Treatment of IIIb and IIIc with 2,4-Dinitrophenylhydrazine.—IIIb and IIIc were given identical treatments with a 2,4-dinitrophenylhydrazine solution. In each case, a 0.05-g. sample of the solid was dissolved in about 25 cc. of a 0.1% solution of 2,4-dinitrophenylhydrazine, acidified with hydrochloric acid. After about 1 hr., a flocculent, yellow-orange precipitate began to appear. Precipitation was complete after 24 hr.

The 2,4-dinitrophenylosazone of glyoxal was prepared in a similar manner; the precipitate appeared immediately. This derivative melted at 300–303° dec.

The osazone formed by treatment of IIIb melted at 302–304° dec. Mixed melting point with the glyoxal derivative was 301–304° dec.

The IIIc derivative melted at 304–306° dec. Mixed melting point was 301–305° dec.

Acknowledgment.—The authors wish to thank R. T. O'Connor and co-workers for assistance in interpretation of infrared spectra and L. E. Brown and A. L. Alford for the analyses.

Oxathiane Synthesis by Mercuric Salt Ring Closure

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Received January 10, 1962

Treatment of allyl sulfide with aqueous mercuric salt solutions yields a pair of isomeric mercury derivatives of dimethyl-*p*-oxathiane as evidenced by the two isomers of 2,6-bis(iodomethyl)-*p*-oxathiane that are isolated after treating the mercurials with iodine. Allyl sulfone undergoes a similar sequence of reactions, but only a single isomer of 2,6-bis(iodomethyl)-*p*-oxathiane 4,4-dioxide is produced. The *cis* structure of this dioxide is proved by its oxidation to a diacid which reversibly forms a monomeric anhydride. The *cis* structure of the dominant product in the allyl sulfide-mercuric salt condensation is demonstrated by conversion to the above *cis*-dioxide. Methallyl sulfide and sulfone undergo parallel condensation reactions.

The first synthesis of a dioxane by treatment of allyl ether with an aqueous mercuric salt solution was performed by Nesmeyanov and Lutsenko.[2] The mercury derivative was precipitated as the halide and converted by iodine to a form of 2,6-bis-(iodomethyl)-*p*-dioxane. Work in our laboratory later showed[3] that two isomers rather than one were produced and established the stereochemistry of the isomers. A study of the factors affecting the proportion of the isomers[4] led to the proposal of a mechanism involving reversible reactions in the mercuration step in which the more thermodynamically stable form would predominate under equilibrium conditions of high hydrogen ion concentration or long standing. One would expect the more stable form of a 2,6-disubstituted dioxane, an analog of a *meta*-disubstituted cyclohexane, to be the *cis* form. Under equilibration conditions the *cis/trans* ratio in the dioxane case is found to be sixteen to one.[4] In the present work this type of synthesis is extended to oxathianes by substitution of allyl sulfide for allyl ether.

Discussion

Subsequent to our investigation of the general reaction of terminal diolefins with aqueous mercuric salts,[5] allyl sulfide was treated with aqueous mercuric acetate solution. A mercurial precipitated from solution which is probably identical with the 2,6-bis(acetoxymercurimethyl)-*p*-oxathiane (Ia) reported by Baker and co-workers.[6] Our yield of the acetoxy mercurial, m.p. 166–182°, was 50%. Several recrystallizations from acetone rendered crystals, m.p. 197–199° dec. An additional 32% yield of 2,6-bis(iodomercurimethyl)-*p*-oxathiane (Ib) was obtained from the filtrate of the reaction mixture by adding potassium iodide.

Iodine replaced the mercuries of both mercurials to give a product which after crystallizations from large volumes of ethanol, could be separated into two compounds which were later shown to be the *cis* isomer II, and a small amount of the *trans* isomer III, of 2,6-bis(iodomethyl)-*p*-oxathiane. The reaction with iodine was complicated by formation of large amounts of tarry materials, probably sulfonium iodide polymers. The diiodide II could not be oxidized directly to the diacid with nitric acid, nor could it be oxidized to a sulfone with hydrogen peroxide; but alcoholic sodium sulfide gave the bicyclic compound, 9-oxa-3,7-dithiobicyclo[3.3.1.]-nonane (IV), evidence of a *cis* configuration.

Further proof of the *cis* configuration of II was obtained by oxidation to a 2,6-bis(iodomethyl)-*p*-oxathiane 4,4-dioxide (V), by peracetic acid. This

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(1) This research was supported by N.S.F. Grant 7335.

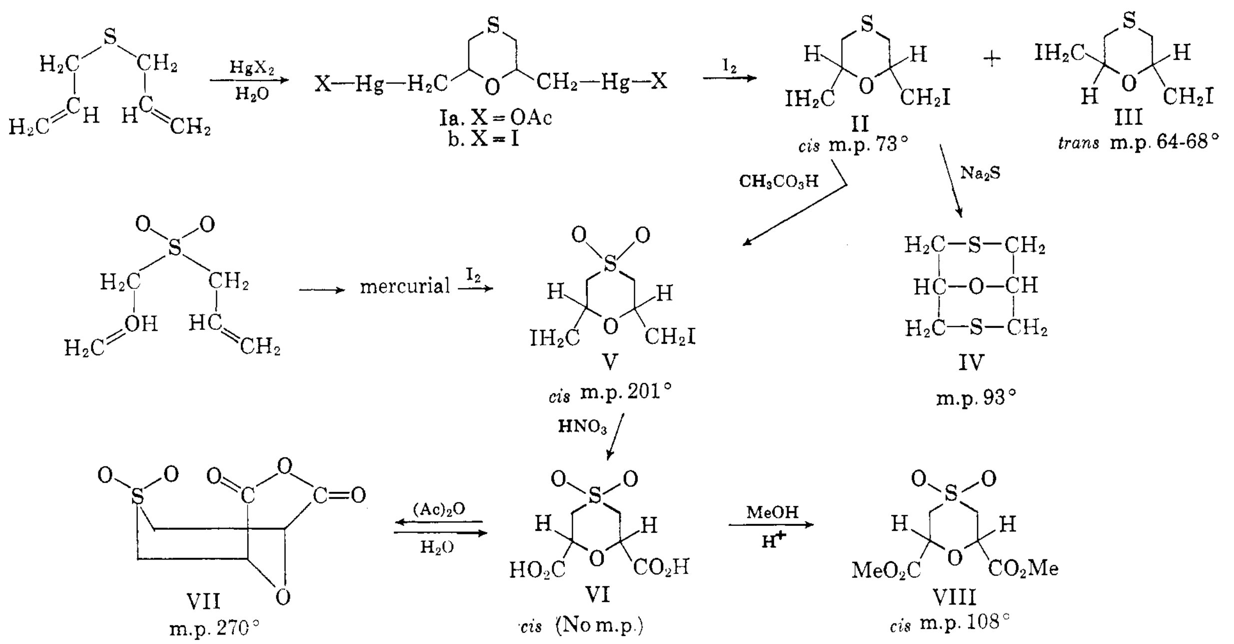
(2) A. N. Nesmeyanov and I. F. Lutsenko, *Bull. acad. sci. U.R.S.S., Classe sci. chim.* 296 (1943).

(3) R. K. Summerbell and J. R. Stephens, *J. Am. Chem. Soc.*, **76**, 731 (1954).

(4) R. K. Summerbell, G. J. Lestina, and H. Waite, *J. Am. Chem. Soc.*, **79**, 234 (1957).

(5) R. K. Summerbell, Erwin S. Poklacki, and Sherri R. Forrester, to be published.

(6) L. Goodman, L. O. Ross, M. O. Greene, J. Greenberg, and B. R. Baker, *J. Med. and Pharm. Chem.*, **3**, 65 (1961). These authors isolated a 25–37% yield of the acetoxy mercurial and tentatively assigned a *trans* structure to their supposedly isomerically pure sample, m.p. 191–193° dec. The experimental basis for the assignment of a *trans* configuration is not stated, as the paper is primarily concerned with the therapeutic value of a series of related mercury compounds in cancer treatment. No yield of the *cis* isomer is mentioned, although, on the basis of our experience with the closely related dioxanes, the *cis* isomer would be expected as the dominant product.



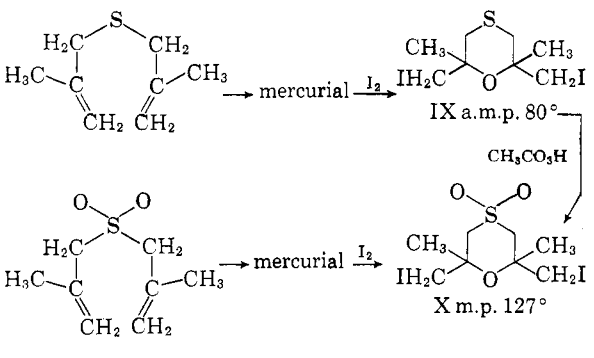
sulfone V was also obtained as the only isomer, after treatment with iodine, of the condensation product of allyl sulfone with aqueous mercuric acetate. The *cis* configuration of sulfone V was demonstrated unequivocally by a series of reactions which included direct oxidation of V to a *p*-oxathiane 4,4-dioxide 2,6-dicarboxylic acid (VI) by the action of concentrated nitric acid, dehydration of the acid to the monomeric anhydride VII, and hydrolysis of the anhydride back to the same dibasic acid VI. Since a volatile, monomeric anhydride of acid VI with a *trans* configuration is sterically impossible, the *cis* configuration can be assigned with confidence to the anhydride VII, the acid VI, the sulfone V and the iodomethyl derivative II.

The dimethyl ester VIII of acid VI was prepared but reduction to the diol with lithium aluminum hydride failed to yield an isolable product. Since the isomer II of 2,6-bis(iodomethyl)-*p*-oxathiane has been assigned the *cis* configuration, the isomer III must have the *trans* configuration; however the small amount isolated precluded the possibility of any other chemical proof of structure.

Methallyl sulfide condensed with aqueous mercuric acetate to form mercurial derivatives rapidly and in high yield. Two isomers of 2,6-dimethyl-2,6-bis(iodomethyl)-*p*-oxathiane (IX), m.p. 70° and 80°, were obtained from the mercurial mixture after treating it with iodine. Only the higher melting isomer could be oxidized to a sulfone X, m.p. 127°, with peracetic acid, and again this same sulfone, 2,6-dimethyl-2,6-bis(iodomethyl)-*p*-oxathiane 4,4-dioxide (X) was the only product obtained from a methallyl sulfone–mercuric acetate condensation after treatment with iodine.

Attempts to determine the stereochemistry of the two isomers of sulfide IX or of sulfone X failed because of inertness of these iodides to alcoholic sodium sulfide solution and to direct oxidation by nitric acid. Under similar experimental conditions the related but less substituted *cis*-iodomethyl compound II had formed IV, and V had been oxidized to VI. Various iodomethyldioxanes[3,7] have been successfully oxidized to acids or lactones. Perhaps the reason for inertness of IX and X is simply steric hindrance and these compounds should be considered as pseudoneopentyl derivatives. The pseudoneopentyl structure of the parent mercurials does not seem to interfere with their reaction with iodine since IX and X are readily formed under mild conditions.

In the absence of evidence to the contrary, it may be assumed by analogy to the earlier proof that II and V are *cis* that X and IXa are *cis* also.



Experimental

2,6-Bis(acetoxymercurimethyl-*p*-oxathiane (Ia) and 2,6-Bis(iodomercurimethyl)-*p*-oxathiane (Ib).—To a stirred solution of 0.5 mole of mercuric acetate in 500 ml. of water, 0.251 mole of allyl sulfide was added rapidly. After 29 hr., a

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[7] R. K. Summerbell and G. J. Lestina, *J. Am. Chem. Soc.*, **79**, 3878 (1957); R. K. Summerbell and J. R. Stephens, *ibid.*, **76**, 6401 (1954).

negative mercuric ion test was obtained. The precipitated acetoxy mercurial Ia was filtered and dried to a constant weight of 81.6 g., m.p. 166–182° dec. A sample was recrystallized from acetone several times, and melted at 197–199° with decomposition. The filtrate of the reaction mixture was made basic and the addition of potassium iodide precipitated an iodomercurial Ib, which when dried weighed 62.6 g. A total yield of 82% was obtained.

cis- and _trans_-2,6-Bis(iodomethyl)oxathiane (II and III).—The above mercurials were combined and refluxed with 610 ml. of chloroform, 120 ml. of water, and 100 g. of iodine for 14 hr., to give 42.4 g. of crude material contaminated with considerable tars (apparently sulfonium salts). The crude material partly solidified on standing to yield 7.3 g. II, m.p. 72.5–73°, after recrystallization from alcohol-acetone mixture.

Anal. Calcd. for $C_6H_{10}I_2OS$: C, 18.75; H, 2.62. Found: C, 18.64; H, 2.62.

The remaining oils were washed with thiosulfate and extracted with chloroform to yield 30 g. of material which was chromatographed through a long column packed with silica gel. Petroleum ether eluted a mineral oil contamination, and 20% ether–petroleum ether eluted 18.96 g. crystals, m.p. 42–50°, which were shown to be impure II by infrared comparison. Final fractions eluted with chloroform were probably the sulfonium salts. Repeated fractional crystallization from large volumes of ethanol isolated *ca.* 0.5 g. of III, m.p. 64–68°, which when mixed with pure II, melted at 46–56°.

Anal. (of III) Calcd. for $C_6H_{10}I_2OS$: C, 18.75; H, 2.62. Found: C, 18.88; H, 2.64.

Attempted Oxidation of II to Diacid.—A mixture of 2 g. of II, m.p. 71°, and 5 ml. of concd. nitric acid was heated on a steam bath to dryness. Nitrogen oxides and iodine vapor were evolved. The oil that remained contained iodine as shown by a Beilstein test, so another 5 ml. of nitric acid was added, and again the mixture was evaporated to dryness. Only a tar that could not be crystallized, remained.

Attempted Oxidation of II to the Sulfone.—An acetone solution of 0.18 g. of II, m.p. 71°, was mixed with excess 20% hydrogen peroxide and shaken overnight. Much iodine was liberated in the solution. After the solvent was evaporated, the residue was extracted with chloroform, decolorized, and dried. Infrared analysis indicated hydroxyl groups but no sulfone group.

Allyl Sulfone.—The method of Baker, Stevens, and Dort[8] was used to obtain 20.77 g. of allyl sulfone, b.p. 101–103° (1.75 mm.) n^{20} 1.4890 in 70% yield (lit., b.p. 101–103° at 2 mm., n^{20} 1.4891).

cis-2,6-Bis(iodomethyl)_p_-oxathiane 4,4-Dioxide (V).—To a mixture of 0.276 mole of mercuric acetate in 276 ml. of water 0.140 mole of allyl sulfone was added rapidly. After 2 hr., the mixture was made basic with sodium hydroxide and filtered. To the filtrate was added 50 g. of potassium iodine, and the precipitated mercurial was filtered and dried. The mercurial (240 g.) was added to a mixture of 600 ml. of chloroform, 400 ml. of water, and 50 g. of iodine, and refluxed for 25 hr., yielding 23 g. of crystals, tars, and unchanged mercurial. The latter was again treated with iodine to produce additional product. Recrystallization from acetone gave 10.28 g. of pure V, m.p. 200.5–201° with sublimation. The remaining tarry materials contained much V, but infrared spectrum showed no other soluble isomer present. The yield was at least 54%.

Anal. Calcd. for $C_6H_{10}I_2O_3S$: C, 17.32; H, 2.42. Found: C, 17.14; H, 2.39.

Oxidation of Sulfide II to Sulfone V.—To a test tube containing 2.5 ml. of peracetic acid was added 0.13 g. of V, m.p. 73°. The mixture was shaken and allowed to stand overnight. Water was added and a precipitate formed. The tube was centrifuged to collect the solids, and after the material was washed once with water and dried, it weighed *ca.* 0.07 g. and melted at 193–197°. After recrystallization from acetone, the crystals melted at 200–201°. Mixed melting point with authentic V was not depressed. Infrared spectrum was identical with that of V.

cis-_p_-Oxathiane 4,4-Dioxide 2,6-Dicarboxylic Acid (VI).—A mixture of 3.03 g. of V and 20 ml. of concd. nitric acid was heated on a steam bath until dry. The crystalline mass was mixed with water and again heated to dryness. Recrystallization from acetone gave 1.20 g. of fine white powdery crystals, m.p. 246°, with decomposition. The yield was 74%.

Anal. Calcd. for $C_6H_8O_7S$: C, 32.14; H, 3.60; neut. equiv. 112.1. Found: C, 32.71; H, 3.70; neut. equiv. 115.8.

_p_-Oxathiane 4,4-Dioxide 2,6-Dicarboxylic Anhydride (VII).—A mixture of 50 ml. of acetic anhydride and 0.81 g. of VI was refluxed for 1 hr. and then distilled to remove most of the acetic anhydride and acid. The remaining solvent was removed at reduced pressure. The 0.5 g. of solids remaining was recrystallized from dry acetone to melt at 254° with sublimation. The entire mixture was sublimed at 200° and 2 mm. pressure to obtain crystals, m.p. 268–270°. The infrared showed the characteristic twin peaks for the anhydride group at 5.50 and 5.67 μ, and was entirely different from the spectrum of the acid VI.

Anal. Calcd. for $C_6H_6O_6S$: C, 34.95; H, 2.93. Found: C, 34.79; H, 2.97.

An aqueous solution of 0.1 g. of anhydride VII was boiled to dryness. The crystalline mass was recrystallized from acetone to give material, the infrared spectrum of which was identical with diacid VI.

Dimethyl-_p_-oxathiane 4,4-Dioxide 2,6-Dicarboxylate (VIII).—A mixture of 2.20 g. of VI in 20 ml. of absolute methanol and 1 drop concentrated sulfuric acid was refluxed 5 hr. The cooled solution deposited 2.14 g. of crystals which melted at 107–108° after recrystallization from methanol.

Anal. Calcd. for $C_8H_{12}O_7S$: C, 38.09; H, 4.80. Found: C, 38.55; H, 4.86.

Attempted Reduction of Dimethyl Ester VIII.—A solution of 1.68 g. of VIII in 90 ml. of ether was added to a stirred suspension of 0.51 g. of lithium aluminum hydride in 50 ml. of ether. The mixture was allowed to stand overnight. Decomposition of the excess hydride was followed by addition of 20 ml. of 10% sulfuric acid. Repeated ether extractions gave no product.

9-Oxa-3,7-dithiabicyclo[3.3.1]nonane (IV).—A solution of 200 ml. of absolute ethanol and 0.0185 mole of II, m.p. 70°, was refluxed in a Soxhlet extractor apparatus in such fashion that 0.054 mole of sodium sulfide in the Soxhlet thimble was slowly added to the solution. After 18 hr., most of the ethanol was distilled and the remainder was removed under reduced pressure. The solid residue was extracted with carbon disulfide to yield 2.97 g. of thick oil. Distillation at 1 mm. gave a liquid, b.p. 112.5°, which solidified and melted at 92.5–93° after purification by sublimation.

Anal. Calcd. for $C_6H_{10}S_2O$: C, 44.41; H, 6.21. Found: C, 44.30; H, 5.94.

Oxidation of IV with peracetic acid gave crystals, m.p. 254°, probably one of the possible sulfones. An attempt to carry out a similar reaction of sulfone V with sodium sulfide failed.

Methallyl Sulfide.—The method of Olsen, Hull, and France[9] was used to obtain 56.8 g. of methallyl sulfide, b.p. 70.5–72° (20 mm.) (lit., b.p. 59–60° at 10 mm.).

2,6-Dimethyl-2,6-bis(iodomethyl)-_p_-oxathiane (IX).—To a solution of 0.5 mole of mercuric acetate in 500 ml. of water was added 0.26 mole of methallyl sulfide. After 3 hr. the mixture was made basic and filtered. To the filtrate was

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(8) H. J. Baker, W. Stevens, and N. Dort, *Rec. trav. chim.*, **67**, 451(1948).

(9) S. R. Olsen, C. M. Hull, and W. G. France, *Ind. Eng. Chem.*, **38**, 1279 (1946).

added aqueous potassium iodide to obtain 257.2 g. of iodomercurial. Refluxing the mercurial with 800 ml. of chloroform, 400 ml. of water, and 50 g. of iodine gave 57.6 g. of a black tarry oil contaminated with sulfonium salts for a 56% crude yield. The reaction time was 24 hr. Chromatography of 5.03 g. through alumina with pentane–ether mixture, eluted 3.11 g. of crystalline material, m.p. 51–77°. The original oily products were seeded with these crystals, and the resulting precipitate was subjected to repeated fractional crystallizations from large volumes of methanol–acetone solvents. Two fractions were obtained: prisms, m.p. 79.5–80.2°, and plates, m.p. 69.5–70.5°. When the samples were mixed, the melting point was 48–58°.

Anal. Calcd. for $C_8H_{14}I_2OS$: C, 23.32; H, 3.42. Found: (m.p. 80°) C, 23.55; H, 3.38. (m.p. 70°) C, 23.57; H, 3.38.

Methallyl Sulfone.—The procedure of Baker, Stevens, and Dort[8] was used. The product distilled at 105–107° (1.5 mm.), and weighed 5.73 g., 50.3% yield.

2,6-Dimethyl-2,6-bis(iodomethyl)-*p*-oxathiane 4,4-Dioxide (X).—To a solution of 0.06 mole of mercuric acetate in 60 ml. of water was added 0.0326 mole of methallyl sulfone. After 45 min. the mixture was made basic and filtered. Addition of 11 g. of potassium iodide precipitated the mercurial which weighed 28.7 g. when dried. The mercurial was refluxed in a mixture of 200 ml. of chloroform, 50 ml. of water and 15 g. of iodine for 22 hr. to yield 8.2 g. of solid material, m.p. 117–124°. Three grams of unchanged mercurial was also recovered. The solid product was recrystallized from alcohol to give pure X, m.p. 127–127.5°.

Anal. Calcd. for $C_8H_{14}I_2O_3S$: C, 21.64; H, 3.18. Found: C, 21.75; H, 3.20.

Chromatography of remaining noncrystalline product through silica gel with petroleum ether–acetone eluent gave additional X and some uncharacterized oil.

Oxidation of Sulfide IX to Sulfone X.—To 2.5 ml. of peracetic acid was added 0.13 g. of IX, m.p. 80°. After 12 hr., water was added and the resulting precipitate was recrystallized from acetone, m.p. 124.5–125.5°. Mixed melting point with authentic X was 125.5–127.5°. The infrared spectra were identical. Sulfide IX, m.p. 70°, did not react under these conditions.

Attempted Oxidation of Sulfone X to the Diacid.—A mixture of 1.43 g. of X and 20 ml. of concd. nitric acid was heated on a steam bath to dryness. Nitrogen oxides and iodine vapor were evolved. The resulting oils showed a positive halogen test (Beilstein) after repeated nitric acid treatments until only a tar remained.

Reaction of Sulfide IX with Sodium Sulfide.—The reaction conditions under which II was treated, gave only unchanged starting material when IX, m.p. 80°, was treated with sodium sulfide.

Reaction of Hydantoin with Acetals

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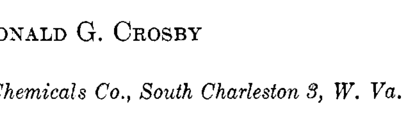
Received January 11, 1962

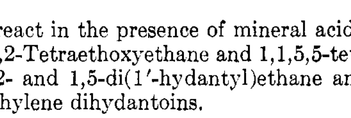
Under anhydrous conditions, hydantoin and 1,1,3,3-tetraethoxypropane react in the presence of mineral acid to give the corresponding salt of 1-(1′-hydantylidine)-3-(1″-hydantyl)propene-2. 1,1,2,2-Tetraethoxyethane and 1,1,5,5-tetramethoxypentane react similarly with hydantoin yielding, after hydrogenation, 1,2- and 1,5-di(1′-hydantyl)ethane and -pentane, respectively. Monoacetals and hydantoin gave the corresponding 1,1′-methylene dihydantoins.

The reaction of hydantoin with aldehydes to give 5-alkylidine derivatives is well known and provides useful intermediates for the preparation of certain α-amino acids.[1] Aromatic aldehydes invariably react with greater facility than aliphatic aldehydes containing α-hydrogens, due to the absence of complicating self-condensation reactions. Hydantoin and its derivatives with an open 1- position are also known to react with formaldehyde in strongly acidic aqueous media to produce 1,1′-methylene dihydantoins.[2] Higher aliphatic aldehydes have apparently not been found to undergo this condensation although their reaction with amides to give methylene diamides has been reported.[3] Thus, it seemed expedient to investigate the reaction of hydantoin with aliphatic aldehydes or appropriate derivatives under conditions which might lead to 5-substituted hydantoins and, hopefully, eliminate or minimize self-condensation. This communication describes the mineral acid-catalyzed reaction of hydantoin with various aliphatic acetals.

1,1,3,3-Tetraethoxypropane (TEP), in a variety of nonaqueous solvents, reacts smoothly with two equivalents of hydantoin in the presence of sulfuric acid to precipitate 1-(1′-hydantylidine)-3-(1″-hydantyl)propene-2 bisulfate (Ia) in 80–100% yield. A hydrochloride (Ib) was similarly formed when anhydrous hydrogen chloride was present in the reaction mixture, but its structure is not as well



Ia. X = HSO_4
Ib. X = Cl



IIa. $n = 2$
IIb. $n = 3$
IIc. $n = 5$

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[1] E. Ware, *Chem. Rev.*, **46**, 403 (1950).

[2] R. Behrend and R. Niemeyer, *Ann.*, **365**, 38 (1909); J. F. Walker, U. S. Patents 2,417,999 and 2,418,000.

[3] For examples see Beilstein's *Handbuch der Organischen Chemie*, Vol. 2, pp. 179, 180 and Vol. 3, pp. 24–26.