Formation of a Pyrazopyrazolone by the Pyrolysis of Antipyrine Diazonium Fluoroborate

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The pyrolysis of antipyrine 4-dizaonium fluoroborate gave an antipyrylazopyrazopyrazolone instead of the desired 4-fluoroantipyrine. This compound was formed by intermolecular and intramolecular coupling of the diazo compound at elevated temperatures.

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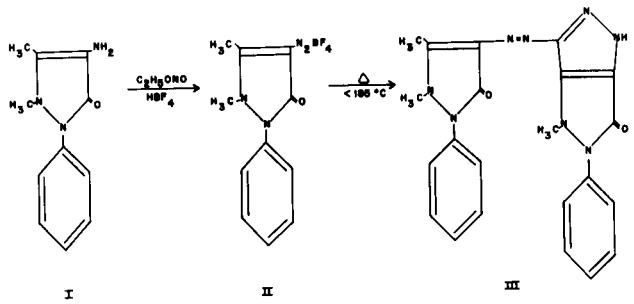
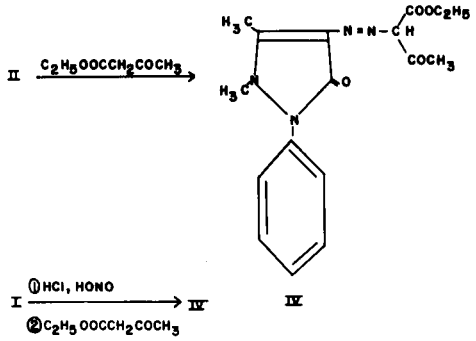
A lipophilic compound, antipyrine, has been labeled with the radioiodines ^{123}I (1) ^{131}I (2), and used to study the symmetry of human brain perfusion by external scanning, using gamma camera techniques. It has been an aid in the diagnosis of human cerebrovascular disease. Another radionuclide, ^{18}F, has desirable physical characteristics for use in nuclear medicine, such as a very short half-life (110 minutes), resulting in a low radiation dose to patients. Fluorine-18 is a pure positron emitter, and the resulting annihilation radiation (511 ke V) is easily detected by nuclear medicine instrumention. Chemically, fluorine substituted for hydrogen of an organic compound has been noted to preserve the biological characteristics of the non-fluorinated compounds because of its small atomic size (3,4). Our interest was in labeling ^{18}F to antipyrine (1-phenyl-2,3-dimethyl-5-pyrazolone) in the 4 position of the pyrazolone ring and studying regional brain perfusion by imaging techniques using a new positron camera. We planned to prepare 4-(^{18}F)-fluoroantipyrine by Schiemann-type reactions, using the following approach: 4-aminoantipyrine is converted to the antipyrine 4-diazonium fluoroborate. Fluorine-18 is exchanged with the diazonium salt. The ^{18}F-labeled salt is then pyrolyzed to the 4-(^{18}F)-fluoroantipyrine. 4-Fluoroantipyrine prepared by any method has not been reported in the chemical literature. The synthesis of heterocyclic substituted fluoro compounds by the Schiemann routine has met with limited sucess (5,6). There have been no reported Schiemann reactions on amino pyrazolones. Diazotization of the 4-aminoantipyrine, however, to a diazonium salt (the diazonium chloride) has been reported (7).

The starting material, 4-aminoantipyrine (1) was diazotized in the presence of fluoroboric acid using ethyl nitrite to produce antipyrine 4-diazonium fluoroborate (II). The identification of the diazonium fluoroborate was confirmed by elemental analyses, ir analysis, mass spectral analysis and preparation of a derivative with ethyl acetoacetic acid. The diazonium fluoroborate is quite stable and can be prepared in quantity and stored in a reagent bottle. The dry diazonium fluoroborate (II) was pyrolyzed at temperatures less than 185° to yield a yellow-orange solid, m.p. 190-193°, that was shown by molecular weight,

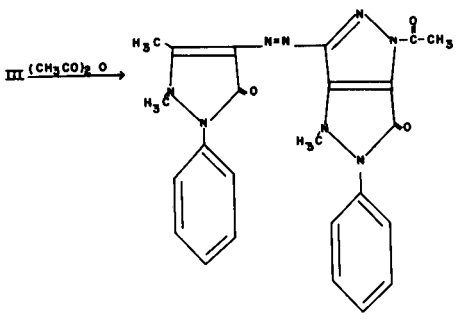
Scheme 1



Scheme 2



Scheme 3



elemental analyses, ir analysis, mass spectral analysis and derivative preparation to be the hydrated form (one water molecule) of 1-*H*-pyrazo-3-(1′-phenyl-2′,3′-dimethyl-3′-pyrazoline-5′-one-4′-azo)-4-methyl-5-phenylpyrazol-6-one (III). A systematic literature search reveals that this compound has not been prepared prior to this time.

A similar compound was prepared by Fukata, *et al.*, (8) from 4-diazo-3,5-dimethylpyrazole when it was heated in *t*-butyl alcohol. As with the fused ring pyrazopyrazole which Fukata, *et al.*, prepared, this product resulted from the intermolecular and intramolecular coupling of the diazo compound at temperatures above its melting point.

EXPERIMENTAL (11)

Antipyrine 4-Diazonium Fluoroborate (II).

4-Aminoantipyrine (I) (8 g., 0.04 mole) was dissolved in 18 ml. of 50% fluoroboric acid (0.13 mole) and 40 ml. of ethyl alcohol. The solution was cooled to 0° and an excess of ethyl nitrite (9) was bubbled into the mixture with stirring. The gold colored solution turned to purple after 1/2 hour of cooling and mixing. Ether (40 ml.) was added, and a milky white precipitate turning into a purple oil formed. The reaction mixture was poured into 100 ml. of ice cold ether. Filtration yielded a yellow precipitate which was recrystallized from acetone and ether to give 10.5 g. (88%) of II. These were yellow crystals having a m.p. 128-132°, and a positive test for fluorine. Ir analysis showed the absence of the NH_2 doublet [ν max (potassium bromide disc) 3350 cm^{-1} and 3450 cm^{-1}] of the aminoantipyrine and presence of the diazo peak [ν max (potassium bromide disc) 2200 cm^{-1}] of the diazonium salt. Mass spectral analysis at 180° and 200° did not show the molecular ion equivalent to structure II, but splitting of $N_2^+BF^-$ from the molecule and association with a proton provided ion 188. Fragments for BF_2 (mass 49) and BF_3 (mass 68) support the presence of $N_2^+BF^-$ in the sample.

Anal. Calcd. for $C_{11}H_{11}BF_4N_4O$: C, 43.75; H, 3.64; N, 18.56. Found: C, 43.67; H, 3.73; N, 18.42.

Ethyl 1-Phenyl-2,3-dimethylpyrazol-5-one-4-azoacetoacetate (IV).

The identity of II was also confirmed by preparing a derivative (IV) (m.p. 179-181°, lit. 174.5-176°) and performing a mixed m.p. (178-179°) with the same compound (IV) prepared by the diazotization of 4-aminoantipyrine in the pressence of hydrochloric acid and addition of ethyl acetoacetic acid (10). See Scheme 2. The mass spectra for IV measured at 200° showed the molecular ion at 344. Fragments corresponding to all parts of IV were identified.

Pyrolysis of Antipyrine 4-Diazonium Fluoroborate.

Compound II (1.340 g.) was heated slowly to 185° in a small beaker on a micro hot plate. To the cooled reaction mixture was added 20 ml. of 5% sodium bicarbonate solution. The solid was broken up in the beaker with continuous stirring and filtered on F porosity sintered glass filter. The yellow-orange solid was washed through the filter with hot absolute ethanol. Yellow-orange crystals (m.p. 190-193°) which precipitated from this solution on cooling in the refrigerator were collected by filtration. Recrystallization from ethanol yielded III (0.323 g., 33%), yellow-orange crystals, m.p. 190-193°. This product gave a negative test for fluorine. Ir analysis showed absence of the diazo peak [ν max (potassium bromide disc) 2200 cm^{-1}] of its progenitor. Also, present were peaks for NH [ν max (potassium bromide disc) 3190 cm^{-1}], and an azo group [ν max (potassium bromide disc) 1670^{-1}]. The mass spectra for III measured at 320° did not provide the 446 molecular ion; mass 398, corresponding to the loss of two methyl groups and the water molecule, was measured. Mass 416, which corresponds to the loss of two methyl groups only was also measured. Masses 201 and 227 which correspond to the fragments of III provided by cleavage between the N = N were also measured.

Anal. Calcd. for M.W. 446. Found: 420.

Anal. Calcd. for $C_{22}H_{20}O_2N_8 \cdot H_2O$: C, 59.18; H, 4.97; N, 25.10; O, 10.75. Found: C, 59.10; H, 4.93; N, 24.98; O, 10.92.

Acetyl Derivative of III.

An acetyl derivative of III was prepared by heating on a water bath 58 mg. of III with 2 ml. of acetic anhydride until all the solid dissolved (about 5 minutes). Upon cooling to room temperature, yellow-orange crystals (m.p. 256-257°) were collected. Recrystallization from glacial acetic acid yielded V (34.5 mg.), yellow crystals, m.p. 259-261°. Ir analysis showed that the NH band of III was absent and an additional band due to the carbonyl group of the acetyl radical appeared at 1740 cm^{-1}. The mass spectrum for V measured at 320° is very similar to that for III. Additionally the mass 271, which corresponds to the acetyl derivative of the aminopyrazopyrazolone generated by cleavage of V at the N = N and association with 2 protons was measured.

Anal. Calcd. for $C_{24}H_{22}N_8O_3$: C, 61.26; H, 4.71; N, 23.82; 0, 10.20. Found: C, 61.09; H, 4.76; N, 23.71; O, 10.35.

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(11) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Ir spectral data were obtained on a Perkin-Elmer Infracord Spectrophotometer. Mass spectral data were obtained on a Finnigan Model 3300 Mass Spectrometer, fitted with a solid probe inlet system and oscillographic recorder. Molecular weight determination on III was done by vapor pressure osmometry.