For this reason, a mixture of benzene and chlorobenzene was finally chosen which gave a pot temperature of 100° at the boiling point. This compromise mixture minimized decarboxylation while ensuring complete demethylation.

An interesting phenomenon concerning the apparent isomerism of I in the solid state has been observed. The freshly crystallized material exhibits a distinct yellow color. After standing several months, the crystals become colorless. Both materials have the same neutralization equivalent. In aqueous solution, both forms give identical ultraviolet spectra. The yellow form converts to the colorless form on being heated in a melting point tube, the final melting point being the same as the colorless form.

Further work is now in progress on I as well as with 2,3,5-trihydroxybenzoic acid[6] and 2,4,5-trihydroxybenzoic acid.[7] The latter two acids have been reported as being yellow. Since both have the same hydroxyhydroquinone structure as I, it seems likely they will show the same type of isomerism.

EXPERIMENTAL[8]

2,3,6-Trimethoxybenzoic acid (II). This material was prepared by the method of Gilman and Thirtle[5] using ethyllithium and after recrystallization from ethylene dichloride was obtained in 77.8% yield, m.p. 148–149.5°; ref. 5 gives m.p. 149–150°.

2,3,6-Trihydroxybenzoic acid (I). To a mixture of 42.3 g. (0.20 mole) of II, 200 g. of benzene, and 315 g. of chlorobenzene was added with vigorous stirring 112 g. (0.84 mole) of anhydrous, sublimed aluminum chloride. The mixture was heated slowly taking approximately 15 minutes to reach refluxing temperature.[9,10] Heating was continued for a total of 45 minutes.

The mixture was cooled under argon, poured over 1 kg. of ice with stirring, and allowed to stand until the ice had melted. The aqueous portion was extracted with 2 × 100 ml. of ether, filtered, and acidified with 100 ml. of concentrated hydrochloric acid. The precipitation of the product was extremely slow. The mixture was allowed to stand overnight.

The product was removed by filtration,[11] washed with 100 ml. of water, air-dried for several hours, and then dried at 70° to constant weight, yielding 18.7 g. The main filtrate was extracted with 3 × 100 ml. of ether. The ether was removed by evaporation and the residue, weighing 12.8 g., was combined with main portion of product.

The product was recrystallized by repeated extractions (four) with the same 400 ml. portion of nitromethane. This technique was repeated with a fresh amount of nitromethane.[12] The total yield of pure material was 19.2 g., yellow, 56.4%, m.p. 188.5–190° with decomposition, blue-green color with alcoholic ferric chloride.

Anal.[13] Calc'd for $C_7H_6O_5$: C, 49.42; H, 3.56. Found: C, 49.35; H, 3.92.

Calc'd for $C_6H_5O_3COOH$: Neut. Equiv.,[14] 170.1. Found: 171.8 (colorless form); 171.9 (yellow form).

Methyl 2,3,6-trihydroxybenzoate. The method of Saraiya and Shah[15] was used. A mixture of 8.3 g. (0.049 mole) of I, 5.1 g. of sodium bicarbonate, 7.6 g. (0.06 mole) of dimethyl sulfate, and 120 ml. of acetone was refluxed for 5 hours. The cooled reaction mixture was filtered and the solid was washed with 100 ml. of acetone. The combined acetone portions were evaporated to dryness under reduced pressure. The cooled residue was treated with 80 ml. of 5% aqueous sodium bicarbonate. The solid which separated was collected, washed with 10 ml. of water, air-dried, and recrystallized from benzene, yielding 3.0 g. of pale yellow crystals, 33%, m.p. 137–139°, brown color with ferric chloride.

An analytical sample was prepared by successive recrystallizations from benzene and *n*-heptane, m.p. 139–140.5°.

Anal.[13] Calc'd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 51.90; H, 4.44.

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(6) Corbett, Hassall, Johnson, and Todd, *J. Chem. Soc.*, 1 (1950).

(7) Thiele and Jaeger, *Ber.*, **34**, 2837 (1901).

(8) Melting points are uncorrected.

(9) If heating is too rapid, the mixture will set to a hard mass which will break up slowly with continued heating.

(10) A gas-scrubbing tower was used as described by Allen, *Org. Syntheses*, Coll. Vol. II, 1st ed., 4 (1943).

(11) It is advisable to use a porcelain spatula. Intense colors develop with iron equipment.

(12) Other solvents such as: acetic acid, acetonitrile, and ethylene dichloride, have been tried with less success.

(13) Analyses were done by: Spang Microanalytical Laboratory, P. O. Box 2, Plymouth, Michigan.

(14) Neutralization equivalents are ours. A *pH* meter is essential since a red color develops as base is added which obscures the end-point with indicators.

(15) Saraiya and Shah, *Proc. Indian Acad. Sci.*, **31A**, 187 (1950).

Derivatives of Sulfenic Acids. XXV. The Reaction of 1,2-Epoxides with 2,4-Dinitrobenzenesulfenyl Chloride[1,2]

DAVID PETERS AND NORMAN KHARASCH

Received February 13, 1956

In continuing our studies of the reactions of sulfenyl halides, the reaction of 2,4-dinitrobenzenesulfenyl chloride (I) with selected 1,2-epoxides has been examined. To our knowledge, no previous account of this reaction has been recorded, although Stewart and Cordts[3] reported an analogous reaction with episulfides, in which the addition of 1-chloro-2-propanesulfenyl chloride to propylene sulfide led to *bis*(1-methyl-2-chloroethyl) disulfide, II, as shown in equation 1.

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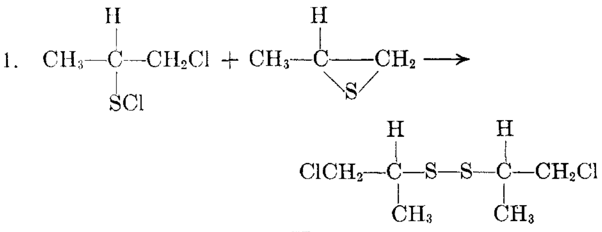
(1) The research reported in this document has been made possible through support and sponsorship extended by the Office of Scientific Research, Air-Research and Development Command, under Contract No. AF-18(600)-844.

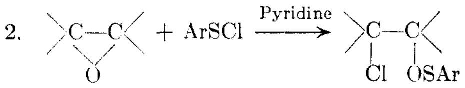
(2) Part 3 in "Studies of Sulfenate Esters (Thioperoxides)." For Part 2, *Cf. J. Am. Chem. Soc.*, **77**, 6541 (1955).

(3) Stewart and Cordts, *J. Am. Chem. Soc.*, **74**, 5880 (1952). Note added in proof: *Cf.*, also, Brintzinger, Schmahl, and Witte, *Ber.*, **85**, 338 (1952), for a description of the reaction of two moles of 2-chloroethanesulfenyl chloride with ethylene oxide.



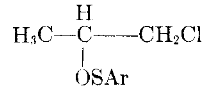
II

Stewart and Cordts found that the above reaction occurs rapidly at room temperature and requires no catalyst. In the present work, however, the reactions of I with ethylene oxide, propylene oxide, cyclohexene oxide, styrene oxide, and the *cis* and *trans* stilbene oxides did not proceed if the epoxides and I, alone, were mixed in an inert solvent, such as ethylene chloride. This was shown by mixing the reagents, in ethylene chloride, letting the mixtures stand for 24 hours, then adding cyclohexene. High yields of the known adduct of I to cyclohexene were obtained, showing that I had not reacted. It was found, however, that the addition of pyridine promotes the reaction (equation 2) with all the above epoxides, except the stilbene oxides, leading to the β-chloroalkyl 2,4-dinitrobenzenesulfenates, III; Ar = 2,4-dinitrophenyl.



III

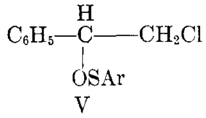
The reactions of I with ethylene oxide and cyclohexene oxide, with pyridine present, occur smoothly to give the desired, excellently crystalline, yellow products. Propylene oxide also reacts readily, but only one of the possible products could be isolated in crystalline form. The structure assigned to this product is IV, since it was also obtained from a sample of 1-chloro-2-propanol, which was unambiguously prepared by reduction of chloroacetone with lithium aluminum hydride.[4] The presence of the second isomer (2-chloropropyl 2′,4′-dinitrobenzenesulfenate) was, however, inferred, since crystalline IV was difficult to isolate from the low-melting reaction product of I and propylene oxide. Reaction of I and *trans*-2-chlorocyclohexanol, under the conditions previously used[5] for the synthesis of 2,4-dinitrobenzenesulfenates (from I and alcohols) readily yielded the same product as was obtained from I and cyclohexene oxide. Ethylene chlorohydrin and I also gave the same product as ethylene oxide and I.



$H_3C-\underset{OSAr}{\overset{H}{C}}-CH_2Cl$

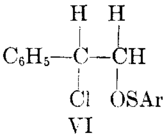
IV

With styrene oxide and I, reaction occurred in the presence of pyridine, but the product was a viscous oil, which showed definite signs of crystallizing, but could not be induced to do so completely. This product was probably a mixture of V and VI, since —on preparation of the sulfenates from the isomeric chlorohydrins of styrene—the compound from 2-chloro-1-phenylethanol was a crystalline solid (m.p. 120–121°), assigned structure V, while the product from 2-chloro-2-phenylethanol was an oil.



$C_6H_5-\underset{OSAr}{\overset{H}{C}}-CH_2Cl$

V



$C_6H_5-\underset{Cl}{\overset{H}{C}}-\underset{OSAr}{\overset{H}{C}H}$

VI

The *cis* and *trans* stilbene oxides were also examined in the reaction with I. It was found that not only do they fail to react in the absence of pyridine, but that they also fail to react in its presence. This inertness of the stilbene oxides, as compared with other 1,2-epoxides, recalls an observation of Boeseken[6] that these epoxides fail to react with boiling dilute acids to give the glycols.

The results of the present study are summarized in Table I. In all cases in which pyridine was employed, there precipitated varying amounts of the highly insoluble *bis*-(2,4-dinitrophenyl) disulfide, which has been frequently encountered in our previous studies of the reactions of I. Since the hydrolysis of the sulfenyl chloride occurs very rapidly in the presence of pyridine, and the disulfide is known to be the major product,[7] we believe that the disulfide results *via* reaction with water present in the system—although the glassware and the solvents used were carefully dried. Thus, the yields of products reported in Table I (especially with the epoxides) are probably determined by the amounts of moisture which remained in the reaction mixtures, rather than by the course of the main reactions with the epoxides or chlorohydrins.

In view of our earlier studies of the mechanism of the reactions of I, and, especially, the role of pyridine in the reactions of I with alcohols,[8] it is probable that the effect of pyridine in the reactions of I with epoxides involves reactions of the epoxides with the pyridine-sulfenyl chloride complex, which

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[4] It is recognized that the alternate synthesis from the chlorohydrins does not—without further evidence—furnish a rigorous assignment of structure, since the possibility exists that the chlorohydrins may dehydrohalogenate, to give the epoxide, and the latter may then lead to the sulfenate esters observed. That this does not occur is indicated by the formation of distinctly different products from the isomeric styrene chlorohydrins, as well as preliminary infrared spectral evidence on the interaction of *trans*-chlorocyclohexanol with pyridine. To prove the point rigorously, however, a kinetic study will be required.

[5] Kharasch, McQuarrie, and Buess, *J. Am. Chem. Soc.*, **75**, 2658 (1953).

[6] Boeseken, *Rec. trav. chim.*, **47**, 694 (1928).

[7] Kharasch, King, and Bruice, *J. Am. Chem. Soc.*, **77**, 931 (1955).

[8] Goodman and Kharasch, *J. Am. Chem. Soc.*, **77**, 6541 (1952).

TABLE I

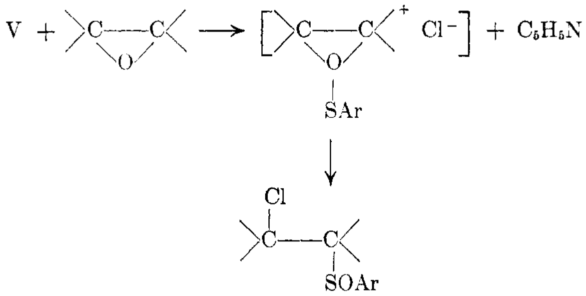
Synthesis of β-Chloroalkyl 2,4-dinitrobenzenesulfenates From 2,4-Dinitrobenzenesulfenyl Chloride (I) And 1,2-Epoxides or Chlorohydrins

Epoxide or Chlorohydrin	Product (Ar = 2,4-dinitrophenyl)	Yield,[a] %	M.P., °C.	Unreacted I in absence of pyridine, %	Analyses Calc'd C	Analyses Calc'd H	Analyses Calc'd N	Analyses Found C	Analyses Found H	Analyses Found N
Ethylene oxide	$ClCH_2CH_2OSAr$	50	120–121	85	34.53	2.53	10.07	34.45	2.55	9.87
2-Chloroethanol		80	121–122		34.53	2.53	10.07	34.83	2.76	10.07
Cyclohexene oxide	$C_6H_{10}ClOSAr$	78	140–145[b]	95	43.30	3.90	8.40	43.43	4.16	8.53
trans-2-Chloro-cyclohexanol		80	140–145[b]		43.30	3.90	8.40	43.02	4.13	8.28
Propylene oxide	$CH_3(ClCH_2)COSAr$[c]	30	106–107	95	36.86	3.07	9.55	36.91	3.24	9.79
1-Chloro-2-propanol		55	106–107		36.86	3.07	9.55	36.55	3.14	9.25
Styrene oxide	Yellow oil[c]				47.32	3.10	7.90	47.80	3.37	7.55
2-Chloro-2-phenyl-ethanol	Yellow oil	45		85						
2-Chloro-1-phenyl-ethanol	$C_6H_5CH(OSAr)CH_2Cl$	50	121–122		47.32	3.10	7.90	47.33	3.20	7.74
Stilbene oxides (*cis* and *trans*)	No reaction			95[e]						

[a] The yields are based on the amounts of 2,4-dinitrobenzene-sulfenyl used. [b] The products melt, with decomposition and darkening, in the temperature range indicated. [c] From the unsymmetrical oxides, the crude products probably contained both isomeric sulfenate esters. [d] The analytical sample showed definite signs of crystallizing, but could not be induced to do so completely. [e] From the *trans* oxide.

has been formulated previously[8] as 2,4-dinitrobenzenesulfenylpyridinium chloride, VII; Ar = 2,4-dinitrophenyl.

$$ArSCl + C_5H_5N: \rightleftharpoons [C_5H_5N \longrightarrow SAr]^+Cl^-$$



This mechanism explains the catalytic role of pyridine (*Cf.* discussion in Ref. 8) and is similar to the one suggested by Stewart and Cordts[3] for the uncatalyzed reaction shown in equation 1, as well as to those suggested for other reactions in which electrophilic reactants attack 1,2-epoxides.[9]

EXPERIMENTAL[10]

Starting materials. Ethylene chloride (pure solvent) and pyridine (Baker and Adams reagent) were refluxed, distilled, and stored over calcium hydride. Ethylene oxide (Eastman) and propylene oxide (Mathieson) were used without further purification. Cyclohexene oxide was prepared by action of perbenzoic acid on cyclohexene.[11] Styrene oxide (Dow Chemicals) was redistilled; b.p. 94–95°/30 mm. The stilbene oxides were prepared from the olefins: *trans* oxide, m.p. 69–70°; *cis* oxide, m.p. 42°. *cis*-Stilbene, b.p. 110–112°/5 mm. was prepared by decarboxylation of α-phenylcinnamic acid, in quinoline, with a copper chromite catalyst.[12] Ethylene chlorohydrin (Eastman) was redistilled, b.p. 128°; and cyclohexene chlorohydrin was prepared from hypochlorous acid and cyclohexene.[13] 2-Chloro-1-phenylethanol (b.p. 114–117°/8 mm.) was prepared by the action of lithium aluminum hydride (0.3 mole) on phenacyl chloride (1.0 mole); compare Refs. 14 and 15 for analogous syntheses. 2-Chloro-2-phenylethanol, b.p. 127–129°/10 mm., was similarly prepared[14,16] from chlorophenylacetyl chloride, obtained *via* phosphorus pentachloride and mandelic acid.[16] 1-Chloro-2-propanol, b.p. 127–131° was made by lithium aluminum hydride reduction of chloroacetone. The latter was prepared by the method of Buchmann and Sargent.[17]

The reaction of 1,2-epoxides with 2,4-dinitrobenzenesulfenyl chloride in the presence of pyridine. The general procedure was as follows. Into a 10-ml. glass-stoppered flask was weighed 0.50 g. (0.002 mole) of I and 5 ml. of ethylene chloride was added by pipette. The epoxide (0.025 mole) was added, followed by 3 to 4 drops of pyridine, and the flask was stoppered and let stand 12 to 24 hours, at room temperature, in the dark. Completion of the reaction was indicated by a negative starch-iodide test for I.[18] The yellow or red solution was diluted with methylene chloride and poured onto a silica column. Washing the column with methylene chloride removed a yellow band, and left a red band (in all cases) on the column. The insoluble *bis*(2,4-dinitrophenyl)disulfide was mechanically filtered by the column. The yellow eluate was evaporated to dryness and the residue was recrystallized

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(9) Elderfield, *Heterocyclic Compounds*, Vol. I, Ch. I. John Wiley and Sons, New York, N. Y., 1950.

(10) The melting points are not corrected. We are indebted to Mr. W. J. Schenck for the microanalyses.

(11) Derx, *Rec. trav. chim.*, **41**, 332 (1922).

(12) Taylor and Crawford, *J. Chem. Soc.*, 1130 (1934).

(13) Coleman and Johnstone, *Org. Syntheses*, Coll. Vol. I, 2nd ed., 158 (1941).

(14) Sroog, Chih, Short, and Woodburn, *J. Am. Chem. Soc.*, **71**, 1710 (1949).

(15) Lutz, Wayland, and France, *J. Am. Chem. Soc.*, **72**, 5511 (1952).

(16) Bischoff and Walden, *Ann.*, **279**, 122 (1894).

(17) Buchmann and Sargent, *J. Am. Chem. Soc.*, **67**, 401 (1945).

(18) Kharasch and Wald, *Anal. Chem.*, **27**, 996 (1955).

from methylene chloride-petroleum ether (b.p. 32-36°) to give the products listed in Table I.

Reaction of I and 1,2-epoxides without pyridine present. These reactions were carried out exactly as described, above, but no pyridine was added. After standing at least 12 hours, at room temperature, cyclohexene (1.0 ml.) was added and the mixture was allowed to stand for several hours. Chromatographing, as above, gave the known adduct of I and cyclohexene, m.p. 117-118°, in the yields shown in Table I.

Reaction of I and chlorohydrins in the presence of pyridine. These reactions were carried out in exactly the same way as were the epoxide reactions. The yields, melting points, and analytical figures are reported in Table I.

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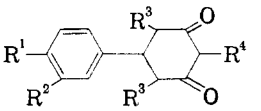
5-(1′,2′,3′-Trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3

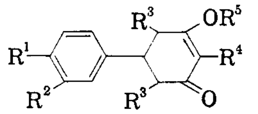
PHILIPPOS E. PAPADAKIS AND ROBERT MATHIESEN

Received February 13, 1956

Compounds of the types (I) and (II) below with different substituents for R^1, R^2, R^3, R^4 and R^5 have been synthesized in the Department of Therapeutics of New York University and in this laboratory by Papadakis and co-workers. Some of these derivatives have been reported previously.[1-5]

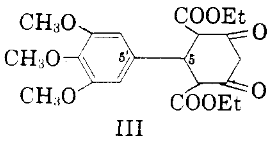


I



II

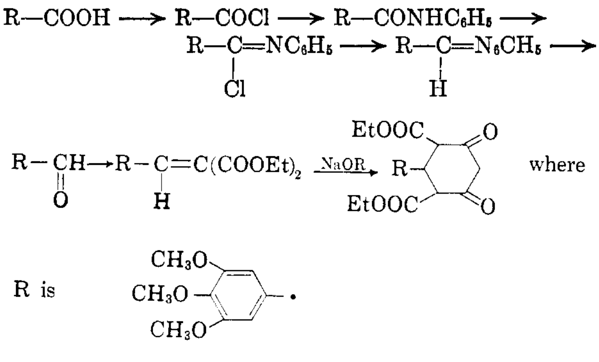
The present report is an extension of previous work and deals with the preparation of 5-(1′,2′,3′-trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 (III). The purpose of this investigation is the preparation of III as an intermediate for the



III

synthesis of compounds having structural relation to known anticancer agents or to other substances of physiological importance.

The sequence of synthesis is as follows:



EXPERIMENTAL

The preparation of *trimethoxybenzaldehyde* from trimethoxybenzoyl chloride is described by A. Sonn and E. Muller[6] and by J. W. Cook and co-workers.[7] The trimethoxybenzaldehyde was distilled at 163-166° and 10 mm. pressure. The distillate crystallized and gave a melting point of 75-76°. (Melting points are uncorrected.) The over-all yield from trimethoxybenzoylanilide to trimethoxybenzaldehyde was 59%.

Ethyl trimethoxybenzylidenemalonate. A mixture of 6.2 g. of 3,4,5-trimethoxybenzaldehyde, 5.1 g. of diethyl malonate, and 0.3 ml. of piperidine was refluxed for five hours at 150°. The product was dissolved in a small amount of alcohol and was reprecipitated with distilled water, m.p. 71-71.5°. The mixture m.p. of the product with trimethoxybenzaldehyde was 58-60°. The yield of pure product was 5.6 g.

Anal. Calc'd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.08; H, 6.45.

5-(1′,2′,3′-Trimethoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3. To a solution of 0.4 g. of sodium in absolute ethanol 2.2 g. of ethyl acetoacetate was added and the mixture was refluxed for an hour. To this, 5.6 g. of ethyl-3,4,5-trimethoxybenzylidenemalonate was added and the mixture was further refluxed for five hours at 110-115°. After cooling to 0°, cold dilute acetic acid was added. The yellowish crystals which formed were recrystallized from ethyl alcohol and were washed with dioxane; yield 3.6 g. of white needles, m.p. 191-192°.

Anal. Calc'd for $C_{21}H_{26}O_9 \cdot {}^1/_2\ H_2O$: C, 58.45; H, 6.07. Found: C, 58.31; H, 6.04. *Anal.* Dried at 100° in a vacuum, Calc'd for $C_{21}H_{26}O_9$: C, 59.71; H, 6.16. Found: C, 59.60; H, 5.84. *Anal.* Calc'd for 3($-OCH_3$) and 2($-OC_2H_5$): % alkoxy, 43.36. Found: 43.35, 43.10.

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(1) Papadakis, *J. Am. Chem. Soc.*, **67**, 1799 (1945).

(2) Papadakis, Scigliano, Chin, and Adrian, *J. Am. Chem. Soc.*, **72**, 4256 (1950).

(3) Papadakis, Scigliano, and Pirruccello, *J. Am. Chem. Soc.*, **75**, 5436 (1953).

(4) Papadakis and Scigliano, *J. Am. Chem. Soc.*, **75**, 5437 (1953).

(5) Papadakis, *J. Org. Chem.*, **19**, 51 (1954).

(6) Sonn and Muller, *Ber.*, **52**, 1934 (1919).

(7) Cook, Graham, Cohen, Lapsley, and Laurence, *J. Chem. Soc.*, 322 (1944).

Meta Amination as a 1,3-Addition Process

AVERY A. MORTON

Received February 17, 1956

The "benzyne" intermediate[1,2] for *meta* amination is a product of a theory that many reactions be-

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(1) Roberts, Simmons, Carlsmith, and Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953).

(2) Roberts, Semenow, Simmons, and Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).