cal with an authentic sample prepared by the procedure of Baer et al.[6]

**B. From Nitro Acetate 2.** The same treatment of 2[10] with ethyl malonate gave **4** in 77% yield.

**C. From Nitro Olefin 3.** Under the same conditions described above except for the decreased amount of 1 N NaOH to 0.9 ml, reaction between 3[9] (98 mg) and ethyl malonate gave **4** in 77% yield. The yield was up to 87% when this reaction was carried out under the conditions described for preparation of **6**.

**Methyl 2-*C*-Acetonyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (5).** To a solution of **3** (98 mg, 0.33 mmol), acetylacetone (75 mg, 0.75 mmol), and the catalyst (12 mg) in benzene (10 ml) was added 1 N NaOH (0.9 ml). The mixture was stirred for 22 h and then evaporated in vacuo to afford a crystalline residue (108 mg), which was recrystallized from ethanol–acetone to afford 95 mg (81%) of **5**: mp 176–177 °C; $[\alpha]^{20}D$ −66.9° (*c* 1, MeOH); ir (KBr) 1715 (CO) and 1560 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11, H, 6.02; N, 3.99. Found: C, 58.40; H, 6.04; N, 4.17.

The same product was also prepared in 80% yield by the similar reaction of **1** (236 mg, 0.67 mmol), acetylacetone (150 mg, 1.5 mmol), and the catalyst (60 mg) in benzene (20 ml)–0.5 N NaOH (5 ml) stirring for 23 h at room temperature.

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(diacetyl)-methyl-3-nitro-β-D-glucopyranoside (6).** To a solution of **3** (29.3 mg, 0.1 mmol), acetylacetone (18 mg, 0.18 mmol), and the catalyst (2 mg) in benzene (3 ml) was added 0.2 N NaOH (0.1 ml). The mixture was stirred for 1.5 h at room temperature and then washed with water (3 × 5 ml). The organic layer was evaporated to afford a NMR spectroscopically pure syrup (35 mg, 89%). The syrup (105 mg) was crystallized from ethanol to give **6** (83%): mp 110–111 °C; $[\alpha]^{20}D$ −153° (*c* 1, $CHCl_3$); ir (KBr) 1710 (CO) and 1560 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.56. Found: C, 57.72; H, 6.03; N, 3.72.

**Methyl 2-*C*-Benzoylmethyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (7).** To a solution of **3** (87.9 mg, 0.3 mmol), dibenzoylmethane (138 mg, ca. 0.4 mmol), and the catalyst (12 mg) in benzene (24 ml) was added 0.2 N NaOH (8 ml). The mixture was stirred for 18 h at room temperature and then evaporated in vacuo to give a crystalline residue. Recrystallization from ethanol gave 102 mg (83%) of **7**: mp 172–173 °C; $[\alpha]^{20}D$ −29° (*c* 1, $CHCl_3$); ir (KBr) 1680 (CO) and 1550 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C, 64.20; H, 5.65; N, 3.39.

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(dibenzoyl)-methyl-3-nitro-β-D-glucopyranoside (8).** Treatment of **3** (58.6 mg, 0.2 mmol) with dibenzoylmethane (89.6 mg, ca. 0.28 mmol) under the conditions used to prepare **6** gave a pure syrup (90 mg, 91%). The syrup was chromatographed on silica gel (C-200, Wako-gel) with benzene. The eluate was evaporated in vacuo to give a syrup, which was crystallized from *n*-propyl alcohol: yield 81%; mp 102–103 °C; $[\alpha]^{20}D$ −194° (*c* 0.5, $CHCl_3$); ir (KBr) 1680 (CO) and 1550 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{29}H_{27}NO_8$: C, 67.30; H, 5.26; N, 2.71. Found: C, 67.18; H, 5.38; N, 2.66.

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(dicyano)-methyl-3-nitro-β-D-glucopyranoside (9).** Treatment of **3** (147 mg, 0.5 mmol) with malononitrile (36.5 mg, 0.55 mmol) under the conditions used to prepare **6** gave a NMR spectroscopically pure crystalline residue (158 mg, 87.8%), which was recrystallized from ethanol to afford 146 mg (81%) of **9**: mp 177–178 °C; $[\alpha]^{20}D$ −40.2° (*c* 1, MeOH); ir (KBr) 1565 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.70. Found: C, 56.92; H, 4.77; N, 11.58.

**Methyl 4,6-*O*-Benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (10).** Treatment of **3** (58.6 mg) with acetone (14.5 mg) under the conditions used to prepare **5** gave **10** in 73% yield, which was identical with an authentic sample.[9]

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-bis(ethoxycarbonyl)methyl-3-nitro-β-D-galactopyranoside (12).** Treatment of 11[10] (58.6 mg) with ethyl malonate under the conditions used to prepare **6** gave a NMR spectroscopically pure residue of **12**, which was recrystallized from ethanol, yield 82%. It was identical with an authentic sample prepared by Baer et al.[6]

**Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-2-*C*-(diacetyl)-methyl-3-nitro-β-D-galactopyranoside (13).** Treatment of **11** (58.6 mg) with acetylacetone under the conditions used for the preparation of **6** afforded a syrup. Its NMR spectrum showed that it consisted of **13** and unknown compound in a ratio of ca. 3:1. Crystallization from ethanol gave 21.6 mg (55%) of **13**: mp 152.5–153.5 °C; $[\alpha]^{20}D$ −53.0° (*c* 1, $CHCl_3$); ir (KBr) 1700 (CO) and 1550 $cm^{-1}$ ($NO_2$).

Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.56. Found: C, 57.90; H, 5.74; N, 3.71.

**Registry No.**—**1**, 18604-56-3; **2**, 3650-61-1; **3**, 25541-58-6; **4**, 20777-18-8; **5**, 29847-30-1; **6**, 57559-94-1; **7**, 57559-95-2; **8**, 57559-96-3; **9**, 29847-31-2; **10**, 25541-57-5; **11**, 3650-62-2; **12**, 20777-19-9; **13**, 57559-97-4; ethyl malonate, 105-53-3; acetylacetone, 123-54-6; dibenzoylmethane, 120-46-7; malononitrile, 109-77-3.

## References and Notes


(1) H. Grisebach and R. Schmid, *Angew. Chem.*, **84**, 192 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 159 (1972).
(2) E.g., A. A. Feast, W. G. Overend, and N. R. Williams, *J. Chem. Soc. C*, 303 (1966).
(3) T. Sakakibara and R. Sudoh, *J. Chem. Soc., Chem. Commun.*, 69 (1974).
(4) T. Sakakibara and R. Sudoh, *Bull. Chem. Soc. Jpn.*, submitted for publication.
(5) H. Paulsen and W. Greve, *Chem. Ber.*, **107**, 3013 (1974).
(6) H. H. Baer and K. S. Ong, *Can. J. Chem.*, **46**, 2511 (1968).
(7) T. Sakakibara, S. Kumazawa, and T. Nakagawa, *Bull. Chem. Soc. Jpn.*, **43**, 2655 (1970).
(8) T. Sakakibara and R. Sudoh, *J. Org. Chem.*, **40**, 2823 (1975).
(9) H. H. Baer and T. Neilson, *Can. J. Chem.*, **43**, 840 (1965).
(10) H. H. Baer, F. Kienzle and T. Neilson, *Can. J. Chem.*, **43**, 1829 (1965).


---

# Quinazolines and 1,4-Benzodiazepines. LXXII.[1] Synthesis of Benzoxazinones from Anthranilic Acids. Revision of Structures Originally Described as 1,4-Benzodiazepines

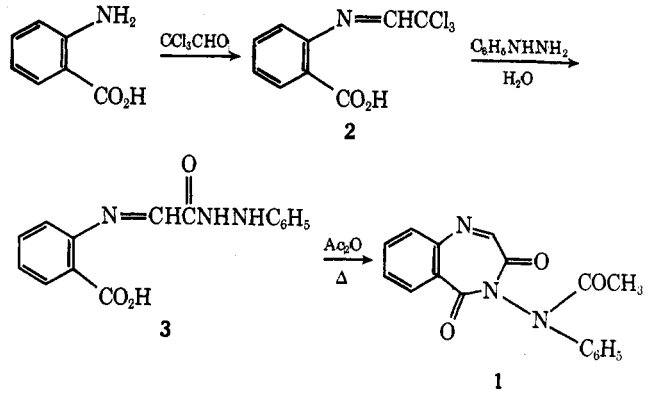

Norman W. Gilman,* John F. Blount, and R. Ian Fryer

*Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110*


*Received October 15, 1975*

A report in the chemical literature[2] in 1904 described the preparation of a compound to which the 1,4-benzodiazepine structure **1** was assigned. The mechanism for the formation of **1** from anthranilic acid was reported as outlined in Scheme I.

**Scheme I**




Owing to our continuing interest in 1,4-benzodiazepines, we have repeated the original work and found that although the reactions proceed ostensibly as described, the structures previously assigned to compounds **1**, **2**, and **3** are incorrect. The final product **1** was found to have the benzoxazinone structure **6a** rather than the 1,4-benzodiazepine structure **1**. The revised pathway for the formation of **6a** from anthranilic acid is shown in Scheme II.

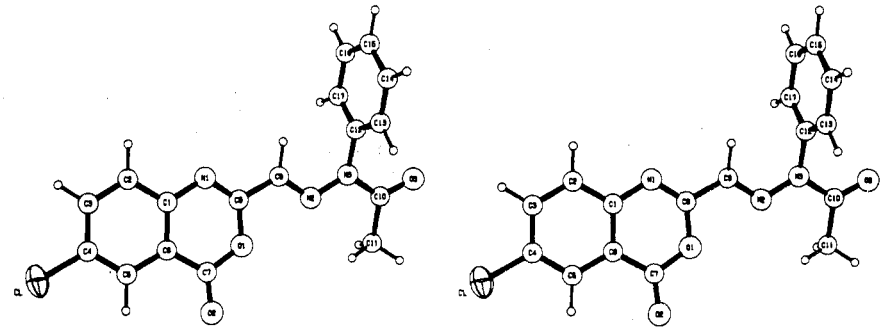
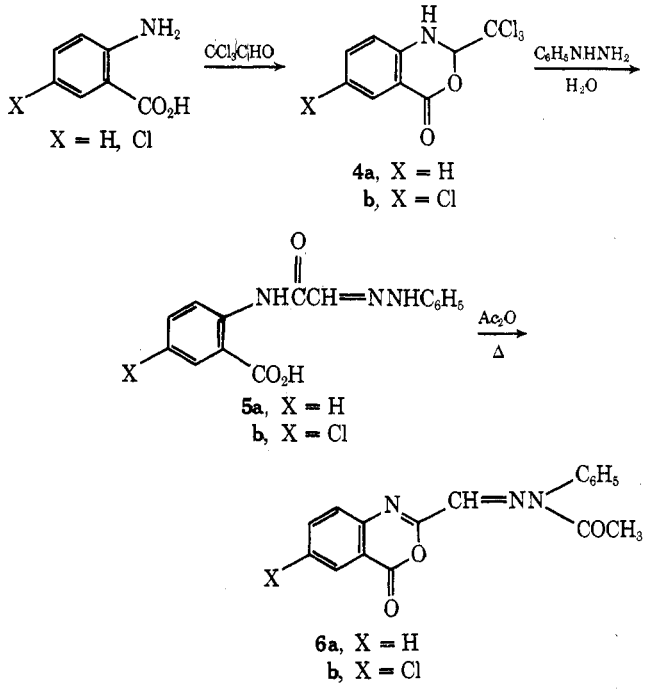


Figure 1. A stereodrawing of the structure of 6b.

Scheme II



The NMR spectrum of 4a (and 4b) showed the presence of a NH proton (doublet, $J$ = 4 Hz) and a methine proton (doublet, $J$ = 4 Hz). The ir spectrum showed a NH band and a lactone absorption peak but no absorption due to an acid group. These data are consistent with 4a (and 4b) but not with 2. The structures of 5a,b were not proven conclusively but were assigned on the basis that the compounds 6a,b were formed on acetylation rather than the 1,4-benzodiazepine 1. Since an interpretation of the spectral data on the final product 6a did not allow a definite assignment of structure, the chloro analogue 6b was subjected to single-crystal x-ray analysis. The spectral data and physical properties (melting point, solubility, TLC behavior, etc.) of compounds 6a, 6b, and intermediates were essentially identical, indicating that the chlorine substituent did not influence the course of the reactions.

Small acicular crystals of 6b were obtained upon crystallization from $CH_2Cl_2$–hexane. Crystals of 6b are triclinic, space group $P\bar{1}$, with $a$ = 4.733 (2), $b$ = 14.418 (5), $c$ = 23.185 (10) Å, $\alpha$ = 91.59 (3), $\beta$ = 93.45 (3), $\alpha$ = 91.49 (3)°, and $Z$ = 4. Intensity data were measured on a Hilger-Watts four-circle diffractometer ($\theta$–$2\theta$ scans, Ni-filtered Cu K$\alpha$ radiation; pulse height discrimination). The size of the crystal used for data collection was 0.04 × 0.05 × 0.55 mm; no absorption correction was made ($\mu$ = 23.4 cm$^{-1}$). Of the 4355 independent reflections measured, only 1441 had intensities which were greater than background.

The crystal structure was solved by a multiple solution procedure[3] and was refined by full-matrix least squares. In the final refinement anisotropic thermal parameters were used for the chlorine atoms and isotropic temperature factors were used for all other atoms. The positions of the hydrogen atoms were calculated and they were included in the structure factor calculations but were not refined. The final unweighted and weighted discrepancy indices are $R$ = 0.096 and $wR$ = 0.080 for the 1441 observed reflections. A difference map based on the final parameters has no features greater than 0.3 eA$^{-3}$ in magnitude.

The unit cell contains two independent molecules. The conformations of the two independent molecules are similar and the bond lengths and angles in the two independent molecules are equivalent. A projection of the molecule is shown in Figure 1.

## Experimental Section[4]

**1,4-Dihydro-2-trichloromethyl-2*H*-3,1-benzoxazin-4-one (4a).** A solution of 20 g (0.146 mol) of anthranilic acid and 22 g (0.15 mol) of chloral in 175 ml of benzene was refluxed for 4 h. The solution was filtered and the filtrate allowed to cool. Filtration gave 14.6 g (37%) of 4a as colorless needles: mp 150–152°; ir (KBr) 3315, 3270 (NH), 1720 cm$^{-1}$ (C=O); NMR ($Me_2SO$-$d_6$) $\delta$ 6.00 (1 H, d, CH), 6.53–7.67 (4 H, m, $C_6H_4$), 8.25 (1 H, d, NH).

Anal. Calcd for $C_9H_6Cl_3NO_2$: C, 40.56; H, 2.27; N, 5.26. Found: C, 40.75; H, 2.22; N, 4.82.

**6-Chloro-1,4-dihydro-2-trichloromethyl-2*H*-3,1-benzoxazin-4-one (4b).** A mixture of 5-chloroanthranilic acid (1.72 g, 10 mmol) and 2 ml of chloral were ground together in a mortar heated on a steam bath. After the chloral had evaporated, 3 ml of chloral was added, followed by a last increment of 2 ml of chloral. The crude product was recrystallized from benzene to give 2.2 g (73%) of 4b as colorless needles: mp 168–170.5°; ir (KBr) 3380, 3280 (NH), 1730 cm$^{-1}$ (C=O); NMR ($Me_2SO$-$d_6$) $\delta$ 6.23 (1 H, d, CH), 7.07–7.70 (3 H, m, $C_6H_3$), 8.70 (1 H, d, NH).

Anal. Calcd for $C_9H_5Cl_4NO_2$: C, 35.92; H, 1.67; N, 4.65; Cl, 47.12. Found: C, 36.15; H, 1.65; N, 4.55; Cl, 46.93.

**2-[1-(Phenylhydrazinyl-2-ylidene)acetylamino]benzoic Acid (5a).** A cold solution of 2 g (19 mmol) of phenylhydrazine in 25 ml of $H_2O$ and 15 ml of 3 N $H_2SO_4$ was added to a slurry of 5 g (19 mmol) of 4a in 60 ml of EtOH. After stirring at room temperature overnight, the solution was refluxed for 1 h, cooled, and filtered to give 2.7 g (50%) of 5a. The analytical sample was prepared by recrystallization from EtOH–$H_2O$: mp 235–237° (lit.[2] mp 243°); ir (KBr) 3300–2300 ($CO_2H$), 1675 cm$^{-1}$ (C=O).

Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.37; H, 4.51; N, 14.64.

**2-[1-(Phenylhydrazinyl-2-ylidene)acetylamino]-5-chlorobenzoic Acid (5b).** This compound was prepared in 76% yield in an analogous manner as that described for the preparation of 5a. The analytical sample was prepared by recrystallization from EtOH–$H_2O$: mp 253–255; ir (KBr) 3275–2300 ($CO_2H$), 1675 cm$^{-1}$ (C=O).

Anal. Calcd for $C_{15}H_{12}ClN_3O_3$: C, 56.70; H, 3.81; N, 13.23. Found: C, 56.52; H, 3.88; N, 13.19.

***N*-[(4-Oxo-4*H*-3,1-benzoxazin-2-yl)methyleneamino]-*N*-phenylacetamide (6a).** The following procedure is a modification of that described by Gärtner and although both methods gave the same product, the yields are greatly enhanced in the modified pro-

cedure. A mixture of 2.2 g (7.8 mmol) of **5a** and 10 ml of acetic anhydride was refluxed for 3.5 h. The solution was cooled and poured into 200 ml of ether and 200 ml of petroleum ether (bp 30–60°) and the resulting solid filtered to give 900 mg (37%) of **6a**. The filtrate was concentrated and the residue refluxed with 20 ml of acetic anhydride for 4 h to give an additional 800 mg (33%) of **6a**. The analytical sample was prepared by recrystallization from acetone–hexane: mp 267–268° (lit.[2] mp 260–262°); ir ($CHCl_3$) 1765, 1700 $cm^{-1}$ (2 C=O).

Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.45; H, 4.26; N, 13.67. Found: C, 66.40; H, 4.36; N, 13.55.

***N*-[(6-Chloro-4-oxo-4*H*-3,1-benzoxazin-2-yl)methyleneamino]-*N*-phenylacetamide (6b).** A mixture of 1.6 g (5 mmol) of **5b** and 25 ml of acetic anhydride was refluxed for 3.5 h, cooled, and poured into ether–petroleum ether. Filtration gave 1.3 g (76%) of **6b**. The analytical sample was prepared by recrystallization from $CH_2Cl_2$–hexane to give **6b** as colorless needles: mp 266–267°; ir ($CHCl_3$) 1770, 1703 $cm^{-1}$ (2 C=O).

Anal. Calcd for $C_{17}H_{12}ClN_3O_3$: C, 59.79; H, 3.54; N, 12.30. Found: C, 59.73; H, 3.33; N, 12.46.

**Acknowledgment.** The authors thank the following members of our Physical Chemistry Department, under the direction of Dr. R. P. W. Scott: Dr. F. Scheidl for elemental analyses, Dr. T. Williams for NMR spectra, and Mr. S. Traiman for ir spectra.

**Registry No.**—**4a,** 57527-44-3; **4b,** 57527-45-4; **5a,** 57527-46-5; **5b,** 57527-47-6; **6a,** 57527-48-7; **6b,** 57527-49-8; anthranilic acid, 118-92-3; chloral, 75-87-6; 5-chloroanthranilic acid, 635-21-2; phenylhydrazine, 100-63-0; acetic anhydride, 108-24-7.

**Supplementary Material Available.** Tables of the positional and thermal parameters for the structure of **6b** (2 pages). Ordering information is given on any current masthead page.

## References and Notes

(1) Part LXXI: A. Walser, T. Flynn, and R. Ian Fryer, *J. Heterocycl. Chem.*, **12**, 717 (1975).
(2) (a) S. Gärtner, *Justus Liebigs Ann. Chem.*, **332**, 226 (1904); (b) J. A. Moore and E. Mitchell in "Heterocyclic Compounds", Vol. 9, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1967, p 345.
(3) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(4) Melting points were determined in a Thomas-Hoover apparatus and are corrected. The ir spectra were determined on a Beckman IR-9 or a Perkin-Elmer 621 instrument. NMR spectra were determined on a Varian A-60 or HA-100 spectrometer, using tetramethylsilane as an internal standard.

---

# An Electron Spin Resonance Study of Kinetics in the SRN1 Reaction of Aryl Halides with Potassium

Olga Perez de Marquez and James Giulianelli

*Departamento de Química, Universidad de Los Andes, Mérida, Venezuela*

Thomas C. Wallace

*Department of Chemical Engineering, Lehigh University, Bethlehem, Pennsylvania 18015*

Dolan H. Eargle, Jr.*

*Department of Pharmaceutical Chemistry, University of California, San Francisco, California 94143*

*Received July 15, 1975*

The reaction of aryl halides with alkali metals is known to be quite rapid,[1-3] with the anion radical of the aryl halide generally decomposing in less than 1 s, even at very low temperatures. The ESR signal normally obtained after the decomposition is that of the parent hydrocarbon anion radical. We have modified the usual reduction procedure[4] in order to observe the decay of the arene hydrocarbon anion radical in its electron exchange reaction with excess aryl halide (step 4 of Scheme II).

In this modification, a $10^{-3}$ M solution of the aryl halide in 2:1 THF–DME is only momentarily brought into contact with a potassium mirror at −135°. The solution (removed from contact with the metal) is immediately plunged into a precooled ESR cavity and the ubiquitous[5] arene hydrocarbon signal observed. Under these circumstances, the aryl halide is readily available for electron exchange with the small amount of freshly produced hydrocarbon anion radical.

With the biphenylyl halides what is actually observed then is the decay of the biphenyl anion radical, a special case of the SRN1 mechanism recently recognized by Bunnett et al.[6] and generalized in Scheme I.[7]

**Scheme I**

$$\text{electron donor} + \text{ArX} \longrightarrow (\text{ArX})\cdot^- \quad (1)$$

$$(\text{ArX})\cdot^- \longrightarrow \text{Ar}\cdot + \text{X}^- \quad (2)$$

$$\text{Ar}\cdot + \text{R}:^- \longrightarrow (\text{ArR})\cdot^- \quad (3)$$

$$(\text{ArR})\cdot^- + \text{ArX} \longrightarrow \text{ArR} + (\text{ArX})\cdot^- \quad (4)$$

The decay of the biphenyl anion radical signal in step 4 follows excellent first-order kinetics,[8] consistent with the SRN1 mechanism. The reaction steps of Scheme II follow the parallel paths of Scheme I, in which the solvent behaves as the "R" donor (steps 3).

**Scheme II**

$$\text{K}\cdot + \text{ArX} \longrightarrow (\text{ArX})\cdot^- + \text{K}^+ \quad (1)$$

$$(\text{ArX})\cdot^- \longrightarrow \text{Ar}\cdot + \text{X}^- \quad (2)$$

$$\text{Ar}\cdot + \text{solvent-H} \longrightarrow \text{ArH} \xrightarrow[\text{of K}\cdot]{\text{remaining traces}} (\text{ArH})\cdot^- \quad (3)$$

$$(\text{ArH})\cdot^- + \text{ArX} \longrightarrow \text{ArH} + (\text{ArX})\cdot^- \quad (4)$$

It must be noted that Scheme II requires one extra reduction as part of step 3 in which the remaining traces of solvated potassium are used up to produce more biphenyl anion radical. The chain proceeds until the ultimate product is unreduced biphenyl. If the final diamagnetic product is once again subjected to a somewhat longer reduction, the biphenyl signal is produced instantaneously and the signal does not decay.

Following the initial decay of the biphenyl signal from biphenylyl fluoride, a dimerization product, quaterphenyl anion radical, was observed to replace the biphenyl signal after some 90 min at −100°. The dimer probably arises from 2Ar·→ Ar–Ar, followed by reduction via residual $ArH\cdot^-$ or K·. Since quaterphenyl was not observed in any of the other reactions, it is possible that a high initial concentration of Ar· from ArF could produce this unique result. The highly reactive ArF would give this high initial concentration.

As may be seen in Table I, we also attempted a similar reduction of 4-nitrilobiphenyl; however, owing to the stabilizing influence of the CN group, we succeeded in obtaining initially only the decay (first order) of the parent anion radical.[9] Upon subsequent reduction at −120°, only the biphenyl signal was found. Evidently, for this system step 2 is quite slow, using up all available solvated metal, and the reaction stops at the step 3 production of biphenyl (unreduced).

We measured the decomposition rates for three of the biphenylyl halides at two temperatures (Table I). Above