Attempted Synthesis of 2,3-Epithioamides from Glycidamides and Dibromoamides

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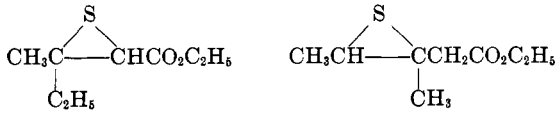
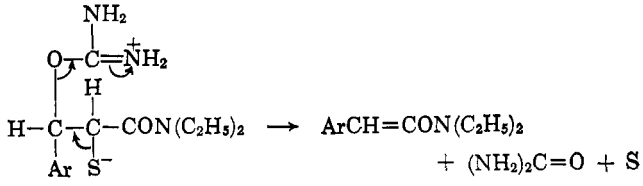
Attempts to synthesize 2,3-epithioamides failed. *trans*-Arylglycidamides with the thiourea produced *trans*-cinnamamides, urea, and sulfur. Under the same conditions, *cis*-arylglycidamides were recovered unchanged. Ethyl 2-acetylthio-3-chloro-2,3-dihydrocinnamate with base gave ethyl cinnamate, cinnamic acid, and sulfur. Two aliphatic 2,3-diacetylthioamides upon treatment with base afforded 1,4-dithianes.

Recently the first successful synthesis of a 2,3-epithio ester, ethyl 2,3-epithio-3-methylvalerate (I) was reported.[1] It was subsequently shown, however, that the compound was, in fact, the 3,4-epithio ester II.[2] In view of these and other failures[3,4] in the synthesis of 2,3-epithio esters, we wish to report our attempts in the preparation of 2,3-epithioamides from the corresponding epoxy amides and 2,3-dibromopropionamides.

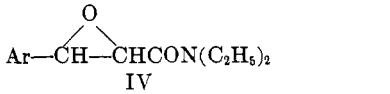


I II

Ethyl *trans*-3-phenyl glycidate (III) with thiourea under a variety of conditions gave ethyl cinnamate, sulfur and urea.[3,4] Similarly *trans*-IVa, b afforded the corresponding N,N-diethylcinnamamides and sulfur.[5]



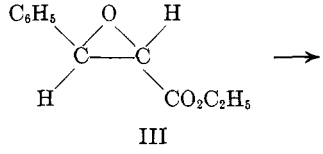
However, *cis*-IVb–d with thiourea in glacial acetic acid–dioxane solution were found to be unreactive; the epoxy amides were recovered unchanged.[7] Under conditions for the conversion of styrene epoxide to the episulfide,[8] IVa also remained unreactive. Since the action of thiourea on epoxyamides did not lead to



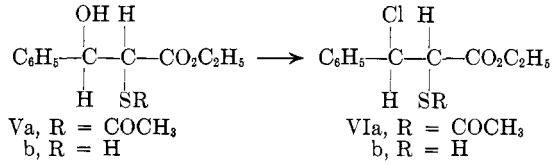
IV

a, Ar = C_6H_5 c, Ar = 2,6-$Cl_2C_6H_3$
b, Ar = 3-$NO_2C_6H_4$ d, Ar = 2,4-$Cl_2C_6H_3$

the desired episulfides, the use of thiolacetic acid and hydrogen sulfide was investigated. The action of thiolacetic acid in pyridine or hydrogen sulfide in alkaline methanol on ethyl *trans*-3-phenylglycidate (III) produced the corresponding hydroxythioacetate Va and hydroxythiol Vb which were converted to the chloro derivatives VIa and VIb with thionyl chloride.

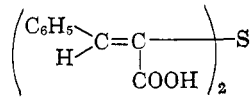


III



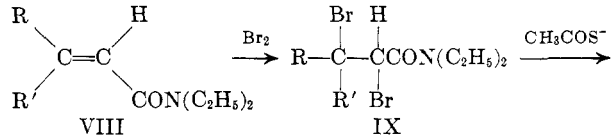
Va, R = $COCH_3$ VIa, R = $COCH_3$
b, R = H b, R = H

Unfortunately treatment of VI with alkali did not yield episulfides. VIa furnished ethyl cinnamate, cinnamic acid, and sulfur, whereas VIb gave VII (structure tentatively assigned) as the only isolable product. In view

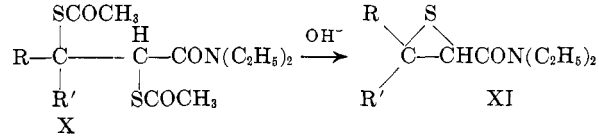


VII

of these failures we turned our attention to 2,3-dibromoamides as a route to episulfides. *erythro*-N,N-Diethylcinnamamide dibromide has been shown to undergo exclusively debromination to *trans*-N,N-diethylcinnamamide upon treatment with thiolacetate ion.[9] The aliphatic dibromides IX gave dithiolacetates X.



VIII IX



X XI

a, R, R′ = CH_3
b, R = CH_3; R′ = H
c, R, R′ = H

Treatment of Xa with aqueous alkali at room temperature afforded a 65% yield of VIIIa and an 80% yield of sulfur. However, under the same conditions, Xb, c each yielded a light yellow oil as the only product. Samples before and after purification through silica

(1) J. A. Durden, Jr., H. A. Stansbury, Jr., and W. A. Catlette, *J. Am. Chem. Soc.*, **81**, 1943 (1959)

(2) T. C. Owen, C. L. Gladys, and L. Field, *J. Chem. Soc.*, 501, 656 (1962).

(3) C. C. J. Culvenor, W. Davis, J. A. MacLaven, P. F. Nelson, and W. E. Savige, *ibid.*, 2573 (1949).

(4) C. C. J. Culvenor, W. Davies, and N. S. Heath, *ibid.*, 278 (1949).

(5) It has been assumed[2,4,6] that the olefins arise from the thermal desulfurization of the episulfide. It also appears likely that in the case of *trans*-IVa, b, *trans*-III, and stilbene oxide, the episulfide is never formed, but instead an intermediate eliminates free sulfur directly.

(6) C. C. J. Culvenor, W. Davies, and W. E. Savige, *J. Chem. Soc.*, 4480 (1952).

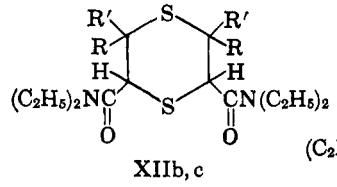
(7) C. C. Tung, A. J. Speziale, and H. W. Frazier, *J. Org. Chem.*, **28**, 1514 (1963); C. C. Tung and A. J. Speziale, *ibid.*, **28**, 2009 (1963).

(8) C. O. Guss and D. L. Chamberlain, Jr., *J. Am. Chem. Soc.*, **74**, 1342 (1952).

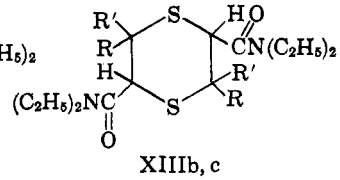
(9) A. J. Speziale and C. C. Tung, *J. Org. Chem.*, **28**, 1353 (1963).

gel gave elemental and infrared analyses consistent with the episulfides XIb, c. Molecular weight determinations, however, were consistent with a dimeric structure. The product derived from Xb reacted with triphenylphosphine but afforded only a 15% yield of triphenylphosphine sulfide and 15% yield of *trans*-N,N-diethylcrotonylamide (VIIIb). The product derived from Xc did not react with triphenylphosphine.

It appears that the action of base on Xb, c led to the stable dithianes XIIb, c or XIIIb, c, rather than the episulfides. Each could arise from the dimerization



XIIb, c



XIIIb, c

of Xb, c or the corresponding episulfides XIb, c. The conversion of a 3,4-epithio ester to a dithiane has been noted.[2]

Experimental

Ethyl 3-Hydroxy-2-acetylthiohydrocinnamate (Va).—To a stirred solution of 38.4 g. (0.20 mole) of ethyl *trans*-3-phenylglycidate (III) and 16.0 g. (0.21 mole) of freshly distilled thiolacetic acid, 16.6 g. (0.21 mole) of pyridine at 25° was added with cooling. The addition required about 1 hr. and the mixture was allowed to stand at room temperature overnight. The mixture, after washing with water, was dissolved in ether and dried over magnesium sulfate; the solvent was evaporated. The yield of light yellow viscous oil was 98%; $n^{25}D$ 1.5396. The product decomposed on distillation and the analysis was made on the crude product.

Anal. Calcd. for $C_{13}H_{16}O_4S$: C, 58.2; H, 6.0; S, 11.9. Found: C, 58.5; H, 5.9; S, 11.9.

Ethyl 2-Acetylthio-3-chloro-2,3-dihydrocinnamate (VIa).—To a stirred solution of 25.0 g. (0.094 mole) of Va in 75 ml. of benzene, 30 ml. of thionyl chloride was added dropwise at 25° over a period of 30 min. under nitrogen. The solution was then heated at reflux temperature (73°) for 2 hr., and the solvent and excess of thionyl chloride was removed *in vacuo*. The product, a light yellow viscous oil, $n^{25}D$ 1.5530, was obtained in 96% yield.

Anal. Calcd. for $C_{13}H_{15}ClO_3S$: C, 54.5; H, 5.3; Cl, 12.4; S, 11.2. Found: C, 54.4; H, 5.6; Cl, 12.0; S, 11.2.

A mixture containing 21.8 g. (0.076 mole) of VIa in 350 ml. of 0.5 *N* aqueous potassium hydroxide (0.17 mole) was heated at reflux temperature for 0.5 hr. The only products isolated were 5.8 g. (32.9% yield) of ethyl cinnamate, 3.9 g. (35% yield) of cinnamic acid, and 0.8 g. (32.8% yield) of sulfur.

Ethyl 3-Hydroxy-2-mercapto-2,3-dihydrocinnamate (Vb).—A slow stream of hydrogen sulfide was passed into a solution of 16.1 g. (0.40 mole) of sodium hydroxide in 142 ml. of methanol at −10 to 0° during 1.5 hr. The reaction mixture was allowed to stand at room temperature overnight, diluted with 400 ml. of water, cooled to 0°, and acidified with 5 *N* sulfuric acid (pH 2). The solution was extracted with 300 ml. of methylene chloride, and washed with 100 ml. of saturated sodium bicarbonate and 100 ml. of water. The methylene chloride extract, after drying over magnesium sulfate, was evaporated to dryness to give light yellow-colored oil. The yield of crude product was 82%; $n^{25}D$ 1.5500. It decomposed upon distillation under nitrogen atmosphere.

Anal. Calcd. for $C_{11}H_{14}O_3S$: C, 58.3; H, 6.2; S, 14.1. Found: C, 58.6; H, 6.0; S, 13.9.

Ethyl 2-Mercapto-3-chloro-2,3-dihydrocinnamate (VIb).—Thionyl chloride (74 ml., 1.0 mole) was added slowly to a stirred solution at 5–10° of Vb (51.0 g., 0.23 mole) in 150 ml. of benzene. The mixture was allowed to warm to 25° and stirred at that temperature for 2 hr. The solvent and unchanged thionyl chloride were removed *in vacuo* to give a light yellow oil ($n^{25}D$ 1.5771) in 91.0% yield. The product decomposed upon distillation and the analysis was made on crude material.

Anal. Calcd. for $C_{11}H_{13}ClO_2S$: C, 54.0; H, 5.4; Cl, 14.5; S, 13.1. Found: C, 54.6; H, 5.2; Cl, 14.8; S, 12.8.

To a solution of 21.9 g. (0.09 mole) of VIb in 150 ml. of methanol at 24°, 8.0 g. (1.20 moles) of sodium hydroxide in 40 ml. of water was added over a period of 35 min. The solution was stirred at room temperature for 10 hr., poured into 500 ml. of water, and extracted with chloroform. The chloroform extract was evaporated to dryness and the semisolid residue was stirred with 80 ml. of warm benzene. The benzene-insoluble material was collected and recrystallized from methanol. The cream-colored solid, after recrystallization from methanol, had m.p. 232–233°, yield 5.7 g.; 5.1 g. more of solid, m.p. 232–233°, was recovered from the benzene filtrate. The infrared data showed C=C band at 6.2 μ. The structure of this compound is tentatively assigned at 2,2′-thiodicinnamic acid (VII).

Anal. Calcd. for $C_{18}H_{14}O_4S$: C, 66.2; H, 4.3; S, 9.7; mol. wt., 326. Found: C, 66.8; H, 4.6; S, 9.6; mol. wt., 322.

N,N-Diethyl-2,3-dithioacetyl-3-methylbutyramide (Xa).—N,N-Diethyl-3,3-dimethylacrylylamide (VIIIa) was prepared from diethylamine and 3,3-dimethylacrylyl chloride.[10] The product, a colorless liquid, b.p. 41–42° (0.2 mm.), $n^{25}D$ 1.4697, was obtained in 92% yield.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0. Found: C, 69.5; H, 11.0; N, 9.0.

The bromination of VIIIa in CCl_4 solution gave a 98% yield of N,N-diethyl-2,3-dibromo-3-methylbutyramide (IXa), m.p. 63.5–64.3°.

Anal. Calcd. for $C_9H_{17}Br_2NO$: C, 34.4; H, 5.4; Br, 50.7; N, 4.5. Found: C, 34.5; H, 5.5; Br, 50.7; N, 4.5.

Pyridine (20.5 g., 0.26 mole) was added dropwise to a solution of 23.1 g. (0 073 mole) of IXa and 19.7 g. (0.26 mole) of thiolacetic acid in 100 ml. of benzene. The temperature of the reaction mixture rose from 25 to 35° and solid separated slowly. The mixture was allowed to stand at room temperature for 2 days. The solid was collected by filtration, washed with benzene, and dried *in vacuo;* yield 25.3 g. (0.146 mole) of pyridine hydrobromide. The benzene filtrate was evaporated to dryness; the residue was redissolved in benzene and washed thoroughly with water. After removing solvent *in vacuo*, there was obtained a light yellow viscous oil, $n^{25}D$ 1.5054, in 92% yield.

Anal. Calcd. for $C_{13}H_{23}NO_3S_2$: C, 51.2; H, 7.6; N, 4.6; S, 21.0. Found: C, 51.2; H, 7.8; N, 4.9; S, 21.3.

A mixture of 6.4 g. (0.021 mole) of Xa and 250 ml. of 0.5 *N* potassium hydroxide (0.125 mole) was stirred vigorously at room temperature for 20 min. At the end of this period, the free sulfur was removed by filtration. The filtrate was saturated with salt, extracted with ether, washed with saturated brine solution, and dried over magnesium sulfate. After evaporation to dryness, there was obtained 2.9 g of amber-colored oil (VIIIa) which was purified by distillation to a colorless liquid, b.p. 50–51° (0.4 mm.), $n^{25}D$ 1.4700, 2.1 g., 65% yield.

***erythro*-N,N-Diethyl-2,3-dithioacetylbutyramide (Xb).**—*trans*-N,N-Diethyl-3-methylacrylylamide (VIIIb)[11] was prepared from diethylamine and crotonyl chloride. The product, a colorless liquid, b.p. 47–48° (0.2 mm.), $n^{25}D$ 1.4737, was obtained in 98% yield.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.1; H, 10.7; N, 9.9. Found: C, 68.1; H, 10.7; N, 10.0.

Bromination of VIIIb in CCl_4 solution gave *erythro*-N,N-diethyl-2,3-dibromobutyramide (IXb) as a light yellow oil, b.p. 105–106° (0.5 mm.), $n^{25}D$ 1.5254, in theoretical yield.

Anal. Calcd. for $C_8H_{15}Br_2NO$: Br, 53.2. Found: Br, 52.7.

Treatment of 112.3 g. (0.37 mole) of IXb with 85.0 g. (1.02 moles) of pyridine as described above afforded a light yellow viscous oil Xb, $n^{25}D$ 1.5136, 94% yield.

Anal. Calcd. for $C_{12}H_{21}NO_3S_2$: C, 49.6; H, 7.2; N, 4.8; S, 22.0. Found: C, 49.6; H, 6.9; N, 4.7; S, 22.3.

2,3-Dimethyl-3,6-bis(diethylcarbamoyl)-1,4-dithiane (XIIb or XIIIb).—Treatment of 30.1 g. (0.10 mole) of Xb with 28.0 g. (0.50 mole) of KOH in 1000 ml. of water, as described for VIa, afforded a light yellow oil, $n^{25}D$ 1.5131, 10.0 g. (56% yield).

Anal. Calcd. for $C_{16}H_{30}N_2O_2S_2$: C, 55.5; H, 8.7; N, 8.1;

(10) L. I. Smith and V. A. Engelhardt, *J. Am. Chem. Soc.*, **71**, 2671 (1949).

(11) The *trans* configuration was determined by n.m.r.: $J_{H_\alpha H_\beta}$ = 16.5 c.p.s.

S, 18.5; mol. wt., 346. Found: C, 54.8; H, 9.1; N, 7.5; S, 18.4; mol. wt., 334 (Rast method), 311 (Mechrolab osmometer in acetonitrile).

A solution of 5.0 g. (0.029 mole) of above product and 8.3 g. (0.031 mole) of triphenylphosphine in 50 ml. of chloroform was heated to reflux for 7 hr. Chloroform was removed; the residue was stirred with 130 ml. of hexane vigorously at room temperature. The hexane-insoluble material was collected and recrystallized from hexane. The crystalline solid, m.p. 161–162°, identified as triphenylphosphine sulfide (no depression in melting point with authentic sample) was obtained in 1.3-g. (0.0044 mole, 15%) yield. There was also isolated 0.7 g. (0.004 mole, 15.2%) of VIIIb from the hexane mother liquors. The very viscous oil was not distillable at 320° (0.15 mm.).

Infrared and elemental analysis of the sample, $n^{25}D$ 1.5131, after standing at room temperature for several months, did not change. However, its refractive index increased: $n^{25}D$ 1.5164. The compound after purification through silica gel gave a light yellow oil, $n^{25}D$ 1.5166, with no change in its infrared spectrum. Elemental analysis and molecular weight of the chromatogrammed sample remained essentially the same.

N,N-Diethyl-2,3-dithioacetylpropionamide (Xc).—N,N-Diethylacrylylamide (VIIIc) was prepared from diethylamine and acrylyl chloride in ether solution, b.p. 39–40° (0.2 mm.), $n^{25}D$ 1.4645, 97% yield.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.2; H, 10.2; N, 11.0. Found: C, 66.1; H, 10.1; N, 11.2.

Bromination of VIIIc in chloroform solution gave N,N-diethyl-2,3-dibromopropionamide (IXc) as a light yellow oil in quantitative yield, b.p. 124–125° (3 mm.), $n^{25}D$ 1.5270, 57% yield.

Anal. Calcd. for $C_7H_{13}Br_2NO$: C, 29.3; H, 4.5; N, 4.9; Br, 55.8. Found: C, 29.6; H, 4.4; N, 4.7; Br, 55.8.

The procedure as described for the preparation of Xa, b was used. The pyridine hydrobromide was obtained in 89.0% yield (based upon 2 mole equiv. of salt for 1 mole equiv. of IXc). The desired product, Xc, $n^{25}D$ 1.5194, was obtained in 94% yield.

Anal. Calcd. for $C_{11}H_{19}NO_3S_2$: C, 47.7; H, 6.9; N, 5.1; S, 23.1. Found: C, 47.3; H, 6.9; N, 5.0; S, 23.3.

2,5-[Bis(diethylaminocarbamoyl)]-1,4-dithiane (XIIc or XIIIc).—The procedure for the preparation of XIIb or XIIIb was used. The product, a light yellow oil, $n^{25}D$ 1.5110, was obtained in 48% yield.

Anal. Calcd. for $C_{14}H_{26}N_2O_2S_2$: C, 52.7; H, 8.2; N, 8.8; S, 20.1; mol. wt., 318. Found: C, 52.7; H, 8.4; N, 8.0; S, 19.2; mol. wt., 313 (Rast method), 291 (Mechrolab osmometer in acetonitrile).

The compound, after standing at room temperature for several days, did not react with triphenylphosphine.

Synthesis and Some Reactions of Triphenylphosphinamino- and (β-N-Disubstituted amino)imines

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Triphenylphosphinamino- and (β-N-disubstituted amino)imines have been prepared by dehydrobromination of hydrazino- and (β-N-disubstituted hydrazino)triphenylphosphonium bromides, respectively. The aminophosphinimines have been treated further with methyl and ethyl iodides, and the structures of the resulting α-N-alkyl hydrazino- and (α-N-alkyl β-N-disubstituted hydrazino)triphenylphosphonium iodides have been confirmed through elemental analyses, hydrolysis to triphenylphosphine oxide and substituted hydrazines, and nuclear magnetic resonance studies. The hydrolysis of (α-N-alkyl β-N-disubstituted hydrazino)triphenylphosphonium iodides represents a new way for the synthesis of 1,1,2-trisubstituted hydrazines.

Recently we reported the preparation of some triphenylphosphinalkyl imines (I, R = alkyl)[1] and their successful utilization for the synthesis of sterically hindered dialkyl amines, such as *t*-butylmethylamine and *t*-butylethylamine, which are not easily available through conventional methods. It was also discovered that triphenylphosphine-*t*-butylamine (I, R = *t*-Bu)

$$Ph_2P{=}NR$$
I

was a very stable compound at ambient conditions. Triphenylphosphinisopropylimine (I, R = *i*-Pr) was less stable but sufficiently resistant towards moisture that an analytical sample could be prepared. All other triphenylphosphinalkyl imines decomposed rapidly to triphenylphosphine oxide and the corresponding alkyl amines when exposed to the atmosphere. Until then, the only stable triphenylphosphinimines known were resonance-stabilized ones,[2-8] such as $Ph_3P{=}NPh$.

(1) H. Zimmer and G. Singh, *J. Org. Chem.*, **28**, 483 (1963).
(2) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).
(3) H. Staudinger and E. Hauser, *ibid.*, **4**, 861 (1921).
(4) F. G. Mann and E. J. Chaplin, *J. Chem. Soc.*, 527 (1937).
(5) A. V. Kirsanov and G. I. Derkach, *Zh. Obshch. Khim.*, **26**, 2631 (1956); *Chem. Abstr.*, **51**, 1821 (1927).
(6) L. Horner and H. Oediger, *Ann.*, **627**, 142 (1959).
(7) V. I. Shevchenko and V. T. Stratienko, *Zh. Obshch. Khim.*, **30**, 1958 (1960); *Chem. Abstr.*, **55**, 6425 (1961).
(8) G. I. Derkach, E. S. Gubnitskaya, and A. V. Kirsanov, *ibid.*, **31**, 3679 (1961).

A plausible explanation for the stability of triphenylphosphine-*t*-butylimine is that the *t*-butyl group, due to its bulk, exercises an effective shielding on the P=N bond.

These results made it appear desirable to study type I compounds further. It was of particular interest to investigate the effects of groups of different electronic and steric requirements on the reactivity of the phosphorus nitrogen double bond, and to investigate whether these phosphinimines could be used as tools in organic and inorganic syntheses. In this paper the synthesis and some properties of triphenylphosphinamino- and (β-N-disubstituted amino)imines (I, R = NH_2 or NXY), as well as their utilization for the preparation of trisubstituted hydrazines, are communicated.

Results and Discussion

Triphenylphosphine dibromide reacted with anhydrous hydrazine or 1,1-disubstituted hydrazines in the presence of triethylamine to give the hydrazino- or (β-N-disubstituted hydrazino)triphenylphosphonium bromides (eq. 1 and Table I).

Under the conditions employed, the free amino group of the hydrazinotriphenylphosphonium bromide (1) failed to react further with triphenylphosphine dibromide to give the diphosphonium bromide (eq. 2).