observed m- and c values with the calculated values. For these series, $\bar{m} = 0.311$, $\bar{c} = -0.0914$. These average values are obviously in good agreement with the calculated values of m and c.

Equation 3 is thus supported, at least for series 9, 10, and 11. Although it is true that these are the series least likely to deviate from the equation, it is nevertheless encouraging to find such agreement.

Acknowledgment.—The author wishes to acknowledge helpful discussion of the content of this paper with Professor H. H. Jaffé, University of Cincinnati.

Thiolesters by Anhydride Reduction with Hydrogen Sulfide

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Phthalic anhydride (or acid) can be reduced by hydrogen sulfide to thiophthalide in high yields. Hydrogen may be substituted for part of the hydrogen sulfide. The reaction appears general, but gives lower yields for other anhydrides. Reduction of cyclohexane-1,2-dicarboxylic anhydride gives 3,4,5,6-tetrahydrothiophthalide. Other aromatic acids or nitriles are reduced completely to hydrocarbon, while aliphatic acids are inert under reaction conditions. While metal sulfides may catalyze the reaction, they are not essential. In their absence, a homogeneous reduction with hydrogen is realized.

In the course of studying the oxidation of organic compounds with sulfur and water, but in the absence of a base, it was found that the reaction was reversible.[1] For example, toluene is oxidized by sulfur and water at 315°. A similar equilibrium exists in the reaction

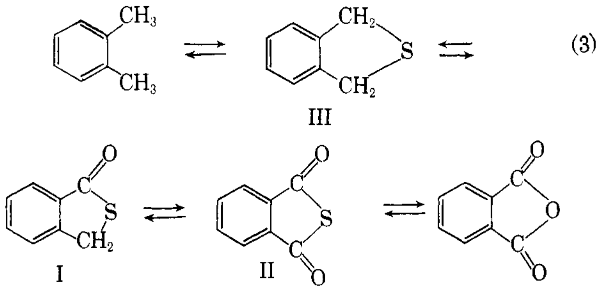
$$C_6H_5CH_3 + 3S + 2H_2O \rightleftharpoons C_6H_5CO_2H + 3H_2S \qquad (1)$$

producing nitriles from hydrocarbon, sulfur, and ammonia.[2]

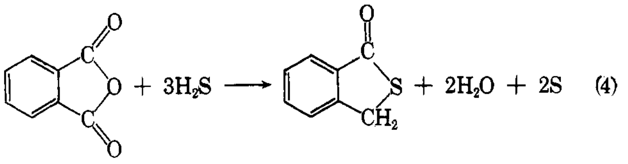
$$C_6H_5CH_3 + 3S + NH_3 \rightleftharpoons C_6H_5CN + 3H_2S \qquad (2)$$

In the reverse reactions, a carboxylic acid or nitrile is reduced to a hydrocarbon with hydrogen sulfide. Sulfur is also formed. By adding hydrogen to the system, sulfur is converted to hydrogen sulfide which tends to drive the reaction to completion. The over-all reaction is reduction of a carboxyl or nitrile group to a methyl group by hydrogen, with hydrogen sulfide as a catalyst. Reduction begins at about 150° but reaches a practical rate at about 250°. Such reductions have not been reported previously. They may have only limited practical value but do have theoretical significance. For example, the system hydrogen, water, benzoic acid, and hydrogen sulfide contains no solid catalyst and hence represents an example of homogeneous catalysis, a relative rarity in reduction by hydrogen. Nitrile reduction represents a similar situation. The number of other groups capable of reduction in this way has not yet been fully explored.

Of greater interest is the reduction of phthalic anhydride from which a number of intermediate compounds were isolated. The yield of any one may be enhanced by the proper choice of conditions and the recycling of undesired intermediates. These intermediate compounds shed light on a probable mechanism of sulfur oxidations. The major reaction sequence involves the following compounds, all of which have been isolated (run 10, Table I).



Small amounts of o-toluic acid also have been found. It has not been established whether this is part of the above sequence or a competing reaction. The most stable entity at 315° in the presence of water, sulfur, and hydrogen sulfide is thiophthalide (I). It can be obtained in 94% yields by reduction of phthalic anhydride or phthalic acid.



I

Some typical results are given in Table I. The reverse reactions, the oxidation of o-xylene to thiophthalide with sulfur and water, has been described.[1]

An example of the spectrum of intermediates (3) is given in run 10 of Table I. In this case, their concentrations were enhanced by adding o-xylene to the system and limiting the amount of hydrogen sulfide employed. As a result, the major products were thiophthalic anhydride (II), thiophthalide (I), and o-xylylene sulfide (III); identification was by a high mass spectrometer. Minor peaks matched masses for di- and trithiophthalic anhydride. Benzoic acid, a major product, probably resulted from decarboxylation of phthalic acid at this temperature. Reduction of the intermediate thiophthalic anhydride with hydrogen sulfide at atmospheric pressure gave thiophthalide.

Table I shows that hydrogen sulfide alone as the reducing agent gives good yields of thiophthalide over the temperature range of 175–315°. Conversions increase with temperature while yields decrease. Above 315°, decarboxylation and reduction to o-xylene and o-xylylene sulfide occurs. The ratio of hydrogen sulfide

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(1) W. G. Toland, *J. Org. Chem.*, **26**, 2929 (1961).

(2) W. G. Toland, *ibid.*, **27**, 869 (1962).

TABLE I

REDUCTION OF PHTHALIC ANHYDRIDE TO THIOPHTHALIDE

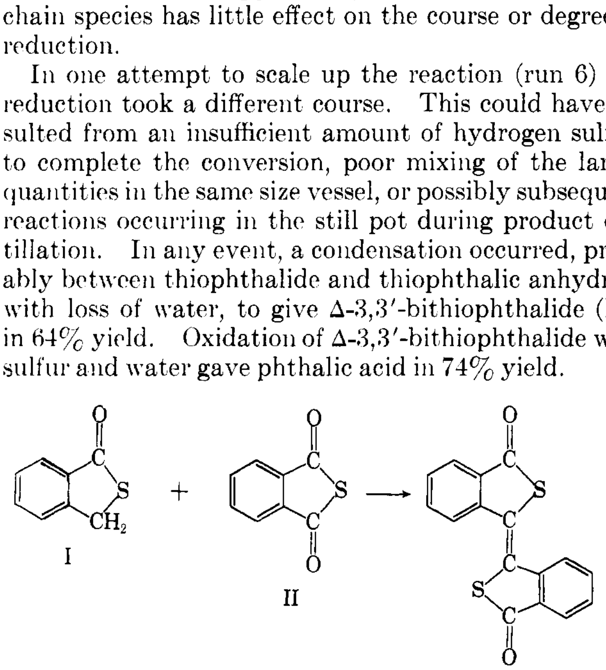
Run no.	1	2	3	4	5	6	7	8	9	10
Charge, moles										
Phthalic anhydride	4.0	4.0	1.0	1.0	2.0	10	2.0	2.0	2.0	2.0
H_2S	4.3	8.2	10	10	10	20	2.1	0.5	3.0	1.0
Hydrogen	0	0	0	0	0	0	11.5	7.0	7.9	2.0[a]
Water	100	100	100	100	0	0	0	100	100	100
Conditions										
Temperature, °C	175	200	80–260	290–315	260	260	260	260	260	315
Time at temp., min.	120	120	120	50	60	120	60	120	145	120
Products, moles										
H_2S	1.7	1.65		6.82	4.44	1.62		0.36	1.41	
Sulfur	1.25	3.2	1.24	1.16	4.44	4.11	0	0	0	
Hydrogen							9.8	5.6		1.5[a]
Phthalic acid	3.52	2.14	0.37	0.042	0	3.46	0.91	1.77	0.59	1.0
Benzoic (B) or toluic (T) acid	0	0	0	0.05 (T)	0	2.1[b]	0	0	0.03 (T)	0.5 (B)
Other					3.0 (H_2O)	11.5 (H_2O)	0.69[c]		0.072[d]	0.07[c]
Tar, grams		20.3	3.0	16.8	0	138.2	11.2	6.6	12.1	0.07[d]
Thiophthalide	0.452	1.68	0.565	0.69	1.91	2.1	0.23	0.10	1.07	0.22
Conversion of phthalic anhydride, %	12.0	47.2	62.8	95.8	100	65.5	55.2	12.8	70.8	50.0
Yield of thiophthalide, mole %										
on H_2S	51.7	77.1		65.2	101.2			214.0	202.0	
on phthalic anhydride	94.2	90.3	89.9	72.2	94.1	64.2[b]	20.4	38.5	74.3	22.0

[a] o-Xylene (substituted for H_2). [b] Δ3,3′-Bithiophthalide. [c] Thiophthalic anhydride. [d] o-Xylylene sulfide.

to phthalic anhydride (or acid) is not critical; but since three moles are required per mole of phthalic anhydride or acid to form thiophthalide, at least this ratio is preferred. Above 10:1 molar ratios, additional hydrogen sulfide probably has little effect. Except in the reduction of thiophthalic anhydride, only autogenous pressures were studied.

In the reduction of phthalic anhydride, water may be used as a solvent, as shown in runs 1–4. Apparently, the tendency to form cyclic structures is so strong in this case that the opportunity for hydrolysis to open chain species has little effect on the course or degree of reduction.

In one attempt to scale up the reaction (run 6) the reduction took a different course. This could have resulted from an insufficient amount of hydrogen sulfide to complete the conversion, poor mixing of the larger quantities in the same size vessel, or possibly subsequent reactions occurring in the still pot during product distillation. In any event, a condensation occurred, probably between thiophthalide and thiophthalic anhydride with loss of water, to give Δ-3,3′-bithiophthalide (IV) in 64% yield. Oxidation of Δ-3,3′-bithiophthalide with sulfur and water gave phthalic acid in 74% yield.

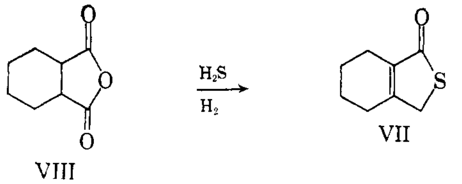


I II IV (5)

The formation of sulfur in the reduction of phthalic anhydride could lead to side reactions with thiophthalide. However, it was shown that under reaction conditions sulfur reacts with hydrogen to form hydrogen sulfide. It was shown that hydrogen in the absence of hydrogen sulfide does not react with phthalic acid. When both hydrogen and hydrogen sulfide are present, thiophthalide is formed in yields at least twice those theoretically obtainable from the hydrogen sulfide alone (runs 8 and 9). In such cases, hydrogen sulfide serves both as a reagent and as a catalyst for the reduction.

The reaction of hydrogen sulfide with 4-cyclohexene-1,2-dicarboxylic anhydride (V) and 1-cyclohexene-1,2-dicarboxylic anhydride (VI) gave thiophthalide in 65% and 91% yields, respectively. The sequence of reactions in these transformations is complex. First, double bond isomerization of the unsaturated cyclic anhydrides (or the corresponding acids) may occur. Second, and more important, sulfur produced during the carbonyl reduction is available to dehydrogenate the partially saturated ring. In addition, any of these tetrahydrophthalic anhydrides (or corresponding acids) which are dehydrogenated by sulfur to phthalic anhydride (or phthalic acid) can be reduced under these reaction conditions to thiophthalide. Anhydride initially reduced by the hydrogen sulfide to thiolactone may be dehydrogenated similarly to thiophthalide.

When a *hydrogen–hydrogen sulfide* mixture was used for reduction of 4-cyclohexene-1,2-dicarboxylic anhydride, a mixture of thiophthalide and the unexpected and previously unreported 3,4,5,6-tetrahydrothiophthalide (VII) was produced. The same products were isolated from the hydrogen sulfide reduction of cyclohexane-1,2-dicarboxylic anhydride (VIII), (Table II). When a *hydrogen–hydrogen sulfide* mixture is used for reduction of VIII, the ratio of VII to I increases.



VIII VII (6)

TABLE II

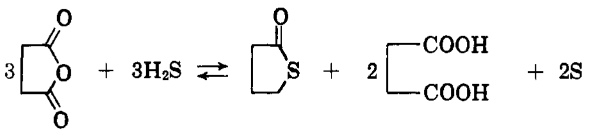
REDUCTION OF CYCLOHEXANE AND CYCLOHEXENE-1,2-DICARBOXYLIC ANHYDRIDES

Anhydride	Reducing agent	% Yield, thiophthalide (I)	% Yield, tetrahydrothiophthalide (VII)
4-Cyclohexene-1,2-dicarboxylic anhydride	H_2S	65	
	H_2S–H_2[a]	23	29
1-Cyclohexene-1,2-dicarboxylic anhydride	H_2S	91	
Cyclohexane-1,2-dicarboxylic anhydride	H_2S	21	25
	H_2S–H_2	23	34
	H_2S–H_2[a]		47

[a] Steel-lined autoclave used.

When, instead of the usual glass-lined autoclave, an unlined steel one was used, only VII was found. Apparently the autoclave walls act as a catalytic surface and allow the hydrogen to easily reduce any sulfur formed.

The reduction of succinic anhydride by hydrogen sulfide gave γ-thiolbutyrolactone (IX) in 24% yield.



(7)

From the over-all equation 7 it is apparent that only 33% of the succinic anhydride can be converted to γ-thiolbutyrolactone since the water formed in the reaction hydrolyzes succinic anhydride to succinic acid. In contrast to *o*-phthalic acid, the carboxyl groups in succinic acid may assume conformations unfavorable for anhydride formation. When succinic acid was subjected to the reducing conditions, only 3.6% of the succinic acid was converted to γ-thiolbutyrolactone.

In the same manner acetic anhydride gave a product which was 7.4 mole per cent ethyl thiolacetate. Hydrogen sulfide reduction of benzoic anhydride in the presence of hydrogen at 177° gave a product containing 9 mole per cent benzyl thiolbenzoate, 36 mole per cent benzene, 51 mole per cent benzoic acid, and traces of other materials. When the temperature was raised to 260°, toluene was the product. Benzoic acid required temperatures of greater than 300° to be reduced to toluene, but under these conditions lauric acid was unchanged. Reaction of hydrogen sulfide with phthalimide gave no identifiable products and dibenzoyl amine (made *in situ* from benzoic acid and benzonitrile) yielded only toluene.

Discussion

The initial step in this type of reduction has been described. Hydrogen sulfide reacts with anhydrides below 100° in the presence of tertiary amine accelerators and between 120 and 160° over activated carbon to produce thiocarboxylic acids.[3] Sulfonic acids apparently also function as catalysts.[4] No reduction is involved in this first step, but rather replacement of one oxygen by a sulfur.

Catalytic reduction of a variety of functional groups to thiols using hydrogen with hydrogen sulfide has been described.[5] Keto- and aldehydocarboxylic acids, anhydrides, esters, and amides are reduced to mercaptocarboxylic compounds. Levulinic acid, for example, gives γ-mercaptovaleric acid and its thio lactone. The anhydride group, however, apparently is unaffected under the conditions of keto group reduction. Simple aldehydes and ketones, thio ketones, thio acids, and cyano groups are all reduced to mercaptans at temperatures up to about 300° but give hydrocarbons above this temperature.

Reductions have been observed in studies of the Willgerodt reaction. When acetophenone is treated with aqueous ammonium sulfide, it gives a mixture of α-phenylethyl mercaptan, α-phenylethyl disulfide, styrene, ethylbenzene, diphenylthiophene, and free sulfur.[6] The sulfide reduction of ketones is complicated by subsequent reactions, some of which may involve the free sulfur produced initially. Similarly, 1-acetylacenaphthene is reduced to 1-ethylacenaphthene in 67% yield by ammonium polysulfide with little of the expected Willgerodt product, 1-acenaphthenacetamide being formed.[6]

While a carbonyl function is also reduced to a methylene in anhydride reduotion, it cannot occur by any of the mechanisms proposed to date for such reductions. The reduction of phthalic anhydride cannot proceed through either an olefinic[7] or a thioepoxide[8] intermediate. The reduction of anhydrides may actually parallel more closely the mechanism involved in sulfate reduction by bisulfide to give thiosulfate[9] and ultimately polysulfide.[10]

An abbreviated schematic series of steps (Scheme 1) illustrates a potential path of phthalic anhydride reduction consistent with known sulfur chemistry. Many reactive reducing species may be present in the reaction mixture. In this reaction scheme examples of several are used: hydrogen sulfide, reaction 1; sulfur, reaction 7; and hydrogen polysulfide, a species formed by reaction of sulfur with hydrogen sulfide, reaction 4. Beginning with the thioanhydride group, the sequence is illustrated in Scheme 1.

A possible reaction sequence for the reduction of cyclohexane-1,2-dicarboxylic anhydride (VIII) is presented in Scheme 2. Intermediate X is formed as suggested in reaction 7 in Scheme 1. However, with X and alternative reaction path, hydrogen sulfide elimination to XI, is possible. Rearrangement of the double bond into conjugation with the carbonyl group gives 3,4,5,6-tetrahydrothiophthalide (VII). Sulfur formed in reactions 6 and 20 can dehydrogenate VII to thiophthalide (I). When hydrogen is also present, it can react with sulfur, reducing the amount of VII oxidized. When the reaction was carried out in an unlined steel

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[3] (a) H. Behringer and H. W. Stein, German Patent 800,412 (November 6, 1950); (b) H. Behringer and H. W. Stein, German Patent Application No. B 388 IV d/120 (October, 1949); (c) H. Behringer, German Patent Application No. B 854 d/120 (November, 1949).

[4] J. C. McCool, U. S. Patent 2,587,580 (March 4, 1952).

[5] M. W. Farlow, W. A. Lazier, and F. K. Signaigo, *Ind. Eng. Chem.*, **42**, 2547 (1950).

[6] (a) C. Willgerodt, *Ber.*, **21**, 534 (1888); (b) E. Baumann and E. Fromm, *ibid.*, **28**, 907 (1895); (c) L. F. Fieser and G. W. Kilmer, *J. Am. Chem. Soc.*, **62**, 1354 (1940).

[7] M. Carmack and D. F. Detar, *ibid.*, **68**, 2029 (1946); J. A. King and F. H. McMillan, *ibid.*, **68**, 525, 632 (1946).

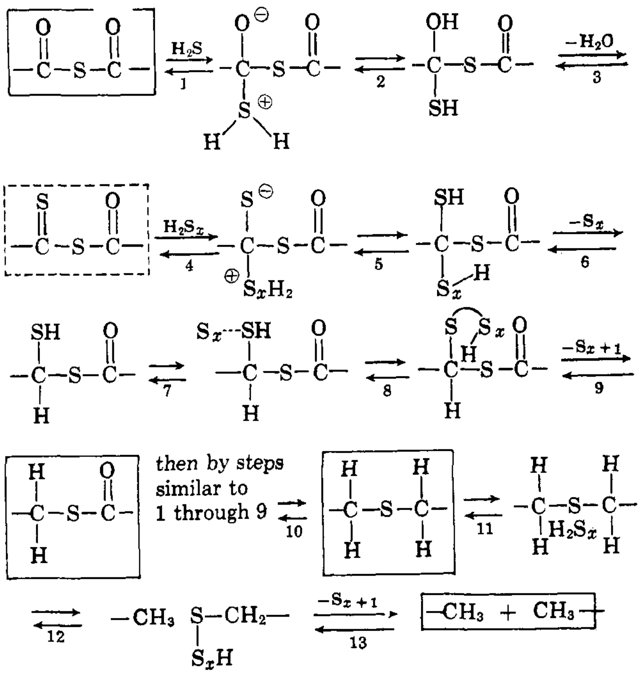
[8] M. A. Naylor and A. W. Anderson, *ibid.*, **75**, 6392 (1953).

[9] W. G. Toland, *ibid.*, **82**, 1911 (1960).

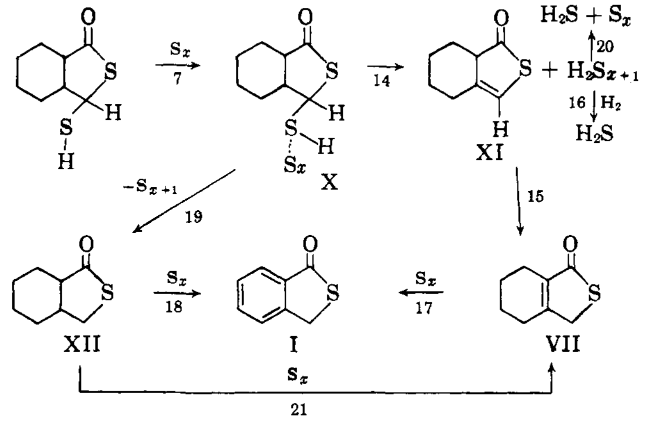
[10] R. E. Davis, *ibid.*, **80**, 3565 (1958).

SCHEME 1

(Dotted species seen in mass spectra; solid lined species isolated.)

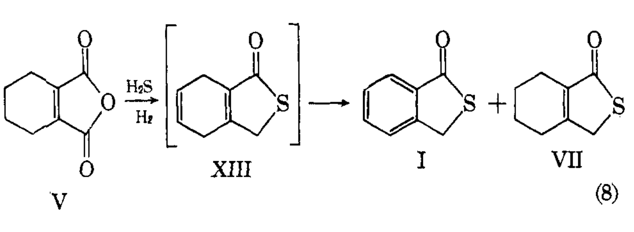


SCHEME 2



autoclave whose walls can catalyze the hydrogen–sulfur reaction, the yield of VII increased considerably. The alternate path, reactions 19 and 21, in which hexahydrothiophthalide (XII) is formed and then selectively dehydrogenated to VII seems unlikely since no XII was found. This would require the dehydrogenation of the completely saturated XII to VII to be more facile than dehydrogenation of the tetrahydrothiophthalide (VII) to thiophthalide (I). However, steps 18 and 19 cannot be ruled out in these cases in which no 3,4,5,6-tetrahydrothiophthalide (VII) is found.

The hydrogen sulfide–hydrogen reduction of 4-cyclohexene-1,2-dicarboxylic anhydride (V) gave a mixture of thiophthalide (I), 23% yield, and 3,4,5,6-tetrahydrothiophthalide (VII), 29% yield. The reduction of cyclohexane-1,2-dicarboxylic anhydride (VIII) under essentially the same conditions gave only VII; no thiophthalide was found. It is unlikely, then, that VII is the precusor of the thiophthalide found in the reduction of 4-cyclohexene-1,2-dicarboxylic anhydride. A possible reaction path for this unusual transformation involves formation of an intermediate, 3,6-dihydrothiophthalide (XIII), which disproportionates to I and VII. Partial prior hydrogenation of 4-cyclohexene-1,2-dicarboxylic anhydride to cyclohexane-1,2-dicarboxylic anhydride cannot be dismissed, but it is not likely, especially in the absence of a catalyst other than the metal autoclave walls.



(8)

Experimental

All runs were conducted in 4.5-l. 316-steel rocking autoclaves equipped with bursting disk, pressure gage, thermowell, bleed valve, and heating jacket.

Reagents were added to the bomb directly where possible. Hydrogen sulfide (and hydrogen) was pressured in after sealing the head. Contents were shaken while heating to temperature which took about 1 hr. After the specified reaction time, the autoclave was allowed to cool overnight to room temperature. Gaseous products were withdrawn through a caustic scrubber to absorb hydrogen sulfide and carbon dioxide. A Dry Ice trap was used when volatile products were expected, and in the phthalic anhydride reduction a wet test meter was used to measure unconverted hydrogen. Liquid and solid products were then worked up as indicated for each type of product.

Phthalic Anhydride Reduction.—Table I summarizes these runs. In those cases where water was used, products were isolated as follows. They were first steam distilled. A chloroform extraction then separated all thiophthalide, benzoic, and toluic acids, as well as other organic by-products. Sulfur partially dissolved in the chloroform, but the bulk of it was recovered by filtration of the chloroform–water mixture. Unchanged phthalic acid was recovered from the water phase by crystallization and by evaporation of the filtrates to dryness. The chloroform solution was extracted with aqueous sodium bicarbonate to remove benzoic and toluic acids, which were isolated by acidifying with dilute mineral acid, filtering, washing, and drying. Identity was established by neutralization equivalent. The remaining chloroform solution was then distilled through a 1-ft. glass helices-packed column. Distillation of the thiophthalide fraction was done at reduced pressure (10–50 mm. of mercury) and select cuts were analyzed by high mass spectrometry, saponification and neutralization equivalents, and elemental analysis for sulfur. Still residues were analyzed for free and total sulfur. By-product tars were found here.

Those runs done with no water present were worked up by diluting with benzene, azeotropically distilling water of reaction, and then fractionally distilling through a 4-ft. zigzag column under reduced pressure.

The green-yellow needles of Δ-3,3'bithiophthalide (IV), m.p. 335°, lit.[11] m.p. 332–333°, obtained in run 6 were soluble only in nitrobenzene and ethyl benzoate. Sublimation gave orange-yellow needles.

In run 9, *o*-xylylene sulfide (III), b.p. 90–100° (2–4 mm.), lit.[12] b.p. 106–107° (9 mm.), was obtained as a yellow oil. The compound was further purified by steam distillation done under an atmosphere of nitrogen.

Anal. Calcd. for C_8H_8S (136.21): C, 70.54; H, 5.29; S, 23.54. Found: C, 69.90; H, 6.05; S, 23.0.

Δ-3,3'-Bithiophthalide (IV) Oxidation.—Δ3,3'-Bithiophthalide (32.8 g., 0.111 mole), sulfur (32 g., 1 g.-atom), and water (1800 g., 100 moles) were charged to the autoclave. The autoclave was held at 260° for 2 hr. The product of the reaction was filtered while still hot, giving a dark solid (27.5 g.) whose analysis showed 79% free sulfur; the aqueous filtrate was partially

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[11] S. Gabriel and E. Lenpold, *Ber.*, **31**, 2646 (1898).

[12] S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Inst. Petrol.*, **40**, 76 (1954).

evaporated and then chilled to yield crude phthalic acid (27.2 g., 0.164 mole, 74%).

Thiophthalic Anhydride (II) Reduction.—Thiophthalic anhydride was prepared from phthalic anhydride and sodium sulfide as described by Reissert and Halle.[13] Hydrogen sulfide was passed through the thiophthalic anhydride (5.0 g., 0.030 mole) for 6 hr. as the reaction mixture was heated to 260°. The reaction took place at atmospheric pressure. Ether extraction of the cooled reaction product left sulfur (0.34 g., 0.011 g.-atom). Mass spectrometry analysis of the residue left after evaporation of the ether showed the following (in mole per cent): thiophthalic anhydride, 87; thiophthalide, 3.0; toluic acid, 0.9; and benzoic acid, 0.2.

Succinic Anhydride Reduction.—Succinic anhydride (200 g., 2.0 moles) and hydrogen sulfide (500 g., 15 moles) were heated in an autoclave at 260° for 1 hr. and then allowed to cool slowly overnight. The foul smelling reaction product was extracted with benzene and filtered, leaving succinic acid (58 g., 0.20 mole) and sulfur (42.5 g., 1.34 g.-atoms). The succinic acid was identified by its infrared spectrum and the percentage sulfur present was determined by free sulfur analysis. The filtrate was distilled, giving γ-thiolbutyrolactone (48.55 g., 0.475 mole, 24%), b.p. 53–57° (4 mm.), $n^{20}\text{D}$ 1.5219–1.5296. Redistillation gave pure γ-thiolbutyrolactone, b.p. 57° (4 mm.), $n^{20}\text{D}$ 1.5277; lit.[14] b.p. 56–57° (4 mm.), $n^{20}\text{D}$ 1.5240; $\nu_{\text{C=O}}$ 1725 cm.$^{-1}$ in carbon tetrachloride.

Anal. Calcd. for C_4H_6SO (102.16): C, 47.02; H, 5.92; S, 31.39. Found C, 46.99; H, 5.91; S, 31.42.

Succinic Acid Reduction.—A mixture of succinic acid (237 g., 2.01 moles) and hydrogen sulfide (320 g., 9.4 moles) was charged to an autoclave. The autoclave was heated to 269° and held at this temperature for 2 hr. The autoclave was allowed to cool slowly overnight before it was vented. The crude product (257 g.), which was a mixture of crystals and black oil, was extracted with benzene (1 l.). Distillation of the benzene extract gave γ-thiolbutyrolactone (7.4 g., 0.072 mole, 3.6%), b.p. 45–56° (1 mm.). The benzene-insoluble material was extracted with hot water and separated from the insoluble tar. Evaporation of the water gave succinic acid, (137 g., 1.16 moles, 58% recovery), m.p. 182–184°, which was identified by its infrared spectrum in Nujol.

Acetic Anhydride Reduction.—Acetic anhydride (510 g., 5.0 moles) and hydrogen sulfide (510 g., 15 moles) were charged to an autoclave. The mixture was heated to 260° for 2 hr. After cooling and venting the unchanged hydrogen sulfide, the mixture was filtered to remove sulfur (59.9 g., 1.86 g.-atoms) and then fractionally distilled through a 36-in. helices-packed column. Ethyl thiolacetate, b.p. 117°, lit.[15] b.p. 116–117° was obtained by washing out the acetic acid in the distillate with water and then redistilling.

The composition, in mole per cent, indicated by mass spectrometry analysis of the crude reaction mixture was acetic acid, 89; ethyl thiolacetate, 7; diethyl disulfide, 1; *n*-butyl mercaptan, 0.8; ethyl mercaptan, 0.6; *n*-propyl mercaptan, 0.2; and methyl mercaptan, 0.1.

Benzoic Anhydride, Benzoic Acid, *m*-Toluic Acid Reduction.—A mixture of benzoic anhydride (56.6 g., 0.250 mole) benzene (780 g., 10 moles), and hydrogen sulfide (34 g., 1.0 mole) was charged to an autoclave. Hydrogen was pressured in to 1500 p.s.i.g. and then the autoclave was heated to 177° for 2 hr. After cooling and venting the autoclave, the benzene was distilled, and the residue (71.9 g.) was allowed to cool. The composition, in mole per cent, of the residue as determined by mass spectrometry analysis was benzene, 36; benzoic acid, 51; benzyl thiolbenzoate, 9; benzoic anhydride, 3; benzyl mercaptan, 1; and a trace of toluene.

A similar run at 260° gave almost all toluene. Benzoic acid was unreactive at 260°, but at about 300° was reduced to toluene in 68% yield. Under similar reducing conditions at 340°, *m*-toluic acid gave *m*-xylene in 13% yield; lauric acid was recovered unchanged.

Phthalimide Reduction.—Phthalimide (148 g., 1.0 mole) and hydrogen sulfide (204 g., 6 moles) were charged to an autoclave. After heating for 2 hr. at 260°, the reaction mixture was slowly allowed to cool. The resulting dark mixture yielded no identifiable products.

Benzonitrile–Benzoic Acid Mixture Reduction.—Benzonitrile (103 g., 1.0 mole), benzoic acid (122 g., 1.0 mole), and hydrogen sulfide (200 g., 5.9 moles) were charged to an autoclave which was heated for 2 hr. at 280° and then allowed to cool slowly. Other than toluene (48 g.), only benzoic acid was recovered from the reaction.

Reduction of V, VI, and VIII.—The reduction of compounds V, VI, and VIII was done as follows. The carboxylic anhydride was put in a 4.5-l. glass-lined autoclave. Hydrogen sulfide, and hydrogen when used, was then charged to the autoclave which was placed in the rocker. Heat was applied until the temperature of the autoclave reached 260°. After 2 hr. at 260°, the rocker was stopped, and the autoclave was allowed to cool overnight. The hydrogen sulfide was vented into aqueous sodium hydroxide and the product was removed from the autoclave.

4-Cyclohexene-1,2-dicarboxylic Anhydride (V) Reduction. A.—4-Cyclohexene-1,2-dicarboxylic anhydride (304 g., 2.00 moles) and hydrogen sulfide (390 g., 11.5 moles) were allowed to react as described above. The crude product was a viscous red-brown oil containing water, 9.6 g. (0.53 mole), which was separated. The remaining oil (350 g.) was analyzed by integration of the vapor phase chromatograph trace and was estimated to be 65% (211 g., 1.41 moles) thiophthalide. Vacuum distillation of the crude product gave thiophthalide, b.p. 105–120° (1 mm.), m.p. 49–52°, in only 45% yield before the material in the pot resinified.

B.—4-Cyclohexene-1,2-dicarboxylic anhydride (322 g., 2.15 moles), hydrogen sulfide (150 g., 4.4 moles), and hydrogen (to 1000 p.s.i.g.) were allowed to react in a 2.5-l. stainless steel autoclave. The crude product (380 g.), a viscous deep red oil, was diluted with benzene and extracted with 10% aqueous sodium hydroxide. The benzene solution was evaporated, leaving a red oil (171 g.) estimated to be 56% 3,4,5,6-tetrahydrothiophthalide (96 g., 0.63 mole, 29%) and 44% thiophthalide (75 g., 0.50 mole, 23%) by integration of the vapor phase chromatography trace. A 12-ft. 25% GE SF-96 silicone-on-firebrick column was used in vapor phase chromatograph separations.

1-Cyclohexene-1,2-dicarboxylic Anhydride (VI) Reduction.—1-Cyclohexene-1,2-dicarboxylic anhydride (125 g., 0.822 mole) and hydrogen sulfide (300 g., 8.8 moles) were allowed to react as described previously. The deep red crude product (144 g.) was filtered, leaving a yellow solid (2.4 g.), m.p. 202–215° with apparent water evolution. The water layer (8.1 g., 0.45 mole) in the filtrate was separated and the thiophthalide content of the organic layer (122 g.) was estimated to be 92% (112 g., 0.746 mole, 91%) by integration of the vapor phase chromatograph trace.

Cyclohexane-1,2-dicarboxylic Anhydride (VIII) Reduction. A.—Cyclohexane-1,2-dicarboxylic anhydride (308 g., 2.00 moles) and hydrogen sulfide (340 g., 10 moles) were allowed to react as described previously. The crude product was a deep red oil with a light colored solid suspended in it. The solid was separated, and the filtrate (150 g.) was estimated to consist of 51% 3,4,5,6-tetrahydrothiophthalide (76.5 g., 0.50 mole, 25%) and 42% thiophthalide (63.0 g., 0.42 mole, 21%) by integration of the vapor phase chromatography trace.

B.—Cyclohexane-1,2-dicarboxylic anhydride (250 g., 1.62 moles), hydrogen sulfide (300 g., 8.8 moles), and hydrogen (to 800 p.s.i.g.) were allowed to react as described previously. The solid in the deep red oil was separated and washed with benzene, giving a white solid diacid (120 g., 0.70 mole, 43%), m.p. 180–215°, neutralization equivalent 86.6, calculated for cyclohexane dicarboxylic acid, 86.1. This was probably a mixture of *cis*- and *trans*-cyclohexane-1,2-dicarboxylic acids, m.p. 190–196° dec.[16] and 215–221°,[17] respectively. The benzene in the filtrate was evaporated under a stream of nitrogen to give a red oil (143 g.) which was estimated from the integrated vapor phase chromatography trace to be 60% 3,4,5,6-tetrahydrothiophthalide (85 g., 0.55 mole, 34%) and 40% thiophthalide (58 g., 0.38 mole, 23%).

C.—Cyclohexane-1,2-dicarboxylic anhydride (385 g., 2.50 moles), hydrogen sulfide (170 g., 5.0 mole), and hydrogen (to 900 p.s.i.g.) were allowed to react in a 2.5-l. steel autoclave as described previously. The product was a deep red oil containing white solid. The solid was separated and then washed with benzene, leaving light greenish white crystals (200 g., 1.16 mole,

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[13] A. Reissert and H. Halle, *Ber.*, **44**, 3029 (1911).

[14] C. M. Stevens and D. S. Tarbell, *J. Org. Chem.*, **19**, 1996 (1954).

[15] R. B. Baker and E. E. Reid, *J. Am. Chem. Soc.*, **51**, 1568 (1929).

[16] W. Reppe, O. Schlechting, K. Kluger, and T. Toepel, *Ann.*, **560**, 57 (1948).

[17] M. S. Newman and H. A. Loyd, *J. Org. Chem.*, **17**, 579 (1952).

47%), m.p. 214–228°, of *trans*-cyclohexane-1,2-dicarboxylic acid. The viscous red filtrate was estimated by integration of the vapor phase chromatography trace to be 90% 3,4,5,6-tetrahydrothiophthalide (179 g., 1.16 moles, 47%). The benzene wash solution was added to the viscous red oil and the resulting solution extracted with 5% aqueous sodium bicarbonate. The benzene was then evaporated and the oil cooled to 0°. The oil partially crystallized, and a sticky yellow solid was collected. Two recrystallizations of the yellow solid from methanol (with charcoal) gave 3,4,5,6-tetrahydrothiophthalide as white crystals (74 g., 0.48 mole, 19%), m.p. 36–43°. Further recrystallizations gave white crystals, m.p. 42–43°; λ_{max} in 95% ethanol: 233 mμ (log ϵ 4.02), 258 inflection (3.43); $\nu_{C=O}$ 1690, $\nu_{C=C}$ 1655 cm.$^{-1}$ in carbon tetrachloride. The nuclear magnetic resonance spectrum[18] showed the following absorptions (in τ-values, tetramethylsilane external standard): 8.25, quartet, unconjugated methylene; 7.70, diffuse multiplet, vinyl methylene; 6.17, singlet, split slightly, vinyl methylene adjacent to sulfur; calculated area ratio 2:2:1; observed, 2.1:2.1:1.

Anal. Calcd. for $C_8H_{10}OS$ (154.31): C, 62.26; H, 6.53; S, 20.68. Found: C, 61.98; H, 6.48; S, 20.52. The molecular weight as determined by mass spectrometry was 154.

When this reaction was repeated in a freshly reamed autoclave, the product oil after separation of the solid diacid, was estimated to contain 69% 3,4,5,6-tetrahydrothiophthalide and 21% thiophthalide.

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[18] The n.m.r. spectrum was obtained on a Varian A-60 spectrometer.

2-Amino-5,6-dihydro-1,3-oxazines. The Reduction of Carboxylic Esters with Sodium Borohydride[1]

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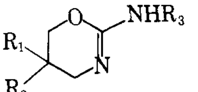
Several 5-substituted 2-amino-5,6-dihydro-1,3-oxazines (Table III) were prepared by the cyclization of the appropriately substituted 1,3-amino alcohols (Table II) with cyanogen bromide. The amino alcohols were prepared most readily by a two-step process: (1) sodium borohydride reduction of α-substituted cyanoacetates to the novel hydracrylonitriles (Table I), and (2) lithium aluminum hydride reduction of these to the requisite amino alcohols. A side product of step 1 has been shown to result from the reduction of the nitrile function with sodium borohydride.

The 2-amino-5,6-dihydro-1,3-oxazine system (I) has apparently received little attention. In 1890 Gabriel and Lauer[2] described the parent compound (I, $R_1 = R_2 = R_3 = H$) and more recently Najer and co-workers[3] reported the synthesis of several N-substituted derivatives (I, $R_1 = R_2 = H$; R_3 = alkyl, aryl, and aralkyl). Our interest in this system concerned the possible biological activity of analogs in which the 5-position was substituted (*e.g.*, I, $R_1 = R_2$ = phenyl; R_3 = H).

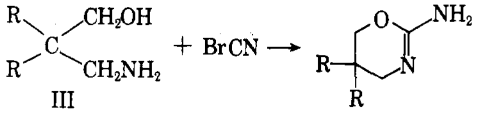


I

$R_3NHCONHCH_2CH_2CH_2Cl$

II

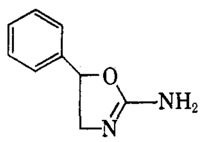
The general method employed by the earlier workers was cyclization of the appropriately N-substituted N′-γ-chloropropylureas (II) in boiling water. Our approach was the cyclization of 2-substituted 1,3-amino alcohols (III) with cyanogen bromide. The



III

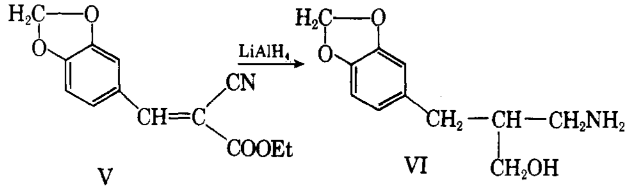
analogous reaction between 1,2-amino alcohols and cyanogen bromide to give the corresponding 2-amino-oxazolines (*e.g.*, IV) has been reported.[4]

The requisite 1,3-amino alcohols were in general new compounds. In the search for a method of preparation,



IV

we were attracted by the report[5] that lithium aluminum hydride reduces α,β-unsaturated cyanoacetates (*e.g.*, V) to the corresponding saturated amino alcohols (VI). Numerous attempts to reproduce these results led only to poor yields of colored oils from which none of the desired amino alcohols could be isolated.[6] Two exceptions were noted, namely, ethyl methylphenylcyanoacetate and ethyl diphenylcyanoacetate (see XXXI and XXXII, respectively, Table II). Evidently, disubstitution of the α-position of ethyl cyanoacetate allows reduction with lithium aluminum hydride to proceed satisfactorily.



V

VI

The desired amino alcohols were finally obtained by either of the two following methods.

1. Nickel-catalyzed hydrogenation of the α,β-unsaturated cyanoacetates (*e.g.*, V) to give the corresponding amino esters (*e.g.*, VII).[7] The latter sub-

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[1] Presented in part at the Fourth Delaware Valley Regional Meeting, Philadelphia, Pa., January 25-26, 1962.

[2] S. Gabriel and S. Lauer, *Ber.*, **23**, 95 (1890).

[3] H. Najer, P. Chabrier, and R. Giudicelli, *Bull. soc. chim. France*, 611 (1959).

[4] G. Fodor and K. Koczka, *J. Chem. Soc.*, 850 (1952); R. R. Wittekind, J. D. Rosenau, and G. I. Poos, *J. Org. Chem.*, **26**, 444 (1961); G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszowski, N. M. Kelley, and J. McGowan, *J. Med. Chem.*, **6**, 266 (1963).

[5] A. Dornow, G. Messwarb, and H. H. Frey, *Ber.*, **83**, 445 (1950).

[6] The extraordinary work-up and isolation techniques employed by Dornow, *et al.*, and the generally poor yields reported suggest that they experienced similar difficulties.

[7] R. R. Burtner and J. W. Cusie, *J. Am. Chem. Soc.*, **65**, 262 (1943), used a similar method to reduce methyl diphenylcyanoacetate to the amino ester.