

Potential Antiradiation Compounds II. Extension of the Nitro-Thiolacetate Route

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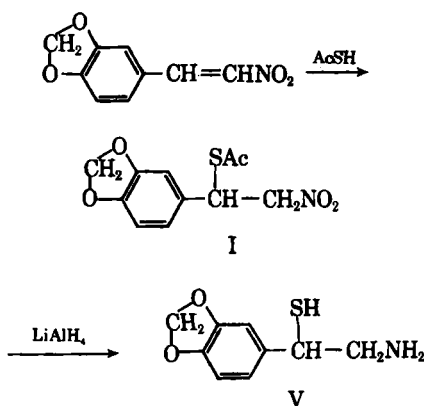
Thiolacetic acid was added to 3,4-methylenedioxy- ω -nitrostyrene to give 1-(3',4'-methylenedioxyphenyl)-1-acetthio-2-nitroethane which was reduced with lithium aluminum hydride to produce 1-(3',4'-methylenedioxyphenyl)-1-mercapto-2-aminoethane. Other substituted nitrostyrenes containing the 3,4-dimethoxy- and 3-methoxy-4-acetoxy groups also reacted with thiolacetic acid to give the corresponding addition products, but 3-acetoxy-4-methoxy- ω -nitrostyrene underwent an anomalous reaction with the formation of elemental sulfur. 1-Phenyl-2-nitro-1-propene added thiolacetic acid to give 1-phenyl-1-acetthio-2-nitropropane, but the latter compound was cleaved by lithium aluminum hydride to benzyl mercaptan and ethylamine.

CONTINUED INTEREST in compounds containing a mercapto group and an amino group on adjacent carbon atoms has prompted us to investigate the possible extension to substituted analogs of the synthetic route previously reported (1) by means of addition of thiolacetic acid to ω -nitrostyrene, followed by reduction with lithium aluminum hydride.

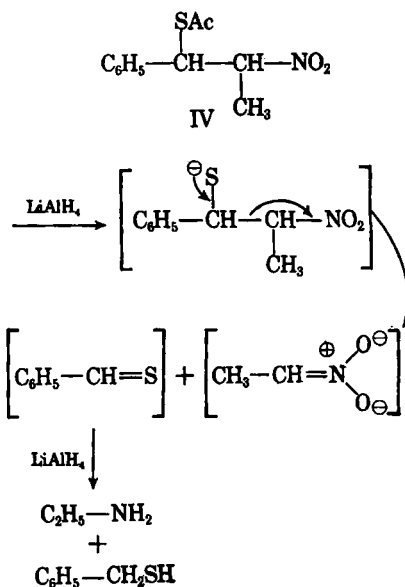
The initial reaction of the sequence—addition of thiolacetic acid across the double bond—proceeded smoothly with the next higher side chain homolog, 1-phenyl-2-nitro-1-propene, to give 1-phenyl-1-acetthio-2-nitropropane (IV).¹ Ring-substituted ω -nitrostyrenes were also investigated, and those with the 3,4-methylene-dioxy, 3,4-dimethoxy, and 3-methoxy-4-acetoxy groups all gave the expected thiolacetate addition product. 3-Acetoxy-4-methoxy- ω -nitrostyrene underwent an anomalous reaction with thiolacetic acid to give a gum which could not be crystallized. Isolation of elemental sulfur from this reaction mixture indicated that an oxidation reduction reaction had taken place.

In the second reaction of the sequence, a typical ring-substituted member of the series, 1-(3',4'-methylenedioxyphenyl)-1-acetthio-2-nitroethane (I), was reduced with lithium aluminum hydride to the mercapto-amine, 1-(3',4'-methylenedioxyphenyl)-1-mercapto-2-aminoethane (V). Because such mercaptans are readily oxidized to disulfide during the process of isolation, the oxidation equivalent was determined with iodine to prove that the isolated product was, in fact, the mercaptan. The yield in this reduction was low (11%), but this could undoubtedly be improved by further workup of the residues from the reduction.

Reduction of the side chain homolog, 1-phenyl-1-acetthio-2-nitropropane (IV), gave cleavage of the carbon chain; none of the expected mercapto-amine



was isolated. The reduction products actually isolated were benzyl disulfide and ethylamine hydrochloride. It would appear that the initial reduction took place at the thiolacetate group to give an intermediate salt of a mercaptan which then underwent reverse aldol condensation. The initial cleavage products, thiobenzaldehyde and the salt of nitroethane, were then reduced to the lithium aluminum complexes of benzyl mercaptan and ethylamine, respectively. During the course of hydrolysis and isolation, the benzyl mercaptan was apparently air-



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Through the courtesy of Dr. Thomas R. Sweeney, Department of Medicinal Chemistry, Walter Reed Army Institute of Research, Washington, D. C., 1-phenyl-1-acetthio-2-nitropropane was reported to show "some activity" in protection of mice against an LD₅₀ dose of radiation at a dosage level in the range 151 to 350 mg./Kg. The next lower homolog, 1-phenyl-1-acetthio-2-nitroethane, synthesis of which has been described previously (1), was reported to show the same level of protection. For comparison, it is of interest that the mercaptoamine derived from the latter compound, 2-mercapto-2-phenylethylamine hydrochloride (1) was reported to show no protective activity when administered at a dosage level in the range 51 to 150 mg./Kg. The test procedure and evaluation scale used are described more fully by Field, L., *et al.*, *J. Med. Chem.*, 7, 39 (1964).

TABLE I.—SUBSTITUTED 1-PHENYL-1-ACETTHIO-2-NITROETHANES

No.	Substituent	M.p., °C.	Yield, %	Formula	C, %		H, %		N, %		O, %		S, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
I	3',4'-Methylenedioxy	96-97	75	$C_{11}H_{11}NO_2S$	49.06	49.30	4.12	4.30	5.20	5.09	29.71	29.57	11.91	11.73
II	3',4'-Dimethoxy	115-116	66	$C_{12}H_{13}NO_3$	50.51	50.24	5.30	5.31	4.90	5.00	28.10	28.22	11.24	11.06
III	3-Methoxy-4'-acetoxy	98-99.5	50	$C_{12}H_{13}NO_4$	49.83	49.88	4.83	4.93	4.47	4.58	30.64	30.50	10.23	10.10
IV	2-Methyl	83-84.5	52	$C_{11}H_{12}NO_2S$	55.23	55.32	5.47	5.41	5.85	5.70	...	...	13.40	13.34

oxidized to the disulfide. Leonard and co-workers (2) observed a similar carbon-carbon cleavage of part of the product during the lithium aluminum hydride reduction of 1-anilino-2-nitro-1-phenylethane. Their isolation of *N*-benzylaniline could be explained by a similar mechanism.

Apparently the cleavage must occur prior to or during the reduction of the nitro group, as derivatives of structurally similar mercapto-amines do not show this cleavage on reduction with lithium aluminum hydride. For instance, 3,4-dimethyl-5-phenylthiazolidine-2-thione is readily reduced in good yield with lithium aluminum hydride to 1-phenyl-1-mercapto-2-(dimethylamino)propane (3).

EXPERIMENTAL

1 - (3',4' - Methyleneedioxyphenyl) - 1 - acetthio-2-nitroethane (I).—Thiolacetic acid (1.6 ml., 0.02 mole) and then 2 drops of tri-*n*-butylamine were added to a suspension of 3.9 Gm. (0.02 mole) of 3,4-methyleneedioxy- β -nitrostyrene (4) in 20 ml. of benzene. The mixture became warm, and the solid slowly dissolved. The product crystallized overnight, as the reaction mixture was allowed to stand at room temperature. After two recrystallizations from ethanol, the yield was 4 Gm. (75%), m.p. 96-97°.

Analyses and data on analogous compounds are shown in Table I.

Reaction of Thiolacetic Acid with 3-Acetoxy-4-methoxy- β -nitrostyrene.—Thiolacetic acid (0.08 ml., 0.001 mole) and then 2 drops of tri-*n*-butylamine were added to a suspension of 0.237 Gm. (0.001 mole) of 3-acetoxy-4-methoxy- β -nitrostyrene (4) in 1.5 ml. of benzene. The solid went into solution with the evolution of heat. A brownish-red gum separated overnight, as the reaction mixture was allowed to stand at room temperature. Addition of ethanol to the gum dissolved most of it, leaving a small amount of yellow crystals (0.024 Gm.), m.p. 113-114.5°, identified as elemental sulfur. The alcohol-soluble gum could not be crystallized.

1 - (3',4' - Methyleneedioxyphenyl) - 1 - mercapto-2-aminoethane (V).—A solution of 13.46 Gm. (0.05 mole) of 1-(3',4'-methyleneedioxyphenyl)-1-acetthio-2-nitroethane in 750 ml. of anhydrous ether was added dropwise to a solution of 9.5 Gm. (0.25 mole) of lithium aluminum hydride in 1 L. of anhydrous ether. The mixture was refluxed with stirring for 10 days. The reaction complex was hydrolyzed by the dropwise addition of 18 ml. of water, followed by 24.3 ml. of concentrated hydrochloric acid. The filtered ether solution was evaporated to dryness, and the white residue was recrystallized from alcohol to give a yield of 1.1 Gm. (11%), m.p. 110.5-112°.

Anal.—Calcd. for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N, 7.10; O, 16.22; S, 16.26; mol. wt., 197.3. Found: C, 54.78; H, 5.76; N, 7.20; O, 16.47; S, 16.17; neut. equiv., 194 and 196 (by semimicro non-aqueous titration with acetic perchloric acid); oxidation equivalent, 194 (by oxidation of mercaptan to disulfide with excess iodine and back-titration with thiosulfate).

Reduction of 1-Phenyl-1-acetthio-2-nitropropane.—A solution of 24 Gm. (0.1 mole) of 1-phenyl-1-acetthio-2-nitropropane in 300 ml. of anhydrous ether was added dropwise to a solution of 15.2 Gm. (0.4 mole) of lithium aluminum hydride in 300 ml. of ether. The mixture was heated under reflux with

stirring for 80 hours. The reaction complex was hydrolyzed by dropwise addition with vigorous stirring of 28.8 ml. of water, followed by 39.5 ml. of concentrated hydrochloric acid. The ether filtrate was evaporated to give 10.5 Gm. of an oily semi-solid. Repeated recrystallization of this residue from mixtures of benzene and petroleum ether gave 2 Gm. of white crystals, m.p. 69–70°. Chemical analysis indicated that this compound was benzyl disulfide. Comparison to an authentic specimen showed identical infrared spectrum and no depression of melting point.

In a subsequent identical run, during the evaporation of the ether solution to dryness, the escaping gases were passed through a trap containing hydrochloric acid. Evaporation of the solution from this trap left a residue of 4.5 Gm., m.p. 95–105°. Re-

crystallization from ethanol-ether mixtures gave 2.5 Gm. (28%) of ethylamine hydrochloride, m.p. 108–109°. This is in agreement with the known melting point of 109° (5). Conversion to the benzamide derivative gave a product which melted at 68–69°, in agreement with the previously reported melting point for *N*-ethylbenzamide of 69° (6).

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Use of Hammett Graphs in Stability Programs

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HAMMETT GRAPHS have been used for many years by organic and physical chemists, primarily for elucidation of reaction mechanisms.

Research programs involving the screening of a host of related compounds may benefit from this sort of approach. By establishing a few pKa values and rate constants, rapid estimates of degradation rates of new compounds can be made simply by a pKa measurement. The advantage of this in pharmaceutical formulation is quite obvious.

The condition that a linear relationship holds (1, 8) is that the entropy of reaction is either zero or is the same for all the hydrolyses (or whatever reaction is pertinent) or that ΔH and ΔS be linearly related.

In general, the substituent parameter is referred to as σ , and the reaction parameter as ρ ; the latter in particular is useful in deducing the actual reaction mechanism. Substituent σ values and reaction ρ values are abundantly reported in the literature (1).

The authors have exemplified the utility of this sort of approach by a study of a series of allylbarbituric acids.

The materials used in this study were obtained by suitable extraction from commercially available dosage forms in the case of talbutal and secobarbital. 5-Allyl-5(2-cyclopenten-1-yl) barbituric acid,¹ itobarbital,² and allobarbital³ were obtained from suppliers. Unsubstituted allylbarbituric acid was synthesized according to the method of Arnold *et al.* (2) and Johnson and Hill (3).

Experimentally, samples were prepared by dissolving 250 mg. of barbiturate in form of the acid in 50 ml. of 95% ethanol. This was then diluted 1:50 with a borate buffer of the following composi-

tion: 0.97 Gm. of boric acid, 1.15 Gm. of potassium chloride, 344 ml. of 0.1 *N* sodium hydroxide and adjusted to 1000 ml. with distilled water, yielding a final pH of 11.8.

Ampuls of these solutions were stored at 85° and assayed at six storage times. The decrease in barbiturate was determined by a decrease in absorbance at the peak wavelength (240–242 mμ) after suitable dilution with the described borate buffer. Pseudo first-order rate constants (hours⁻¹) are denoted *k* in Fig. 1 and Table I.

The pKa's of the barbiturates were determined spectrophotometrically. pKa° and *k*₀ in the following refer to the unsubstituted allylbarbituric acid.

In a more formal treatment (4, 5, 7, 9, 10), the reaction constant is calculated from substituent constants based on dissociation constants in water. The σ -constants as defined here hence refer to the dissociation constants relative to the dissociation of unsubstituted allylbarbituric acid. Statistical im-

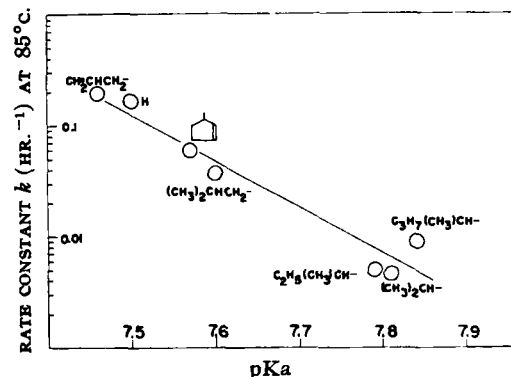


Fig. 1.—Form in which rate constants can most conveniently be calculated for an unknown substance with known pKa with previous knowledge of rate constant and pKa of compounds related to the substance in question. [Brønsted plot (11).]

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² Itobarbital was kindly supplied by Mr. S. Weinstein, Sandoz Pharmaceuticals, Hanover, N. J.

³ Allobarbital was kindly supplied by Mr. J. Cooper, Ciba Pharmaceutical Co., Summit, N. J.