with NAA (or rather its rearrangement product,[14] the diazonium acetate) to give acetic acid and regenerate ArN=N—O—N=NAr.

Rüchardt has also investigated[12] the Gomberg–Bachmann reaction,[15] in which the arylating reagent is a diazonium salt and base, and has shown that in this case, also, the diazoanhydride is an essential intermediate. Here again the arylcyclohexadienyl radicals are scavenged (to give arylbenzenes) efficiently by ArN=NO· radicals.

In view of the similarity of the Gomberg–Bachmann and NAA reactions established by Rüchardt, it was to be expected that the former would also lack the criteria of dihydrobiaryl formation, apparent isotope effects, and appearance of dideuterated biaryls. As it happens, we had already obtained the pertinent data for the Gomberg–Bachmann reaction of benzene-*d* with *p*-methyl-, *p*-methoxy-, and *p*-chlorobenzenediazonium salts and are placing them on record at this time to round out the now well-understood picture of free-radical arylation. Table I gives the calculated apparent isotope effects and per cent of dideuterated biaryl in the Gomberg–Bachmann arylations indicated (each carried out in duplicate). The isotopic purity of starting benzene-*d* and the deuterium content of biaryl, both determined mass spectrometrically, are also included.

TABLE I

GOMBERG–BACHMANN REACTIONS WITH BENZENE-*d*

Arylating group	Apparent isotope effect[a]	Mole % biaryl-d_2[b]	Isotopic purity of benzene-*d*, mole %	Mole % biaryl-d_1
p-$CH_3C_6H_4$	1.01	0.10	97.02	80.85
p-$CH_3C_6H_4$	0.99	0.13	97.02	80.54
p-$CH_3OC_6H_4$	1.03	0.08	97.12	81.25
p-$CH_3OC_6H_4$	1.00	0.11	97.12	80.65
p-ClC_6H_4	1.07	0.04	97.18	81.73
p-ClC_6H_4	1.07	0.08	97.18	81.72

[a] Apparent isotope effects up to 1.12 were obtained in the NAA and PAT reactions previously. In contrast, apparent isotope effects in the diaroyl peroxide reactions usually range from 1.3 up. [b] Comparable data for NAA and PAT reactions are 0.0–0.23 mole %, for diaroyl peroxide reactions 0.39–0.53 mole %.

Our results suggest the presence of an efficient radical scavenger in the intermediate stages of the Gomberg–Bachmann reaction, and are in complete agreement with Rüchardt's postulated mechanism.

Experimental

Gomberg–Bachmann Reaction.—The reaction of *p*-toluidine is typical. *p*-Toluidine (0.58 g., 5.4 mmoles) was dissolved in 2 ml. of concentrated hydrochloric acid and diazotized at 0–5° with 0.6 g. of sodium nitrite dissolved in 2 ml. of water. The solution of the resulting diazonium salt was added slowly, with vigorous stirring, to a mixture of 30 g. (0.38 mole) of benzene-*d* (97.02% isotopically pure by mass spectrometry at reduced ionizing voltage) and aqueous sodium acetate (3.0 g. in 7 ml. of water) maintained at 6–10°. After completion of the addition, the mixture was stirred at 6–10° for 0.5 hr. and then at room temperature for 6 hr. The dark benzene layer was separated, washed three times with aqueous sodium bicarbonate followed by water, dried over calcium chloride, and concentrated on a steam bath. The residue was dissolved in 5 ml. of ether, mixed with 2 g. of activated alumina, and dried in a film evaporator. The residue, impregnated on alumina, was placed on top of an alumina column (25 g.) and was extracted repeatedly with petroleum ether (b.p. 60–90°). The first 100 ml. of eluate on concentration gave *ca.* 350 mg. of 4-methylbiphenyl, m.p. 42–44.5°, raised to 46.5–47° (lit.[3] m.p. 46.5–48°) by sublimation under reduced pressure and crystallization from methanol.

Anal.[16] Calcd. for $C_{13}H_{11.19}D_{0.81}$: C, 92.36; H, 7.15; D, 6.77 atom %. Found: C, 92.01, 92.05; H, 7.10, 7.22; D, 6.60 atom %.

Anal.[16] Calcd. (for the second experiment): D, 6.71 atom %. Found: C, 92.40; H, 7.16; D, 6.56 atom %.

p-Methoxybiphenyl was prepared similarly and had m.p. 89.5–90° (lit.[3] m.p. 89°).

Anal.[16] Calcd. for $C_{13}H_{11.19}D_{0.81}$: C, 84.38; H, 6.54; D, 6.77 atom %. Found: C, 84.12; H, 6.52; D, 6.78 atom %.

Anal.[16] Calcd. (for the second experiment): D, 6.72 atom %. Found: C, 84.23; H, 6.44; D, 6.74 atom %.

p-Chlorobiphenyl was prepared analogously and had m.p. 79–79.5° (lit.[3] m.p. 78.5–79°).

Anal.[16] Calcd. for $C_{12}H_{8.18}D_{0.82}$: C, 76.10; H, 4.79; D, 9.08 atom %. Found: C, 76.25, 76.35; H, 4.85, 4.76; D, 9.07, 9.05 atom %.

(14) D. F. DeTar, *J. Am. Chem. Soc.*, **73**, 1446 (1951); R. Huisgen and L. Krause, *Ann.*, **574**, 157 (1951); R. Huisgen, *ibid.*, **574**, 171 (1951).

(15) W. E. Bachmann and R. A. Hoffman, *Org. Reactions*, **2**, 224 (1944).

(16) Analyses are based on the assumption of H–D exchange in the analyst's train (*cf.* ref. 3) and were performed by Mr. Josef Nemeth, Urbana, Ill.

Structure of Salts of 4,6-Dinitrobenzofuroxan[1]

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The structure of salts of 4,6-dinitrobenzofuroxan (I) became of interest because elemental analysis indicated that the salts are hydrated, but the investigators could not conclusively determine the amount of water present.[3–7] A cursory study questioned the concept of water of hydration because the water in the potassium salt was not evolved at temperatures up to the decomposition temperature of 160° and because of the sharpness of the O–H stretching mode at 3480 cm.$^{-1}$, shown by infrared spectroscopy.

Drost[3] suggested loss of a ring proton to give an anion such as II and simple hydration of the salt. Gaughran,[7] *et al.*, proposed the same structure owing to the similarity of the infrared spectrum of I and the various salts.

Various structures chemically incorporating the equivalent elements of water as shown (III to V) were considered. However, subsequently it was found that Jackson and Earle[6] had proposed, without experimental evidence, similar structures.

Experimental facts from deuteration studies and proton magnetic resonance prove that structures II and III are not possible. Structures IV and V are

(1) This contract was supported by Sandia Corp. through purchase order 13-7664.

(2) This is an essential portion of a thesis submitted to the Metallurgy Department, University of Utah, in a partial fulfillment of the requirement for a Doctor of Philosophy Degree.

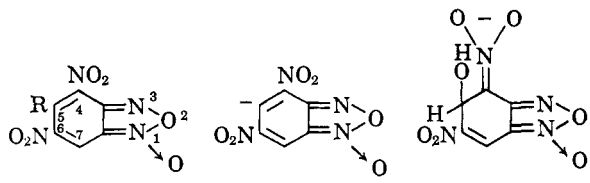
(3) P. Drost, *Ann.*, **307**, 49 (1899); **313**, 299 (1900).

(4) T. Zincke and P. Schwartz, *ibid.*, **307**, 32 (1899).

(5) A. G. Green and F. M. Rowe, *J. Chem. Soc.*, **103**, 2023 (1913).

(6) C. L. Jackson and R. B. Earle, *Am. Chem. J.*, **29**, 89 (1903).

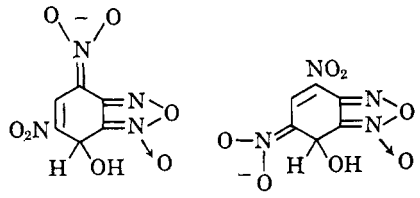
(7) R. J. Gaughran, J. P. Picard, and J. V. R. Kaufman, *J. Am. Chem. Soc.*, **76**, 2233 (1954).



I, R = H
VII, R = 1/2H, 1/2D

II

III



IV

V

resonance forms of the anion consistent with all experimental observations.

Potassium dinitrobenzofuroxan (VI) prepared in D_2O showed a very sharp absorption band at 2520 cm.$^{-1}$ due to the O–D stretching mode. In order to test for deuterium exchange, this salt was converted to I by treatment with DCl. The C–H out-of-plane deformation modes at 690 and 730 cm.$^{-1}$ were unchanged and no C–D stretching mode was observed even though I has a C–H stretching mode. Thus, structure II was eliminated because it would have incorporated deuterium in its structure changing at least one of the deformation modes and possibly the stretching mode.

In order to identify the C–H out-of-plane deformation modes at 690 and 730 cm.$^{-1}$, 5-deuterio-4,6-dinitrobenzofuroxan (VII) was prepared. The absorption band at 690 cm.$^{-1}$ was unchanged and was thus assigned to the 7-proton; the band at 730 cm.$^{-1}$ was decreased by ~50% and the corresponding C–D deformation mode of the 5-position appeared at 540–550 cm.$^{-1}$ as required when a deuteron replaces a proton. (Maximum deuterium content was 50% owing to symmetry of an intermediate in the synthesis.) This salt did not show a C–D stretching mode between 2200 and 2300 cm.$^{-1}$ and thus any conclusions drawn from the absence of a C–D stretching mode in the salt spectrum are not conclusive.

Proton magnetic resonance of VII and its sodium salt gave insight into the structure of the anion. The sodium salt was used owing to the insolubility of the potassium salt in water. The spectrum of VII in CH_2Cl_2 showed two peaks with an area ratio of 1.7:1. The larger peak at 9.04 p.p.m. was thus attributed to the 7-position and the smaller at 8.77 p.p.m. to the 5-proton. The spectrum of the anion also showed two peaks with the same area ratio of 1.7:1 with the 7-proton at 6.02 p.p.m. and 5-proton at 8.57 p.p.m. thus eliminating III. The chemical shift value of 6.02 p.p.m. compared with 9.04 p.p.m. for the acid indicates that the 7-proton of the salt is in a much less aromatic environment than in the acid. The addition of a hydroxyl group would require tetrahedral bonding and decrease the aromaticity and the conjugation around the 7-positions shown by IV–VII. Recently, Crampton and Gold[8,9] found a similar situation in which chemical shifts of 6.17 and 8.46 p.p.m. from tetramethylsilane as internal reference were observed for the N,N-dimethylpicramide–sodium methoxide complex, and 6.14 and 8.42 p.p.m. for the 1- and 3,5-protons, respectively, of the 1,3,5-trinitrobenzene–sodium methoxide complex.

The infrared spectrum of VI has an absorption band at 730 cm.$^{-1}$ corresponding to the C–H out-of-plane deformation of the 5-proton and the corresponding band for the 7-proton is absent as one would expect if the OH were added in the 7-position changing the conjugated planar structure to that of tetrahedral bonding.

Boulton and Katritzky[10] found that 5-methyl-4-nitrobenzofuroxan rearranges completely to 7-methyl-4-nitrobenzofuroxan. There is no evidence for this type of rearrangement (III ↔ V) because the infrared spectrum of VII after salt formation and acidification did not show a change in the relative intensities of the C–H absorption bands at 690 and 730 cm.$^{-1}$.

Experimental

Preparation of Potassium Dinitrobenzofuroxan (VI).—I (1.13 g., 0.05 mole) was dissolved in 125 ml. of a 1:1 acetone–water mixture at 40°. A solution of 0.55 g. (0.055 mole) of $KHCO_3$ in 20 ml. of water was slowly added, and CO_2 was evolved. The solution was slowly cooled to 5° with stirring. The golden platelets were filtered off, washed with acetone, and vacuum dried; yield 1.0 g., m.p. 209° (explodes).

Preparation of VI in D_2O.—I (1.13 g., 0.05 mole) was added to 15 ml. of 99.6° D_2O. A solution of 0.55 g. (0.055 mole) of $KHCO_3$ in 10 ml. of D_2O was allowed to equilibrate for 1 hr. The solutions were mixed, warmed to 35°, and allowed to react for 1 hr. The mixture was cooled to 10° and the platelets were filtered off, washed with 10 ml. of cold D_2O and acetone, and vacuum dried; yield 1.0 g., m.p. 207° (explodes).

Treatment of VI·D_2O with DCl.—VIII·D_2O (0.25 g., 0.0088 mole) was treated with 5 ml. of concentrated DCl (99.5% D). It was collected by filtration, washed with D_2O, and vacuum dried; m.p. 175°.

Preparation of *p*-Deuterionitrobenzene (VIII).—The method used for the synthesis of *p*-deuterionitrobenzene was a modification of the Alexander and Burger[11] method using materials of a higher deuterium content. The hydrochloric acid was prepared by dissolving 36.5 g. (1.0 mole) of HCl gas in 60 ml. of D_2O to form 80 ml. of DCl (88% D). The D_3PO_2 was prepared by treating 1 mole of H_3PO_2 (3.0 mole of H) with 60 ml. of D_2O (6.0 moles of D), allowing 48 hr. for exchange at 25°, vacuum evaporating, and repeating this procedure two more times. The D_3PO_2 had a theoretical 96% D content. Deuterium oxide was used in place of water in all instances; yield 9.5 g. (38.6%), b.p. 209°.

4-Deuterio-2-nitroaniline (IX).—VIII was catalytically reduced with a Pd–C catalyst in ethyl alcohol; the *p*-deuterioaniline was acetylated with acetic anhydride and sodium acetate. *ortho* nitration and isomer separation was performed by the Witt and Utermann method described by Heidelberger.[12]

5-Deuteriobenzofuroxan (X).—IX (1.5 g.) was oxidized with a sodium hypochlorite solution as described in *Organic Synthesis*[13]; yield 1.5 g. (100%).

5-Deuterio-4,6-dinitrobenzofuran (VII).—The Drost[2] method of nitration was used. Dinitration of X can proceed by two equivalent sequences. The first nitro group is substituted in the 4-position yielding a 1:1 mixture of 4-nitro-5-deuteriobenzofuroxan and 4-nitro-6-deuteriobenzofuranoxan. The second nitro group is substituted in the 6-position; hence a 1:1 mixture of I and VII is formed; m.p. 170°, lit.[3] m.p. 172°.

(8) M. R. Crampton and V. Gold, *Proc. Chem. Soc.*, 299 (1964).
(9) M. R. Crampton and V. Gold, *ibid.*, 4293 (1964).
(10) A. J. Boulton and A. R. Katritzky, *ibid.*, 257 (1962).
(11) E. R. Alexander and R. E. Burge, Jr., *J. Am. Chem. Soc.*, **72**, 3100 (1950).
(12) M. Heidelberger, "An Advanced Laboratory Manual of Organic Chemistry," Chemical Catalog Co., New York, N. Y., 1923, pp. 15–16.
(13) F. B. Mallory, *Org. Syn.*, **37**, 1 (1957).

Recrystallization of VII from acetic acid caused rearrangement and appearance of the 7-deuterio compound. Harris, *et al.*,[14] reported that this reaction does not take place in molten I at 180°.

(14) R. K. Harris, *et al.*, *J. Chem. Soc.*, 197 (1963).

The Synthesis of Aminoethyl-Substituted Selenium Compounds

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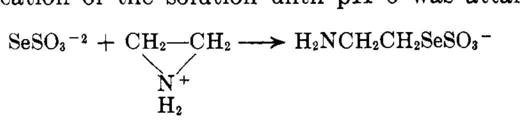
Selenium analogs of sulfur-containing pharmacologically active compounds have received attention owing to their interesting biological properties. Though organoselenium compounds tend to exhibit chemical instability and marked toxicity to animals, a number of potentially useful therapeutic agents have been prepared and studied.[1] The sulfur-containing compound, cysteamine (2-aminoethanethiol), and its derivatives possessing the aminoethyl moiety, such as cystamine [bis(2-aminoethyl) disulfide] and 2-aminoethanethiosulfuric acid, have been demonstrated to be good antiradiation agents.[2] Selenocystine and selenomethionine were reported[3] recently to show antiradiation activity *in vitro* superior to cystine and methionine, respectively. Several aminoethylselenium compounds were, therefore, synthesized for evaluation as potential radioprotective drugs and for comparison with their sulfur analogs.

2-Aminoethaneselenosulfuric acid (I), first prepared

$$H_2NCH_2CH_2SeSO_3H$$
I

by Günther and Mautner,[4] was found to be a valuable precursor for most of the selenium compounds made. An alternative method for its synthesis consisted of combining potassium selenosulfate and ethylenimine in aqueous solution, followed by the gradual acidification of the solution until pH 6 was attained.



Aqueous solutions of I are unstable above 60° resulting in the slow formation of sulfur dioxide. When an aqueous solution of I was heated under reflux for 62 hr. until sulfur dioxide was no longer evolved, the product isolated in quantitative yield was selenocystamine [II, bis(2-aminoethyl) diselenide] hydrosulfate.[5] The formation of these compounds may be accounted for by the mechanism shown below. The nucleophilic attack of a water molecule on the sulfur atom of I (written here in its zwitterionic form) gen-

$$H\ddot{O}H: + {}^{-}O\text{-}SO_2SeCH_2CH_2NH_3^+ \longrightarrow H_3\overset{+}{N}CH_2CH_2Se^- + H_2SO_4$$

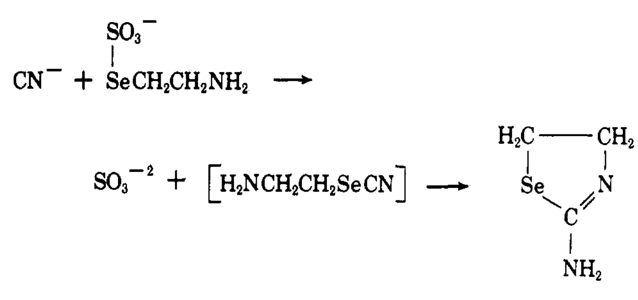
$$H_3\overset{+}{N}CH_2CH_2Se^- + (SO_3^-)SeCH_2CH_2NH_3^+ \longrightarrow (H_3\overset{+}{N}CH_2CH_2Se\text{—})_2 + SO_3^{-2}$$

$$H_2SO_4 + SO_3^{-2} \longrightarrow SO_2 + SO_4^{-2} + H_2O$$

erates the selenide ion and sulfuric acid. A similar step has been proposed[6] for the acid hydrolysis of a Bunte salt (alkyl or aryl thiosulfate). The selenide ion then attacks another molecule of I, the displacement now occurring at the selenium atom. This is comparable with the reaction of a mercaptide with a Bunte salt to form a disulfide. The diprotonated selenocystamine thus formed reacts with the sulfate ion to give the observed product.

When I was heated for 5 hr. without solvent at 105–110°, no sulfur dioxide was detected and the melting point of the compound was unchanged. Pyrolysis of the compound at 145–150° resulted in the formation of sulfur dioxide, which was detectable for 2.5 hr., and a high yield of II hydrosulfate.

The sulfur–sulfur bond in organic thiosulfates is attacked by various nucleophiles and it was anticipated that these ionic species would also be effective toward the selenium–sulfur bond in selenosulfates. Footner and Smiles[7] reported that the cyanide displacement on sulfur in a Bunte salt gives the corresponding thiocyanate and sulfite ion. The action of cyanide on the sodium salts of 2-aminoethanethiosulfuric acids in aqueous solution results in the formation of 2-aminothiazolines.[8] Similarly, the cyanide displacement performed on sodium 2-aminoethaneselenosulfate produced, in addition to sulfite ion, 2-aminoselenazoline. The latter was isolated as the



hydrobromide salt, inasmuch as the free base is an unstable oil which polymerizes rapidly.

Unsymmetrical amino disulfides are formed when mercaptides are allowed to react with amino Bunte salts.[9] When the sodium mercaptide of 1-decanethiol was added to a methanol solution of sodium 2-aminoethaneselenosulfate at about 0°, sodium sulfite precipitated instantaneously with the mercaptan undetectable within 2 min. In addition to the main product,

(1) For a review article, see D. Dingwall, *J. Pharm. Pharmacol.*, **14**, 765 (1962).

(2) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962.

(3) F. Shimazu and A. L. Tappel, *Radiation Res.*, **23**, 210 (1964).

(4) W. H. H. Günther and H. G. Mautner, *J. Med. Chem.*, **7**, 229 (1964).

(5) When the analogous sulfur compound, 2-aminoethanethiosulfuric acid, was heated under reflux in aqueous solution for 70 hr., there was no detectable evolution of sulfur dioxide. A small amount of sulfate was found in solution and 92% of the 2-aminoethanethiosulfuric acid was recovered unchanged.

(6) B. Milligan and J. M. Swan, *J. Chem. Soc.*, 2172 (1962); J. L. Kice, *J. Org. Chem.*, **28**, 957 (1963).

(7) H. B. Footner and S. Smiles, *J. Chem. Soc.*, **127**, 2887 (1925).

(8) D. L. Klayman, unpublished results.

(9) D. L. Klayman, J. D. White, and T. R. Sweeney, *J. Org. Chem.*, **29**, 3737 (1964).