[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

The Reduction of Fluorenone by Hydrazine—Some Observations on the Mechanism of the Wolff-Kishner Reaction

JOHN H. WEISBURGER AND PRESTON H. GRANTHAM

Received May 10, 1956

The reduction of fluorenone by the Huang-Minlon modification of the Wolff-Kishner reaction requires a six-fold excess of hydrazine hydrate in order to secure the best yield of fluorene. With decreasing amounts of hydrazine, increasing quantities of 9,9′-bifluorene, and other unidentified products are obtained. The initial reaction results in the formation of fluorenone ketazine. The excess hydrazine appears involved in the subsequent decomposition of the azine, possibly by furnishing hydrogen to a fluorenyl radical. Support for this idea comes from the interchangeability of thiophenol for hydrazine. $\Delta^{9,9'}$-Bifluorene is also reduced to fluorene by hydrazine.

The reduction of fluorenone derivatives has been found to be a useful method for the preparation of substituted fluorenes which could not be synthesized by more direct procedures.[1–4] In connection with pilot studies on the preparation of carbon-14 labeled fluorene from fluorenone[5,6] by the Huang-Minlon modification of the Wolff-Kishner reaction we had occasion to investigate the effect of varying the the proportions of hydrazine hydrate to fluorenone. It was found (Table I) that at equivalent molar ratios of hydrazine and fluorenone, relatively small amounts of fluorenone and substantial quantities of 9,9′-bifluorene were obtained. With increasing proportions of hydrazine, more fluorene and less 9,9′-bifluorene was produced. Complete conversion to fluorene occurred with a six-fold excess of hydrazine.

These results prompted us to investigate this reduction in some detail. The experiments showed that under the conditions of the Wolff-Kishner reaction the rapid initial step always led to fluorenone ketazine even in the presence of a large excess of hydrazine. Fluorenone hydrazone could be prepared only in the absence of alkali.[7] Hence the effect of increasing amounts of hydrazine on the reduction of the azine was studied and a behavior parallel to that observed with fluorenone was noted. In the absence of hydrazine the azine gave only unidentified colored oily mixtures. 9,9′-Bifluorene was the main recognizable product with low ratios of hydrazine, while fluorene was obtained when larger amounts of the reducing agent were employed.

Although $\Delta^{9,9'}$-bifluorene was never isolated it might be produced in the decomposition of fluorenone azine, according to the relation $R{=}N{-}N{=}R \rightarrow R{=}R + N_2$, where R is fluorenylidene. Under the conditions of the Wolff-Kishner reaction this compound was reduced to 9,9′-bifluorene and fluorene, thus providing indirect, even if circumstantial evidence that $\Delta^{9,9'}$-bifluorene might be an intermediate in the reaction.

It is generally assumed that in those cases where the azine is the primary reaction product in the Wolff-Kishner reaction, the azine must be reduced to the hydrazone before decomposition of the latter to hydrocarbon and nitrogen can occur.[8] Therefore fluorenone hydrazone was subjected to the conditions of the reaction which can be simply written (R = 9-fluorenylidene):

$$R{=}N{-}NH_2 \rightleftarrows RH_2 + N_2$$

On the basis of this equation straight forward decomposition of the hydrazone should yield the hydrocarbon and nitrogen. However, in the absence of hydrazine oily products similar to those given by the azine were obtained. The hydrazone was probably not converted to the azine during the reaction in view of the absence of the characteristic colored precipitate of the azine. Thus, the reaction is considerably more complex than indicated by the equation shown above. It seems more likely that free radical intermediates occur in this reaction, as discussed later. Fluorene was found only in the presence of an excess of hydrazine. Under those conditions alkali was not required.[6,8]

In earlier investigations on the mechanism of the Wolff-Kishner reduction kinetic studies on the evolution of gas showed in general the expected yield of nitrogen.[9,10] However, in these cases no attempts were made to isolate the hydrocarbon produced, or else a rather poor yield of the hydrocarbon was reported. When the reduction was used on a preparative scale, an excess of hydrazine was customarily added to the reaction mixture so that the effect of

---

(1) Bergmann and Orchin, *J. Am. Chem. Soc.*, **71**, 1111 (1949).

(2) Sawicki, Ray, and Glocklin, *J. Org. Chem.*, **21**, 243 (1956).

(3) Weisburger and Weisburger, *J. Org. Chem.*, **20**, 1396 (1955).

(4) Weisburger, *J. Am. Chem. Soc.*, **77**, 1914 (1955).

(5) Heidelberger and Rieke, *Cancer Research*, **11**, 640 (1951).

(6) Harris, White, and McNeil, *J. Chem. Soc.*, 4216 (1955).

(7) Wieland and Rosee, *Ann.*, **381**, 229 (1911).

(8) Todd, in Adams, *Org. Reactions*, **4**, 378 (1948).

(9) Todd, *J. Am. Chem. Soc.*, **71**, 1356 (1949).

(10) Szmant, Harnsberger, Butler, and Barie, *J. Am. Chem. Soc.*, **74**, 2724 (1952).

lowered ratios of hydrazine was not heretofore noted.

The data in Table I show a requirement for an excess of hydrazine in the decomposition of either fluorenone hydrazone or azine in order to obtain fluorene. It is, therefore, evident that hydrazine has an ulterior function, besides the formation of these intermediates in the reduction. The fact that thiophenol but not mercaptoethanol can replace hydrazine in the decomposition of the fluorenone hydrazone to yield fluorene suggests that the excess hydrazine generally acts by terminating a series of free radical reactions. The mechanism of the reaction can be assumed to involve the following steps. Fluorenone hydrazone can be conceived to form either the corresponding anion or diimine[cf. 10] which then could decompose into nitrogen and the 9-fluorenyl free radical. This radical could thereafter undergo a number of reactions depending on the environment. Excess hydrazine would produce fluorene by providing a terminating reactant for the fluorenyl radical. With lower amounts of hydrazine, both production of fluorene and the dimerization of the radical giving 9,9′-bifluorene could take place. In the absence of hydrazine the fluorenyl radical could undergo a wide variety of reactions with itself, yielding polymers, or with the solvent to give some of the oily substances which were observed.

TABLE I

DEPENDENCE OF FLUORENONE REDUCTION PRODUCTS ON MOLAR RATIO OF HYDRAZINE HYDRATE

Compound	Ratio $N_2H_4 \cdot$-H_2O^a	Fluorene, %	Bifluoryl, %
Fluorenone	1.1	8	54
Fluorenone	2.1	68	18
Fluorenone	2.5	87	7
Fluorenone	3.5	87	9
Fluorenone	5.0	95	5
Fluorenone	6.4	97	0
Fluorenone	7.7	98	0
Fluorenone	8.3	97	0
Fluorenone azine	0^c	—	—
Fluorenone azine	0.25	—	5
Fluorenone azine	0.5	7	75
Fluorenone azine	2.5	73	15
Fluorenone azine	6.5	85	6
Fluorenone azine	15.0	88	9
Fluorenone azine^b	1.0	14	—
Fluorenone azine^b	6.0	96	0
Fluorenone hydrazone	0^c	—	—
Fluorenone hydrazone	7.5	95	0
Fluorenone hydrazone^b	7.5	97	0
Fluorenone hydrazone	$7.5^{c,d}$	—	0
Fluorenone hydrazone	7.5^e	68	0.4
$\Delta^{9,9'}$-Bifluorene	2.5	70	19
9,9′-Bifluorene^f	7.5	0	96
Fluorene^f	8.6	100	0

[a] The figures in this column represent the ratio of moles of hydrazine hydrate per mole of fluorenyl residue. [b] Potassium hydroxide omitted in this experiment. [c] Only unidentified oils were obtained. [d] Mercaptoethanol substituted for hydrazine. [e] Thiophenol substituted for hydrazine. [f] Control experiments. It can be noted that fluorene and 9,9′-bifluorene are stable under the conditions of the reduction.

A somewhat similar phenomenon was encountered recently by Cohen and Wang[11] in a study of the decomposition of azodiphenylmethane in the presence of diphenylmethane-C^{14}. These authors obtained a 95% yield of 1,1,2,2-tetraphenylethane with only a minor exchange of radioactivity. However, in the presence of thiophenol, exchange of radioactivity did occur and the yield of the dimer dropped to 59%. Thus, addition of thiophenol reduced dimer formation. The same type of mechanism may prevail in the case of the Wolff-Kishner reduction, when hydrazine minimizes dimer or polymer formation in the free radical decomposition of the hydrazone or of the azine. The fact that the reduction proceeds only at elevated temperatures would also suggest a free radical mechanism. It is of course possible that our results with the reduction of fluorenone represent a special case; the applicability of our data to different compounds will have to be studied by others.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage. Further identifications were made by infrared and ultraviolet spectra recorded on a Perkin-Elmer model 21, and a Cary model 11 spectrophotometer, respectively.

General reduction procedure. The compound to be reduced (Table I) (6 millimoles) was dissolved or suspended in 8 ml. of distilled diethylene glycol on a steam-bath. The required amount of hydrazine hydrate was pipetted in and a solution of approximately 1.2 g. (8 pellets) of potassium hydroxide in 5 ml. of diethylene glycol (prepared by brief warming in a test tube) was added. The mixture was kept on the steam-bath for ten minutes, then gently heated with a direct flame for three hours under a reflux condenser. Most of the fluorene produced sublimed into the condenser. In the presence of an excess of hydrazine hydrate, color changes from red-brown to dark green, light green, and greyish to colorless were observed; with low amounts of hydrazine only the first two stages were noted. At the end of the reduction period the material in the condenser was returned to the flask by rinsing with 5 ml. of ethanol followed by brief refluxing. The reaction mixture was acidified with 8 ml. of 12 *N* hydrochloric acid, diluted with 50 ml. of water, and cooled in ice. The crude product obtained on filtration was worked up in one of three ways depending on its properties.

a. White product with a melting point higher than 105°: The nearly pure fluorene was dissolved in benzene and percolated through a column of Merck alumina (1 × 8 cm.). Fluorene, m.p. 115°, was obtained on removal of the solvent.

b. White product with a melting range below 105°: The crude material was vacuum-sublimed fractionally at 10–20 microns pressure. Fluorene sublimed in 3–5 hours, depending on the amount, with a bath temperature of 70°, while 9,9′-bifluorene sublimed at an appreciable rate only with a bath temperature of 140°. Recrystallization of the fractions from benzene-ethanol (1:2 to 1:3) yielded fluorene, m.p. 115°, and 9,9′-bifluorene, m.p. 246°,[12] respectively.

In several of the experiments using a 2.5- to 5-fold excess of hydrazine hydrate an unsublimed residue, m.p. 250–

---

(11) Cohen and Wang, *J. Am. Chem. Soc.*, **77**, 4435 (1955).

(12) Graebe and Stindt, *Ann.*, **291**, 2 (1896).

280° was left in the apparatus after the removal of 9,9′-bifluorene. This product could in turn be sublimed at 220° and recrystallized from benzene-ethanol to give small needles, m.p. 292–294°. Insufficient amounts of this compound were available for a complete characterization. It was a hydrocarbon (single analysis: C, 92.7, H, 6.18, Mol. weight, 500). The ultraviolet absorption spectrum was like that of fluorene, the infrared record was similar but not identical to that of trifluorene.[13]

c. *Colored pasty materials:* Such mixtures, obtained with low ratios of hydrazine in the reductions, were taken up in benzene to give reddish-brown solutions (any insoluble residues were discarded). Percolation through an alumina column usually gave brown bands and a red eluate from which the solvent was removed. The gummy solid was subjected to vacuum-sublimation. Initial fractions (bath temperature 50–70°) as well as late fractions (bath 160–200°) were generally oily, unidentified substances (absence of an infrared band around 3 microns, however, indicated the absence of compounds like 9-hydroxyfluorene). Center fractions at the proper temperatures yielded fluorene and 9,9′-bifluorene in the amounts indicated in Table I.

Fluorene ketazine. Fluorenone (5.9 millimoles) in 8 ml. of diethylene glycol was treated with 46 and 5.4 millimoles of hydrazine hydrate, respectively, in two separate experiments. Potassium hydroxide (1.2 g.) in 5 ml. of solvent was added and the mixtures were kept on the steam-bath for ten minutes. On cooling and filtering, these runs gave 2.9 and 2.7 millimoles (98 and 92% yield), respectively, of fluorenone azine, m.p. 263–265°. Recrystallization of each batch from 18 ml. of xylene afforded a 75% yield of the azine, m.p. 265–269°.[7,14]

Anal. Calc'd for $C_{26}H_{16}N_2$: C, 87.61; H, 4.53; N, 7.86. Found: C, 87.78; H, 4.78; N, 7.73.

These experiments formed the basis of the following improved preparation of the azine: A solution of 17 g. of potassium hydroxide in 60 ml. of ethanol was added to a hot mixture of 16.3 g. of fluorenone, 36 ml. of 85% hydrazine hydrate, and 225 ml. of ethanol. Formation of the azine was completed by refluxing for $^1/_4$ hour. Upon cooling 15.9 g. (99%) of violet needles, m.p. 262–267°, were filtered off.

BETHESDA 14, MARYLAND

---

[13] Pinck and Hilbert, *J. Am. Chem. Soc.*, **68**, 2014 (1946); we are grateful to Dr. Pinck for providing us with samples of authentic trifluorene (tribiphenylenepropane) for comparative purposes.

[14] Staudinger and Kupfer, *Ber.*, **44**, 2197 (1911).