the National Science Foundation through Grant No. CHE75-17018 and an energy-related postdoctoral fellowship to R.G.F.

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Conversion of the Carcinogen *N*-Acetoxy-2-acetamidofluorene to 4-Hydroxy-2-acetamidofluorene

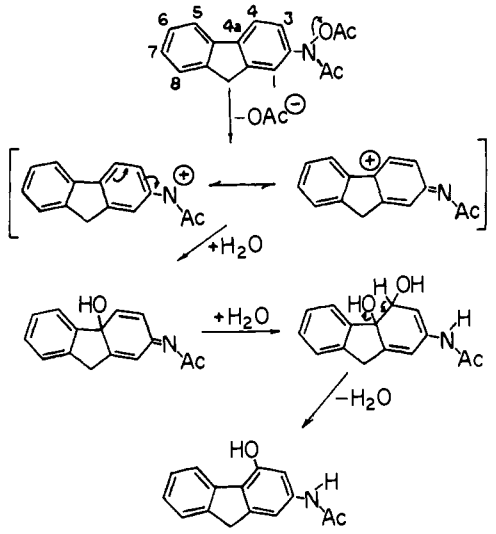
Sir:

An erroneous observation has led to the discovery of a novel substitution reaction between water and the carcinogen *N*-acetoxy-2-acetamidofluorene (*N*,*O*-diacetyl-*N*-(2-fluorenyl)hydroxylamine, **1**). Gutmann et al. have reported that the principal product (60% of starting material) from solution of **1** in 0.14 M saline containing 0.01 M phosphate (pH 7.4) is 1-acetoxy-2-acetamidofluorene.[1] This conclusion was based solely on retention time of the unknown product on a high pressure liquid chromatography column, and contradicted earlier studies on reactions of **1.** In that earlier work,[2] the rate of formation of water-soluble radioactivity from *N*-$CH_3{}^{14}CO_2$-*N*-arylacetamide was determined. Release of radioactivity from labeled **1** was a pseudo-first-order reaction, and in 40% acetone the reaction was followed to the point of 60% release of radioactivity, with no indication that the reaction would stop short of 100% release. Because of the discrepancy between this result and that of Gutmann et al., it seemed likely that the principal product observed in the later work was a new substance, which fortuitously had the same retention time as the standard 1-acetoxy-2-acetamidofluorene. I now show that virtually no rearrangement takes place under the conditions described by Gutmann et al. and that the major product reported by that group is actually 4-hydroxy-2-acetamidofluorene (*N*-(4-hydroxy-2-fluorenyl)acetamide).

N-$CH_3{}^{14}CO_2$-2-acetamidofluorene was prepared by acetylating 435 mg of *N*-hydroxy-2-acetamidofluorene with 185 mg of labeled acetic anhydride in 5 mL of pyridine cooled in ice. After the reagents were mixed, the reaction was allowed to stand at room temperature for 1 h and was then precipitated into ice water. The precipitate was centrifuged, washed twice with ice water by mixing and recentrifugation, filtered on a glass frit, again washed, and dried overnight over $CaCl_2$ under vacuum; 427 mg (84%) of product was obtained, which was radiochemically homogeneous (TLC, silica gel, 5% ethyl acetate in benzene) and had a specific activity of 1.08×10^5 dpm/mg. This material (1.5 mg) was dissolved in acetone and added to the buffer described by Gutmann et al. (1 mL of acetone + 100 mL of buffer; 5 mL of acetone + 500 mL of buffer). After 2 h at 37 °C, 1-mL samples were removed for counting, the mixtures were extracted with ether, the remaining aqueous phase and the combined ether extracts (for each reaction) were again sampled, the ether was evaporated under reduced pressure, and the residues were chromatographed on silica gel thin layer plates. The residue from the first study was applied as a stripe 2.5 cm wide, developed with 5% ethyl acetate in benzene, the chromatogram was scanned on a radiochromatogram scanner, and all of the distinct UV-visible bands were scraped into test tubes and eluted with 95% ethanol. Samples were then assayed by ultraviolet spectrophotometry and liquid scintillation counting. The major product had an R_F very close to that of authentic 1-acetoxy-2-acetamidofluorene. However, <10% of the total radioactivity was recovered in the ether extract. After chromatography, the total recovery of radioactivity dropped to ~1%. The apparent specific activity (cpm/mL/A_{280}) of the major product was 2% of that of the starting material, demonstrating clearly that this compound was not a rearrangement product. The residue from the second study was applied as a spot to a corner of a preparative TLC plate, then chromatographed in two directions in the usual solvent. The spots were eluted and assayed as before. Following this procedure, virtually all radioactivity was removed from the detectable products. Thus, it was established that rearrangement of **1** is an insignificant reaction in aqueous medium at moderate temperature. It now remained to determine the identity of the major product.

Easily handled quantities of the unknown (**2**) were obtained by adding five 100-mg portions of **1** in 40 mL of acetone to 4 L of buffer at 37 °C and extracting the mixture with ether at least 2 h after each addition and before the next addition. This process was necessary because higher concentrations of **1** or its solvolysis products led to competing reactions which reduced the yield of **2.** The combined extracts were evaporated, and the residue was chromatographed on a column of silica gel eluted

Scheme I



with 25% ethyl acetate in benzene. Although both TLC and the column procedure show clearly a product which appears to be at least half of the detectable material, only ~10% of the starting material can be isolated in this fraction as pure solid. Other products were isolated in still smaller quantities as expected. However, a high-melting compound which was almost insoluble in ether or ethyl acetate, and did not migrate on TLC, may account for the remainder of the starting material. Even the dilution used here is a significantly higher concentration than that used by Gutmann et al., and this higher concentration may result in extensive formation of dimers or higher polymers which would reduce the yield of **2** below that found by Gutmann et al. A mass spectrum showed that **2** was a hydroxylated acetamidofluorene, an observation confirmed by the infrared spectrum. NMR spectrometry suggested that the aromatic ring not carrying the nitrogen was not further substituted. Ultraviolet spectra in neutral and basic ethanol confirmed that the substance was a phenol, but the UV spectrum was clearly different from those of both 1- and 3-hydroxy-2-acetamidofluorene (which also are much less polar on adsorption chromatography). Thus, unlikely as it seemed, the only rational conclusion was that **2** is 4-hydroxy-2-acetamidofluorene. This conclusion was initially confirmed by comparison of the UV spectrum with that of 4-hydroxy-2-formylaminofluorene.[3] Further confirmation was obtained by comparison of the infrared spectrum of the acetate of **2** with the spectrum of authentic 4-acetoxy-2-acetamidofluorene, generously provided by Dr. T. L. Fletcher.

This conversion is a most unusual reaction, for all previously known reactions of **1** take place on the nitrogen atom,[4] or on positions 3 and 1.[5] This past experience was confirmed by my being able to prepare 3-chloro-2-acetamidofluorene[6] in 40% yield simply by dissolving **1** (500 mg in 50 mL of acetone) in 1 L of 1 M NH_4Cl heated to 50 °C, extracting the warm mixture 2 h later, and recrystallizing the residue from the extract. I suggest that **2** arises from initial hydroxylation of position 4a of the intermediate *N*-acetyl-*N*-fluorenylnitrenium ion, followed by further hydration of the ensuing quinone imide methide,[7] and dehydration of the resulting diol (Scheme I). This mechanism is suggested by an examination of the coefficients of the lowest unoccupied molecular orbital of the nitrenium ion, which shows position 4a to be more reactive than any other aromatic carbon. An explanation of why other nucleophiles do not attack this carbon will have to await molecular orbital calculations which specifically address the interaction between the delocalized nitrenium ion and sulfur, nitrogen, or chloride. Steric accessibility is not a factor in attack by chloride, according to space-filling models.

This study points out again the tenuous nature of identifications based only on chromatographic properties, and renders pointless much of the discussion offered previously by Gutmann et al. regarding the possible role of *N*-acetoxyacetamidofluorenes in mammary gland carcinogenesis by the corresponding hydroxamic acids. On the other hand, this finding may have considerable significance for further studies on the mechanism of carcinogenesis by 2-acetamidofluorene and other aromatic amines. The sulfate ester of *N*-hydroxy-2-acetamidofluorene is believed to be the ultimate reactive form in the carcinogenic action of 2-acetamidofluorene toward the liver of the male rat.[5b] In the absence of other nucleophiles, it would be expected to react with water similarly to **1**; yet 4-hydroxy-2-acetamidofluorene has not been observed among the urinary metabolites of 2-acetamidofluorene or its *N*-hydroxy derivative.[8] Hence, it appears that bound forms of 2-acetamidofluorene in the rat represent virtually all of the sulfate ester. Therefore, the level of binding to macromolecules and other intracellular nucleophiles is a direct measure of the amount of active intermediates formed, rather than an unknown proportion of some larger amount. It is thus possible to estimate what proportion of the total dose of 2-acetamidofluorene is converted to reactive metabolite. It is also possible that minute quantities of 4-hydroxy-2-acetamidofluorene were overlooked in previous metabolic studies. This point may deserve reinvestigation.

Acknowledgments. This work was supported by Grant CA 18632 from the National Cancer Institute of the U.S. Public Health Service. I thank R. Hodson and S. R. Fisk for technical assistance. The NMR spectrum was provided by Dave Wilbur, Frederick Cancer Research Center; the mass spectrum was obtained by Elliott Hills, Michigan Cancer Foundation.

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Synthesis and Crystal Structure of $H_4Ru_4(CO)_{10}(Ph_2PCH_2CH_2PPh_2)$. Evidence for an Edge–Terminal-Edge Hydride Scrambling Pathway

Sir:

The contrasting hydride ligand positions adopted in highly symmetrical H_4M_4 cluster compounds—edge bridging in D_{2d} $H_4Ru_4(CO)_{12}$[1] vs. face bridging in T_d $H_4Re_4(CO)_{12}$[2,3] and $H_4CO_4(\eta^5\text{-}C_5H_5)_4$[4]—pose the question whether interconversion between the two arrangements could provide a mechanism for hydride scrambling over the M_4 framework. Hydride