The Acid Hydrolysis of 1-Alkyl- and 1,1-Dialkyl-2-*p*-tolylsulfonylhydrazines

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The treatment of 1,1-dimethyl-2-*p*-tolylsulfonylhydrazine with acid gave *p*-tolylthio *p*-toluenesulfonate, *p*-tolyl disulfide, methyl chloride, nitrogen, ammonia, methylamine, dimethylamine, trimethylamine, 1,1-dimethylhydrazine, and trimethylhydrazine as products. Under similar conditions, 1-methyl-2-*p*-tolylsulfonylhydrazine gave methylhydrazine, methyl bromide, nitrogen, *p*-tolyl disulfide, and *p*-tolythio *p*-toluenesulfonate, and 1,1-dibenzyl-2-*p*-tolylsulfonylhydrazine gave benzaldehyde, benzylhydrazine, and *p*-tolylthio *p*-toluenesulfonate. 1,1,2-Trimethyl-2-*p*-tolylsulfonylhydrazine could not be prepared by the treatment of trimethylhydrazine with *p*-toluenesulfonyl chloride. Decomposition occurred and gave 1,1-dimethylhydrazine and *p*-tolylthio *p*-toluenesulfonate. The formation of the various products can be explained by the prior dissociation of the sulfonylhydrazines into diazenium and sulfinate ions.

Trimethylamine-*p*-toluenesulfonimide was prepared in earlier work by the methylation of 1,1-dimethyl-2-*p*-tolylsulfonylhydrazine with methyl iodide and subsequent treatment of the resulting hydrazonium iodide with alkali.[2] Extension of the synthesis to the preparation of the benzyldimethyl derivative proceeded differently in the alkylation step and gave benzyl *p*-tolyl sulfone as one of the products. A possible course for this reaction is a prior dissociation of the sulfonylhydrazine to azenium and sulfinate ions followed by an alkylation of the sulfinate ion.

$$(CH_3)_2NNHSO_2C_6H_4CH_3\text{-}p \longrightarrow (CH_3)_2\overset{+}{N}{=}NH + p\text{-}CH_3C_6H_4SO_2^-$$

To obtain more evidence for this mechanism and to simplify the products formed, the action of acids on 1,1-dimethyl-2-*p*-tolylsulfonylhydrazine, 1-methyl-2-*p*-tolylsulfonylhydrazine, and 1,1-dibenzyl-2-*p*-tolylsulfonylhydrazine was studied. 1,1-Dimethyl-2-*p*-tolylsulfonylhydrazine, when heated with concentrated hydrochloric acid, gave *p*-tolylthio *p*-toluenesulfonate, *p*-tolyl disulfide, methyl chloride, nitrogen, and the hydrochlorides of ammonia, methylamine, dimethylamine, trimethylamine, 1,1-dimethylhydrazine, and trimethylhydrazine as products. The nitrogen and methyl chloride were evolved during the initial stages of the reaction and the *p*-tolylthio *p*-toluenesulfonate and *p*-tolyl disulfide separated as an insoluble oil. The ammonia, amines, and hydrazines were obtained as salts by evaporation of the acid layer. The ammonium chloride was separated from the other salts by its insolubility in absolute ethanol and the composition of the remaining products was established by gas chromatography after treatment with alkali.

The isolation of *p*-tolylthio *p*-toluenesulfonate and *p*-tolyl disulfide confirms the formation of the sulfinate ion. Sulfinic acids are known to undergo acid catalyzed disproportionation to thiosulfonate esters and sulfonic acids[3] and to be reduced easily to the former compound and to diaryl disulfides.[4]

The other products must result from the decomposition of the azenium ion. To prove this postulate, 1,1-dimethylazenium bromide was prepared by the bromine oxidation of 1,1-dimethylhydrazine at 0° in hydrochloric acid using the method of McBride and Kruse[5,6] and was allowed to decompose at room temperature. The basic products obtained were the same as those obtained in the acid hydrolysis of the sulfonyl hydrazine. The volatile gases consisted of a mixture of methyl bromide, methyl chloride, and nitrogen.

The actual mechanism for the formation of these compounds is not known. One possibility which can account for some of the products formed involves successive displacements of halide ion on the diazenium ion and the subsequent formation of diimide, which is a powerful reducing agent.[7-9] This

$$(CH_3)_2\overset{+}{N}{=}NH + X^- + H^+ \longrightarrow CH_3X + CH_3\overset{+}{N}H{=}NH$$

$$CH_3\overset{+}{N}H{=}NH + X^- \longrightarrow CH_3X + HN{=}NH$$

$$HN{=}NH \longrightarrow N_2 + 2H^+ + 2e$$

$$(CH_3)_2\overset{+}{N}{=}NH + 2e + 2H^+ \longrightarrow (CH_3)_2NHNH_2^+$$

$$(CH_3)_2NHNH_2^+ + 2e + 3H^+ \longrightarrow NH_4^+ + (CH_3)_2NH_2^+$$

intermediate could reduce the azenium ion to 1,1-dimethylhydrazine. Dimethylamine and ammonia could be formed by the reductive cleavage of the salt of 1,1-dimethylhydrazine by diimide. This type of reduction by diimide has not been observed in neutral medium but may be a possibility in acid solutions.

Another possibility is the reaction of the azenium ion with diimide to form an intermediate similar to

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that postulated in the oxidation of hydrazine in acid medium for the formation of ammonium ions.[10]

The possible formation of diimide under these conditions is being studied further.

The mode of formation of methylamine, trimethylamine, and trimethylhydrazine is not clear. The alkylation of ammonia, dimethylamine, and 1,1-dimethylhydrazine by the methyl halide or 1,1-dimethylazenium ion is a possibility but seems unlikely in acid medium.

The differences in the yields of basic products in the two methods used can be accounted for by the consumption of a portion of the diimide in the reduction of sulfinic acid to the thiosulfonate ester and the disulfide. The yield of these products obtained

$$p\text{-}CH_3C_6H_4SO_2H \xrightarrow{HN=NH} p\text{-}CH_3C_6H_4SSO_2C_6H_4CH_3\text{-}p + (p\text{-}CH_3C_6H_4S)_2$$

precludes the possibility that a disproportionation of the sulfinic acid is the sole source of the thiolsulfonate ester and diaryl disulfide.

The hydrobromic acid cleavage of 1-methyl-2-*p*-tolylsulfonylhydrazine gave *p*-tolylthio *p*-toluenesulfonate, *p*-tolyl disulfide, methylhydrazine, methyl bromide, and nitrogen. Bromine oxidation of methylhydrazine gave similar volatile and basic products. The intermediate methyldiazenium bromide is very unstable and decomposes immediately at 0°. The mechanism of this decomposition would be similar to that proposed for the decomposition of the 1,1-dimethylazenium ion with the exception of the cleavage reaction.

Extension of the acid cleavage reaction to 1,1,2-trimethyl-2-*p*-tolylsulfonylhydrazine could not be carried out because of the instability of this compound. Treatment of *p*-toluenesulfonyl chloride with trimethylhydrazine gave 1,1-dimethylhydrazine and *p*-tolylthio *p*-toluenesulfonate. Oxidation of trimethylhydrazine with bromine gave no gas evolution; 2-methylene-1,1-dimethylhydrazine hydrobromide was formed as the main product. This compound could be formed by a migration of the double bond in the trimethylazenium ion with a loss of a proton or by an elimination reaction in-

$$(CH_3)_2\overset{+}{N}=NCH_3 \longrightarrow (CH_3)_2NN=CH_2 + H^+$$

$$(CH_3)_2\underset{Br}{N}NCH_3 \longrightarrow (CH_3)_2NN=CH_2 + HBr$$

volving N-bromotrimethylhydrazine. The results obtained from the reaction of *p*-toluenesulfonyl chloride with trimethylhydrazine would favor diazenium ion formation. The 1,1-dimethylhydrazine actually isolated in this reaction would result

$$(CH_3)_2NNHCH_3 \xrightarrow{TsCl} (CH_3)_2\overset{CH_3}{\underset{|}{N}}\overset{+}{N}\text{—}SO_2C_6H_4CH_3\text{-}p \longrightarrow (CH_3)_2\overset{+}{N}=NCH_3 + p\text{-}CH_3C_6H_4SO_2^-$$

from the hydrolysis of the 2-methylene-1,1-dimethylhydrazine.

1,1-Dibenzyl-2-*p*-tolylsulfonhydrazine upon acid hydrolysis gave benzaldehyde, *p*-tolylthio *p*-toluenesulfonate, and benzylhydrazine. The bromine oxidation of 1,1-dibenzylhydrazine gave similar products. These results indicate that the intermediate 1,1-dibenzylazenium ion undergoes a migration of the double bond to a position which is conjugated with the aromatic ring. The inter-

$$(C_6H_5CH_2)_2\overset{+}{N}=NH \longrightarrow C_6H_5CH_2\overset{+}{N}\text{—}NH_2 \quad (C_6H_5CH \text{ double-bonded})$$

mediate salt upon hydrolysis produces the products mentioned.

Bibenzyl, which is formed by the action of base on 1,1-dibenzyl-2-benzenesulfonylhydrazine,[11] was not found in this reaction.

The alkylation of 1,1-dimethyl-2-*p*-tolylsulfonylhydrazine with benzyl chloride was reinvestigated and found to form benzyl *p*-tolyl sulfone and similar basic and volatile products to those obtained by the acid hydrolysis of 1,1-dimethyl-2-*p*-tolylsulfonylhydrazine and the bromine oxidation of 1,1-dimethylhydrazine.

The results obtained in this investigation indicate that 1-methyl-, 1,1-dimethyl-, and 1,1-dibenzyl-2-*p*-tolylsulfonylhydrazine in their reactions undergo a prior dissociation into diazenium and sulfinate ions and give products which result from these intermediates.

Experimental[12]

1-Methyl-2-p-tolylsulfonylhydrazine.—To an ether solution (100 ml.) of 30 g. (0.65 mole) of methylhydrazine and 65.5 g. (0.65 mole) of triethylamine, 124 g. (0.65 mole) of *p*-toluenesulfonyl chloride was added slowly at 0°, and the reaction mixture was stirred for 2 hr. The triethylamine hydrochloride was removed by filtration and washed with dry ether and the combined ether extracts were washed with a minimum of water. Removal of the ether gave 1-methyl-2-*p*-tolylsulfonylhydrazine, which was crystallized from 80% ethanol. The product, melting at 66–71°, weighed 60 g. (46%). After recrystallization from hexane the product melted at 72–73°.

Anal. Calcd. for $C_8H_{12}N_2SO_2$: C, 47.99; H, 6.04. Found: C, 48.17; H, 6.01.

1,1-Dimethyl-2-p-tolylsulfonylhydrazine[2] and 1,1-dibenzyl-2-*p*-tolylsulfonylhydrazine[11] were obtained in yields of 72 and 65%, respectively, by this procedure.

Acid Hydrolysis of 1,1-Dimethyl-2-p-tolylsulfonylhydrazine.—A suspension of 35.5 g. (0.166 mole) of 1,1-dimethyl-2-*p*-tolylsulfonylhydrazine in 150 ml. of concentrated hydrochloric acid was heated at 100° and the methyl chloride and nitrogen (400 ml.) evolved were collected. These gases were identified by gas chromatography using di-2-ethylhexyl sebacate and activated charcoal columns, respectively, at 25°.

After the vigorous reaction subsided, the reaction mixture, which had become homogeneous, was heated further for 6 hr. Upon cooling, an oil formed and solidified. Extraction of the reaction mixture with three 30-ml. portions of

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(12) Melting and boiling points are not corrected.

TABLE I

RETENTION TIMES FOR AMINES AND HYDRAZINES ON COLUMN F AT 25° AND 25 P.S.I. OF HELIUM

Compound	Authentic sample Time, min.	Acid hydrolysis products Time, min.	Acid hydrolysis products Relative area %	Bromine oxidation products Time, min.	Bromine oxidation products Relative area %
CH_3NH_2	1:12	1:12	2.5	1:06	7
$(CH_3)_2NH$	1:36	1:30	48.4	1:30	30
$(CH_3)_3N$	:48	:36	10.5	:42	3
$(CH_3)_2NNH_2$	9:18	9:31	36.3	9:12	52.2
$(CH_3)_2NNHCH_3$	6:36	6:30	2.4	6:14	2.7

ether gave, after removal of the solvent, 19 g. of *p*-tolylthio *p*-toluenesulfonate contaminated with *p*-tolyl disulfide. Extraction with petroleum ether (b.p. 60–68°) gave 1.9 g. of *p*-tolyl disulfide; m.p. 46–47° (lit. m.p. 46°).[13] The residue (17 g.), upon recrystallization from 95% ethanol, gave *p*-tolylthio *p*-toluenesulfonate; m.p. 74–75°. A mixture with an authentic sample[14] melted at the same point.

The acid layer from the reaction mixture was evaporated to dryness under reduced pressure and gave a solid (7.5 g.). Repeated extractions with absolute ethanol gave 0.7 g. of ammonium chloride which was identified by its melting point and nitrogen analysis.

Removal of the alcohol followed by treatment with alkali gave a mixture of bases which were analyzed by gas chromatography using a Perkin Elmer Column F (tetraethylene glycol dimethyl ether). The results are shown in Table I.

Bromine Oxidation of 1,1-Dimethylhydrazine.—To a solution of 1,1-dimethylhydrazine (30 g.) (0.5 mole) in concentrated hydrochloric acid (125 ml.) at 0°, bromine (80 g.) (0.5 mole) was added dropwise. The bromine color was discharged immediately. The resulting solution was divided into two equal portions. One portion (70 ml.) at 0° was made basic with sodium hydroxide and extracted with ether. Removal of the solvent gave tetramethyltetrazine (12.2 g.) (85%); b.p. 35° (15 mm.). The melting point of the picrate, 79–80°, agreed with the value reported in the literature.[5]

The above procedure was carried out to confirm the presence of the 1,1-dimethyldiazenium ion.

The second part (70 ml.), upon warming to room temperature, evolved a gas which, from analysis by gas chromatography on tetraethylene glycol dimethyl ether and activated charcoal columns, proved to be a mixture of methyl bromide, methyl chloride, and nitrogen.

The acid fraction upon evaporation to dryness gave a solid from which 1.6 g. of ammonium chloride was obtained by repeated extractions with absolute ethanol. Removal of the alcohol followed by treatment with alkali gave 9.0 g. of a liquid boiling under 100°. The analysis of this mixture by gas chromatography is shown in Table I

Acid Hydrolysis of 1-Methyl-2-*p*-tolylsulfonylhydrazine.—A mixture of 30 g. (0.15 mole) of 1-methyl-2-*p*-tolylsulfonylhydrazine and 125 ml. of 48% hydrobromic acid was heated at 100° for 6 hr. During the initial heating, a vigorous reaction occurred with the evolution of methyl bromide and nitrogen. The resulting mixture, upon extraction with three 50-ml. portions of ether, gave 17.3 g. of crude *p*-tolylthio *p*-toluenesulfonate melting at 67–72°. Extraction of the crude material with petroleum ether (b.p. 60–68°) gave 1.6 g. of *p*-tolyl disulfide; m.p. 46–47°. Recrystallization of the residue from 95% ethanol gave 15 g. of *p*-tolylthio *p*-toluenesulfonate melting at 74–75°.

Evaporation of the acid layer gave a solid which, after recrystallization from absolute ethanol, weighed 4.3 g. and melted at 83–86°. A second recrystallization from an absolute ethanol–ether mixture gave a sample melting at 88–89° which proved identical with methylhydrazine hydrobromide prepared from methylhydrazine and hydrogen bromide in ether.

Anal. Calcd. for CH_7N_2Br: C, 9.46; H, 5.55. Found: C, 9.71; H, 5.74.

Oxidation of 1-Methylhydrazine with Bromine.—The addition of 80 g. of bromine dropwise to a solution of 1-methylhydrazine (23 g.) (0.5 mole) in 150 ml. of 48% hydrobromic acid at 0° produced an immediate evolution of nitrogen and methyl bromide. After the cessation of the gas evolution, the reaction mixture was stirred for an additional 2 hr. The addition of ether to the soution precipitated 30.2 g. (0.24 mole) of 1-methylhydrazine hydrobromide melting at 87–89°.

Reaction of Trimethylhydrazine with *p*-Toluenesulfonyl Chloride.—Trimethylhydrazine[15] (27 g.) (0.36 mole) at 0° was added dropwise to solid *p*-toluenesulfonyl chloride (34.3 g.) (0.18 mole) over a period of 1 hr. The resulting yellow solution was treated with water and extracted with ether. Removal of the ether gave 8 g. of crude *p*-tolylthio-*p*-toluenesulfonate. No disulfide was obtained. The water layer upon evaporation gave a black sirupy residue which was added to a hot solution of potassium hydroxide, and the volatile liquid boiling below 100° was collected. Redistillation from solid potassium hydroxide gave a fraction (14 g.) boiling over the range 53–81°. Analysis by gas chromatography indicated a mixture of 1,1-dimethylhydrazine and trimethylhydrazine.

Very similar results were obtained using triethylamine as a solvent.

Oxidation of Trimethylhydrazine with Bromine.—A solution of trimethylhydrazine (10 g.) (0.12 mole) in 70 ml. of 48% hydrobromic acid at 0° was treated dropwise with 19 g. (0.12 mole) of bromine with vigorous stirring. No gas evolution occurred at this point or when the solution was heated to 100°. The addition of ether gave a precipitate (12.7 g.) which melted at 120–130° with decomposition. Recrystallization from a mixture of ether and ethanol gave a white solid melting at 130° with decomposition. The sample did not lower the melting point of 2-methylene-1,1-dimethylhydrazine hydrobromide prepared from 2-methylene-1,1-dimethylhydrazine[13] and hydrogen bromide in ether, and the infrared spectra of the two samples were identical.

Anal. Calcd. for $C_3H_{10}N_2Br$: C, 23.53; H, 5.92. Found: C, 23.14; H, 5.89.

Acid Hydrolysis of 1,1-Dibenzyl-2-p-tolylsulfonylhydrazine.—A suspension of 1,1-dibenzyl-2-*p*-tolylsulfonylhydrazine (15 g.) in 40 ml. of concentrated hydrochloric acid was heated at 100° for 8 hr. Extraction with ether gave a liquid which upon distillation at reduced pressure gave benzaldehyde (3.4 g.); b.p. 110° (100 mm). The benzaldehyde was characterized as the 2,4-dinitrophenylhydrazone; m.p. 235°. A mixture of the latter with an authentic sample melted at the same point. The residue from the distillation gave, upon crystallization from 80% ethanol, 3.5 g. of *p*-tolylthio *p*-toluenesulfonate. The acid layer, upon cooling to 0°, gave 2.5 g. of benzylhydrazine hydrochloride; m.p. 136–140°. Recrystallization from a mixture of ethyl acetate and ethanol gave a sample melting at

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141.5–143° with decomposition. The literature reports a melting point of 145° with decomposition.[16]

Bromine Oxidation of 1,1-Dibenzylhydrazine.—A well stirred solution of 12 g. (0.057 mole) of 1,1-dibenzylhydrazine in 60 ml. of 48% hydrobromic acid at 0° was treated dropwise with bromine (9.1 g.) (0.057 mole). The resulting solution was heated at 100° for 2 hr., cooled, and extracted with ether. Removal of the ether gave 5 g. of benzaldehyde.

The acid layer, upon cooling to 0°, gave 5 g. of benzylhydrazine hydrobromide melting at 165° with decomposition. The product was characterized by liberating the free hydrazine with base and forming the benzaldehyde benzylhydrazone m.p. 64–65° (lit. m.p. 63°).[17] A mixture with an authentic sample melted at the same point.

The Reaction of Benzyl Chloride with 1,1-Dimethyl-2-*p*-tolylsulfonylhydrazine.—A solution of 50 g. (0.23 mole) of 1,1-dimethyl-2-*p*-tolylsulfonylhydrazine and 30 g. (0.23 mole) of benzyl chloride in 90 ml. of benzene was refluxed for 2 hr. Evolution of methyl chloride and nitrogen occurred at the start of the refluxing. During the reaction, ammonium chloride (1.5 g.) precipitated on the sides of the flask.

The resulting solution was poured into ice water and the benzene layer was separated. Removal of the solvent gave 38 g. (67%) of benzyl *p*-tolyl sulfone melting at 143°. The literature reports a melting point of 144°.[11]

The aqueous layer was concentrated to a sirup and added to a hot solution of potassium hydroxide. The distillate boiling below 100° was dried over sodium hydroxide and analyzed by gas chromatography on a tetraethylene glycol dimethyl ether column. The products identified with their relative percentages were methylamine 2%, dimethylamine 54%, trimethylamine 1.5%, 1,1-dimethylhydrazine 31%, and trimethylhydrazine 10%.

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Potential Anticancer Agents.[1] LXXXI. 2′-Deoxyribofuranosides of 6-Mercaptopurine and Related Purines

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Condensation of a protected 2-deoxyribofuranosyl chloride (II) with chloromercuri-6-chloropurine (I) afforded the anomeric protected 6-chloropurine-2′-deoxyribofuranosyl nucleosides, which were separated by alumina chromatography. These anomers were converted to the corresponding α- and β-2-deoxyribofuranosides of several 6-substituted purines. The thiol (VI) in the β-series, especially, is of interest for possible antitumor properties.

The useful anticancer drug, 6-mercaptopurine (6-MP), is believed[2,3] to exert its activity as the corresponding nucleotide. The riboside of 6-MP, a possible precursor to the ribotide, was prepared[4] in a search for improved activity and was found[5] to have a much greater therapeutic index in mice with a transplanted tumor, although this was not borne out in human testing; cross resistance with 6-MP was also found. The effectiveness of 6-MP and its derivatives and analogs prepared to date is severely limited by the development of resistance to the drugs. Among possible mechanisms of resistance, deletion of the enzymatic process for converting the purine to the nucleotide[2,6] or cleavage of the active nucleotide back to the purine base[7] seems to be important. The 2-deoxyriboside of 6-MP (β-VI) is desirable as a possible nucleotide precursor which might be less susceptible to the mechanisms of resistance or might circumvent them entirely. So far, only an enzymatic synthesis[8] of β-VI, in low yield and with incomplete purification and characterization, has been reported. The chemical synthesis of 2′-deoxyribonucleosides, compared to that of ribonucleosides, presents special difficulties related to increased lability of the glycosidic linkage[9] and lack of steric control[10] in its formation. Recently, nucleosides of adenine[11] and of some pyrimidines[12,13] have been prepared directly from protected 2-

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