafluoronitrosocyclobutane (1) or nonafluoronitrosocyclopentane (2) with several primary amines. The expected condensation reactions occurred to form the azo products.[10] Corresponding reactions occur with 2. However, when methylamine is used instead of the aromatic amines the reaction takes a quite different and intriguing path. Although $CF_3N{=}NCH_3$ is the high-yield product from the reaction of CH_3NH_2 with CF_3NO,[11] no azo compound is obtained from the reaction of methylamine with 1. Instead, a sublimable, crystalline product with the empirical formula $C_6H_7F_4N_3O$ is formed. A firm structural assignment from spectroscopic data was difficult. The correct structure was determined by X-ray methods, showing that the compound is 3 which may result via the mechanism in Scheme I.



Scheme I



The elimination of HF, leading to an azoxy compound, is preferred to the loss of H_2O which would result in the formation of an azo material. The electron shift to form the stable conjugated azoxybutene system aids the attack of the methylamine at the more positive carbon, followed by further loss of HF to give the isolated product.

Although electrophilic fluorinated nitrosoalkanes have been reacted with dozens of aliphatic, alicyclic, and aromatic compounds that contain the nucleophilic NH_2 group, no evidence has been found for the formation of azoxy compounds in addition to the expected azo materials.[11] It should be noted that the analogous azoxy product was formed when 2 was reacted with methylamine. The existence of the latter was demonstrated by comparing the ^1H and ^{19}F NMR, UV, IR, MS, and elemental analysis data with those of 3 whose structure is reported in this paper.

Experimental Section

All reagents were used as received from commercial suppliers. Methylamine was obtained from Matheson. Heptafluoronitrosocyclobutane and nonafluoronitrosocyclopentane were prepared by literature methods.[10]

Gases and volatile liquids were handled in a conventional Pyrex glass vacuum system equipped with a Heise Bourdon tube gauge and a Televac thermocouple gauge. Starting materials were measured quantitatively by PVT techniques. Spectrometers used were IR, Perkin-Elmer 599; ^{19}F and ^1H NMR, JEOL FX-90Q FT at 84.26 and 90 MHz, or Varian EM-360L at 54.6 MHz; MS, Hitachi Perkin-Elmer RMU-6E at 17 eV; UV, Beckman Acta MVII, scanning from 250 to 800 nm, using $CHCl_3$ solutions contained in 1-cm cuvettes. For the NMR studies, $CDCl_3$ and/or $CFCl_3$ were used as solvents and as internal or external references; ^{19}F chemical shifts upfield from that of $CFCl_3$ were assigned negative values. for IR, KBr disks were employed. Elemental analyses were by Beller Mikroanalytisches Laboratorium, Göttingen, FRG.

1 (6 mmol) and methylamine (8 mmol) were added to methanol (10 mL, liquid N_2 temperature) in a 250-mL round-bottomed flask equipped with a 19/26 inner ground glass joint to which was attached a Kontes Teflon-brand stopcock. The flask was then

(1) Cis and trans are based upon Cahn-Ingold-Prelog priorities for fluorine and nitrogen.
(2) (a) University of California, Davis. (b) Oregon State University. (c) University of Idaho.
(3) American Association of University Women International Fellow, 1982-83.
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0022-3263/85/1950-1136$01.50/0