have been established for the nitration of phenylacetic acid, the oxidation of nitrophenylacetic acids, the reduction of these compounds to amino acids and the bromination of aminobenzoic acids. Using this procedure, which yields reproducible results, it was found that 14.4% of the meta isomer is formed when nitric acid at 0° acts upon phenylacetic acid.

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE PLAUT RESEARCH LABORATORY OF LEHN & FINK, INC.]

BACTERICIDAL PROPERTIES OF MONOETHERS OF DIHYDRIC PHENOLS. III. THE MONOETHERS OF PYROCATECHOL. COMPARATIVE NOTES ON THE THREE SERIES OF MONOETHERS

BY EMIL KLARMANN, LOUIS W. GATES AND VLADIMIR A. SHTERNOV

RECEIVED OCTOBER 27, 1931 PUBLISHED MARCH 5, 1932

The third and last group of monoethers studied in this series of investigations[1] comprises the derivatives of pyrocatechol.

The antibacterial action of the parent compound pyrocatechol and of its methyl ether, guaiacol has been studied by many investigators in the past. It is not intended to give a complete tabulation of these findings; the general conclusion may be drawn from them, that as a bactericidal agent, pyrocatechol is less effective than phenol while guaiacol shows practically the same potency as phenol. This is not true, however, of the inhibitory action. Thus according to Cooper and Mason[2] the minimum concentration of pyrocatechol required to inhibit the growth of *B. coli* at 37° is almost one-half that of phenol, while in the case of *B. fluorescens liquefaciens* it is even less.

The preparation of certain higher alkyl monoethers of pyrocatechol from the corresponding diethers is referred to in the German patents Nos. 78,910, 92,651 and 94,852.[3] However, the antibacterial efficacy of these ethers does not appear to have been determined. In addition to these compounds the phenyl monoether is also known. It has been prepared by Ullmann and Stein[4] by treating the solution of the methyl phenyl ether of pyrocatechol in benzene with aluminum chloride.

The series of monoethers of pyrocatechol prepared and studied by us comprises the straight chain aliphatic derivatives up to and including the *n*-heptyl ether, the *sec.*-amyl ether, the phenyl ether and the alphyl aromatic derivatives up to and including the phenyl propyl ether.

In preparing these compounds we followed generally the methods applied

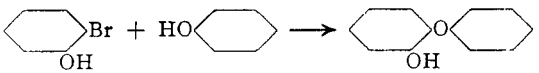
[1] Klarmann, Gatyas and Shternov, THIS JOURNAL, **53**, 3397 (1931); **54**, 298 (1932).

[2] F. A. Cooper and J. Mason, *J. Hygiene*, **26**, 118 (1927).

[3] Friedländer, *Fortschritte der Teerfarbenfabrikation*, **4**, 122–124.

[4] F. Ullmann and A. Stein, *Ber.*, **39**, 623 (1906).

in the preparation of the resorcinol and hydroquinone monoethers, *i. e.*, utilizing the reactivity of the halogen alkyl and alpharyl compounds with the phenolic hydroxyl group. The phenyl ether (*o*-hydroxydiphenyl oxide) which cannot be prepared by this reaction was obtained by condensation of *o*-bromophenol with potassium phenolate in the presence of copper catalyst.



Bactericidal Action of the Monoethers of Pyrocatechol.—The bactericidal action of the monoethers of pyrocatechol was determined with *B. typhosus* and *Staph. aureus* as test organisms. The minimum concentrations required to kill the bacteria in five, ten and fifteen minutes at 37°, and the phenol coefficients calculated therefrom, are given in Table I.

TABLE I

BACTERICIDAL ACTION OF MONOETHERS OF PYROCATECHOL

	B. typhosus Bactericidal concentrations			Phenol coeff.	*Staph. aureus* Bactericidal concentrations			Phenol coeff.
	5 min.	10 min.	15 min.		5 min.	10 min.	15 min.	
Pyrocatechol	1:110	1:140	1:150	0.87	1:40	1:45	1:55	0.58
Aliphatic Ethers								
Methyl	1:120	1:130	1:140	0.91	1:55	1:60	1:60	0.73
Ethyl	1:225	1:275	1:275	1.8	1:120	1:120	1:130	1.6
n-Propyl	1:500	1:600	1:650	4.1	1:275	1:300	1:300	3.8
n-Butyl	1:1400	1:1500	1:1600	9.8	1:750	1:750	1:800	10
n-Amyl	1:3250	1:3250	1:3250	22	1:1800	1:1800	1:2000	23
Sec.-amyl	1:2500	1:2750	1:2750	18	1:1400	1:1500	1:1600	20
n-Hexyl	1:2500	1:2500	1:2500	17	1:2000	1:2250	1:2500	28
n-Heptyl	1:1200	1:1400	1:1600	9.7	1:2500	1:2750	1:3250	37
Aromatic Ethers								
Phenyl	1:2250	1:2500	1:2500	17	1:800	1:850	1:850	11
Benzyl	1:2500	1:2750	1:2750	19	1:900	1:1200	1:1200	15
Phenylethyl	1:3250	1:3250	1:3500	22	1:1000	1:1600	1:1800	21
Phenylpropyl	1:2000	1:2000	1:2500	15	1:1300	1:1500	1:1600	19
Control								
Phenol (av.)	1:130	1:140	1:160	1	1:70	1:80	1:90	1

Thus the bactericidal action of pyrocatechol monoethers appears to be a function of the molecular weight and of the structure of the substituting radical. In the case of the aliphatic ethers the germicidal power against *B. typhosus* increases steadily, reaching a maximum with the *n*-amyl derivative, while with *Staph. aureus* no maximum is observed up to the *n*-heptyl compound. The *sec.*-amyl ether is less effective against either organism than the normal compound. Among the aromatic ethers the phenylethyl derivative is the most effective against both *B. typhosus* and *Staph. aureus*.

Comparison of the Bactericidal Action of the Monoethers of the Three Dihydric Phenols.—When comparing the bactericidal potency of the monoethers of the three dihydric phenols (Table II), it is found that the monoethers of pyrocatechol are generally less effective than the corresponding hydroquinone and resorcinol derivatives. Some exceptions are found among the aromatic monoethers, the pyrocatechol phenylpropyl monoether being more effective against *B. typhosus*, and the benzyl ether against *Staph. aureus* than the corresponding hydroquinone ethers. In no case, however, is the germ-killing potency of the resorcinol ethers surpassed by that of the corresponding pyrocatechol compounds.

TABLE II

COMPARISON OF THE BACTERICIDAL ACTION OF THE MONOETHERS OF THE THREE DIHYDRIC PHENOLS

	Phenol coefficients					
	B. typhosus			*Staph. aureus*		
	Resorcinol 0.4	Hydroquinone >12	Pyrocatechol 0.87	Resorcinol 0.4	Hydroquinone 0.44	Pyrocatechol 0.58
Aliphatic Groups						
Methyl	1.3	1.0	0.91	1.2	0.8	0.73
Ethyl	3.6	1.5	1.8	3.0	1.5	1.6
n-Propyl	6.9	5.4	4.1	5.4	4.1	3.8
n-Butyl	20	14	9.8	18.0	9.3	10
n-Amyl	38	29	22	36	30	23
Sec.-amyl	26	19	18	31	26	20
n-Hexyl	46	18	17	125	100	28
n-Heptyl	21	17	9.7	330	200	37
n-Octyl	2.3			580	360	
Aromatic Groups						
Phenyl	40	41	17	37	28	11
Benzyl	21	21	19	16	14	15
Phenylethyl	35	25	22	39	29	21
Phenylpropyl	34	10	15	89	13	10

This is rather remarkable if one considers that of the three dihydric phenols resorcinol shows the lowest bactericidal potency. Another noteworthy fact is that in the case of the pyrocatechol and hydroquinone monoethers the maximum germicidal action upon *B. typhosus* is shown by the *n*-amyl derivatives, while in the case of resorcinol the potency of the *n*-hexyl ether surpasses that of the *n*-amyl derivative. The bactericidal efficacy of the higher aliphatic ethers of pyrocatechol against *Staph. aureus* is very much below the rather spectacular efficacies of the corresponding resorcinol and hydroquinone monoethers.

The conditions encountered are also evident from Figs. 1 to 3, Figs. 1 and 2 showing the relation between the molecular weight of the substituting aliphatic group and the germicidal effect upon *B. typhosus* and

Staph. aureus, respectively, while Fig. 3 deals with the effect of the aromatic ethers upon both bacteria.

The bacteriological experiments are being continued with the following pathogenic germs: *B. coli*, *B. pyocyaneus*, *Streptococcus haemolyticus* and *Vibrio cholerae*. Preliminary results indicate that the Gram negative *B. coli* and *B. pyocyaneus* behave like the Gram negative *B. typhosus* when exposed to the compounds under discussion, while the Gram positive *Strept. haemolyticus* resembles *Staph. aureus* very closely in this respect. *Vibrio cholerae* is enormously sensitive to some of these compounds, but it reacts more like the Gram positive bacteria in spite of its Gram negative character. It is known to behave in this fashion in other instances also.

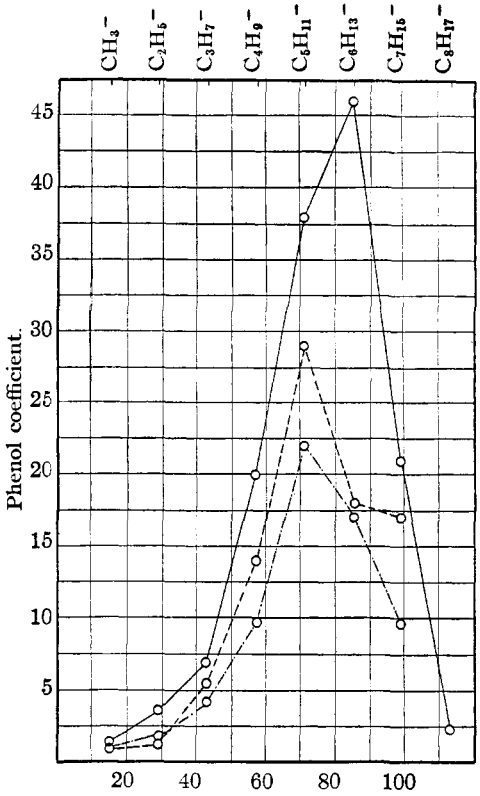
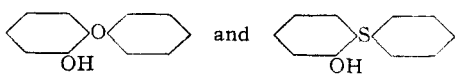


Fig. 1.—The effect of the molecular weight of the aliphatic radical on the bactericidal action of monoethers of dihydric phenols. Test organism, *B. typhosus:* ——, resorcinol monoethers, — — —, hydroquinone monoethers; — · — · —; pyrocatechol monoethers.

A detailed description of the bacteriological and toxicological findings will be reported elsewhere.

The phenyl ethers of the three dihydric phenols, which may also be regarded as isomeric hydroxyphenyl oxides, permit a comparison from the point of view of germicidal potency with the corresponding three isomeric hydroxydiphenyl sulfides prepared by Hilbert and Johnson.[5] This matter already has been referred to in our preceding publication[1] with emphasis upon the differences in the testing methods. The compounds under consideration are, *e. g.*, in the case of the pyrocatechol phenyl ether



[5] G. E. Hilbert and T. B. Johnson, THIS JOURNAL, 51, 1526 (1929).

Thus, *caeteris paribus*, such a comparison is ultimately one of the effect of oxygen and of sulfur, respectively, serving as connecting links of the two nuclei, upon the bactericidal action of the two classes of compounds.

TABLE III

COMPARISON OF THE BACTERICIDAL ACTION UPON *B. Typhosus* OF HYDROXYDIPHENYL OXIDES AND SULFIDES

	Phenol coeff.		Phenol coeff.
o-Hydroxydiphenyl oxide	17	*o*-Hydroxydiphenyl sulfide	33
m-Hydroxydiphenyl oxide	40	*m*-Hydroxydiphenyl sulfide	68
p-Hydroxydiphenyl oxide	41	*p*-Hydroxydiphenyl sulfide	115

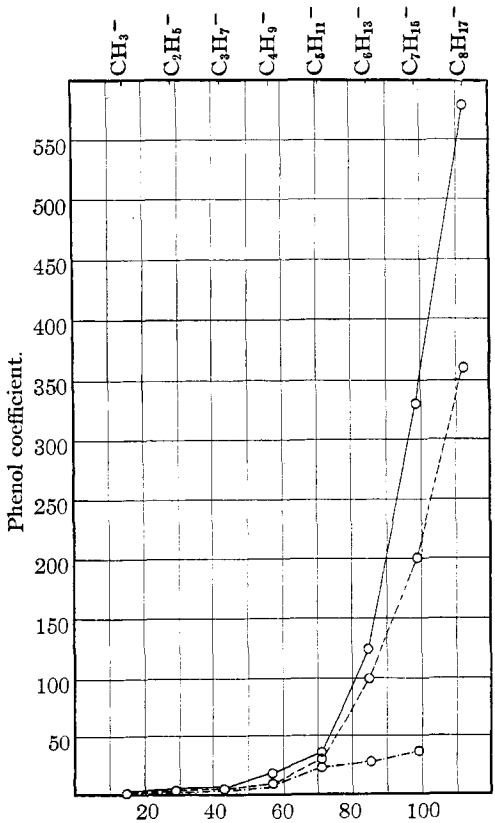


Fig. 2.—The effect of the molecular weight of the aliphatic radical on the bactericidal action of monoethers of dihydric phenols. Test organism, *Staph. aureus:* ——, resorcinol monoethers; - - -, hydroquinone monoethers; —·—·—, pyrocatechol monoethers.

The figures in Table III indicate that the three hydroxydiphenyl sulfides are more effective germicides than the corresponding oxides, when tested against *B. typhosus*.

The favorable effect of substitution by aliphatic and aromatic radicals upon the antibacterial action of phenols, has prompted us to take up the investigation of the antibacterial properties of substituted aromatic amines, phenol-ether amines and aminophenols; at this time we are in possession of some promising preliminary findings.

Experimental Part

(a) **Chemical.**—The methods used in the preparation and purification of the pyrocatechol monoethers were essentially the same as those applied in the case of the resorcinol and hydroquinone monoethers, *i. e.*, pyrocatechol could be brought into reaction with the alkyl or alpharyl halides in the presence of potassium hydroxide or carbonate. It seems unnecessary to give a

detailed description of the methods used in preparing the pyrocatechol monoethers and separating them from the diethers produced simultaneously; it is sufficient to refer to the experimental parts of the preceding publications.

It is of interest, however, that the pyrocatechol monoethers are very readily volatile with steam, more so than the corresponding hydroquinone and resorcinol derivatives. This property facilitated the purification, and particularly the separation from unconverted pyrocatechol. The latter is somewhat volatile with steam, but can be removed from the distillate practically completely by simple decantation of the aqueous layer. Steam distillation was not applied in the case of the *n*-hexyl, *n*-heptyl and phenylpropyl ethers, since these compounds of comparatively high molecular weight do not distil over with sufficient rapidity.

Final purification was achieved by repeated distillation under reduced pressure and recrystallization wherever feasible.

Since the pyrocatechol monophenyl ether (*o*-hydroxydiphenyl oxide) was prepared by a different method, a complete statement of the experimental conditions is given below.

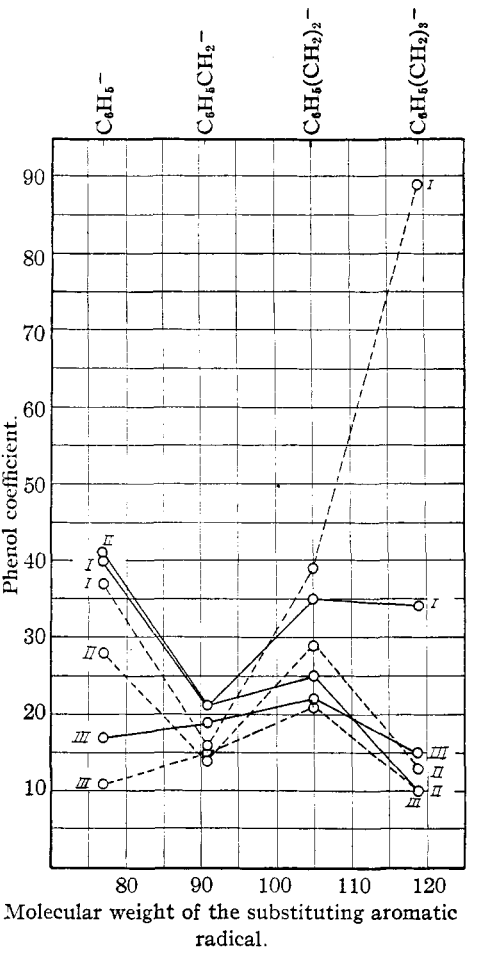


Fig. 3.—The bactericidal action of certain aromatic and alkyl-aromatic monoethers of dihydric phenols: I, resorcinol monoethers; II, hydroquinone monoethers; III, pyrocatechol monoethers. Test organisms: ——, *B. typhosus;* — — —, *Staph. aureus.*

Preparation of *o*-Hydroxydiphenyl Oxide.—Phenol (31 g.) and potassium hydroxide (22 g.) were mixed with a small amount of water to bring about complete solution, and heated in an oil-bath at about 150–160° until practically all the water was driven out. The solidified mass was finely ground and 57.7 g. of *o*-bromophenol and 0.3 g. of freshly reduced, finely subdivided, copper were added. The vessel was connected with a condenser and the mixture refluxed for six hours in an oil-bath with frequent shaking. The reaction product formed a heavy black oil. It was treated with water, acidified

and extracted with ether. The phenolic bodies were extracted with a 10% potassium hydroxide solution; the extract was acidified and subjected to steam distillation. At first a colorless oil came over consisting of a mixture of phenol and bromophenol; it was discarded. Then a white mass began to crystallize in the condenser. The distillation was continued until no more crystals collected in the distillate. The filtered crystalline product was dried and recrystallized from a mixture of benzene and petroleum benzene. The substance melted at 104°.

The analytical data of the pyrocatechol monoethers are given in Table IV.

TABLE IV

ANALYTICAL DATA

	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	B. p. °C.	B. p. Mm.	M. p., °C.
Aliphatic Ethers								
Ethyl	$C_8H_{10}O_2$	69.54	69.63	7.29	7.55	74–76	4	..
n-Propyl	$C_9H_{12}O_2$	71.01	71.22	7.96	8.17	80–83	4	..
n-Butyl	$C_{10}H_{14}O_2$	72.26	72.44	8.49	8.53	93–96	5	..
n-Amyl	$C_{11}H_{16}O_2$	73.31	73.00	8.95	8.74	104–106	4	..
Sec.-amyl	$C_{11}H_{16}O_2$	73.31	73.91	8.95	8.89	102–104	5	..
n-Hexyl	$C_{12}H_{18}O_2$	74.20	74.20	9.34	9.42	114–116	3.5	..
n-Heptyl	$C_{13}H_{20}O_2$	74.98	74.98	9.68	9.99	125–127	4	..
Aromatic Ethers								
Phenyl	$C_{12}H_{10}O_2$	77.43	77.39	5.42	5.73	...	...	104[a]
Benzyl	$C_{13}H_{12}O_2$	78.01	77.44	6.05	6.27	157	6	..
Phenylethyl	$C_{14}H_{14}O_2$	78.48	78.61	6.59	6.83	...	...	48[b]
Phenylpropyl	$C_{15}H_{16}O_2$	78.92	79.04	7.07	7.48	...	...	51[c]

[a] Recrystallized from a mixture of benzene and petroleum benzene.

[b] Recrystallized from 25% alcohol.

[c] Recrystallized from hexane and then from 25% alcohol.

(b) **Bacteriological.**—The method used in determining the germicidal action of the pyrocatechol derivatives studied was the same as that used in our work on the resorcinol and hydroquinone monoethers.

On the whole the monoethers of pyrocatechol were found to require an even greater proportion of alcohol in the minimum germicidal concentrations than the compounds of resorcinol and hydroquinone, with the exception of the *n*-heptyl and the phenylpropyl ethers. However, not more than 20% of alcohol was present in the final dilutions. The *n*-heptyl monoether required 40% of alcohol in the test with *B. typhosus* and 35% in that with *Staph. aureus;* the phenylpropyl monoether required 20 and 30% of alcohol, respectively.

Summary

In continuation of the work on the bactericidal properties of monoethers of dihydric phenols, the following derivatives of pyrocatechol were studied bacteriologically: methyl (guaiacol), ethyl, *n*-propyl, *n*-butyl, *n*-amyl, *sec.*-amyl, *n*-hexyl, *n*-heptyl; phenyl, benzyl, phenylethyl and phenylpropyl.

All pyrocatechol monoethers studied are bactericidal agents, but of varying potency, dependent upon the molecular weight and the structure of the substituting radical. While pyrocatechol is less effective than phenol, and guaiacol (its monomethyl ether) is practically as potent, the germicidal efficacy against *B. typhosus* increases with the increasing length of the aliphatic chain, reaching a maximum with the *n*-amyl ether and decreasing thereafter. With *Staph. aureus* no maximum is observed up to the *n*-heptyl ether. The *sec.*-amyl derivative is less effective in either case than the normal one. In the case of the aromatic ethers the maximum potency against both bacteria is shown by the phenylethyl ether.

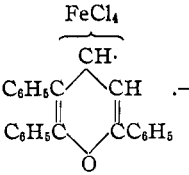
The hydroquinone monoethers, with certain exceptions, are more effective bactericides than the corresponding pyrocatechol derivatives, while the resorcinol monoethers are generally the most potent. The higher mono-alkyl ethers of pyrocatechol do not reach the extraordinary heights of bactericidal action upon *Staph. aureus* shown by the corresponding resorcinol and hydroquinone ethers. The maximum effect upon *B. typhosus* in the series of hydroquinone and pyrocatechol monoethers is shown by the *n*-amyl ethers, while in the resorcinol series it is reached with the *n*-hexyl ether.

Preliminary results of experiments with other pathogenic microörganisms indicate that the bactericidal effect of the monoethers of the three dihydric phenols upon the Gram negative bacteria *B. coli* and *B. pyocyaneus* resembles those obtained with *B. typhosus*, from the quantitative point of view and also from that of the position of the maximum of germicidal potency. The results with the Gram positive *Streptococcus haemolyticus* follow those obtained with *Staph. aureus* very closely. *Vibrio cholerae* is found to be very susceptible to the action of certain of the compounds studied; as to the position of the maximum of germicidal action, however, there is more resemblance to the behavior of the Gram positive bacteria in spite of the negative Gram reaction of the cholera germ.

The comparison of the action upon *B. typhosus* of the three phenyl ethers (hydroxydiphenyl oxides) with that of the three hydroxydiphenyl sulfides reveals the bactericidal superiority of the latter.

BLOOMFIELD, NEW JERSEY

Addition Reactions of Vinyl Phenyl Ketone. II. Desoxybenzoin. By C. F. H. Allen and W. E. Barker.

Page 737. Formula VIII should be 

.—C. F. H. Allen

The Photochemical Reaction between Quinine and Dichromic Acid. I. Quantum Yields. By George S. Forbes, Lawrence J. Heidt and Charles G. Boissonnas.

Page 960. The correct spelling of the name of the third author is Charles G. Boissonnas.

Page 967. In the last line of footnote 27, the numerical value should be "405 mμ" instead of "450 mμ."—George S. Forbes.

Bactericidal Properties of Monoethers of Dihydric Phenols. III. The Monoethers of Pyrocatechol. Comparative Notes on the Three Series of Monoethers. By Emil Klarmann, Louis W. Gates and Vladimir A. Shternov.

Page 1210. In the section headed (b) Bacteriological, the last two sentences of the second paragraph should be replaced by the statement: "However, not more than 15% of alcohol was present in most of the final dilutions. The *n*-heptyl and the phenylpropyl monoethers required 30% of alcohol in the test with *Staphylococcus aureus*, the phenylethyl, 25%."—E. Klarmann.

Calcium Nitrate. III. Heats of Hydration and of Solution of the Binary System Calcium Nitrate–Water. By Warren W. Ewing, Alfred N. Rogers, John Z. Miller and Edward McGovern.

Page 1339. At the bottom of the page, the ΔH values for strontium nitrate tetrahydrate should be plus instead of minus.—Warren W. Ewing.

The Isolation of Pure, Anhydrous Ethyl Alcohol from Non-Alcoholic Human and Animal Tissues. By Alexander O. Gettler, Joseph B. Niederl and A. A. Benedetti-Pichler.

Page 1484. In Table II the heading of the fourth column should read "Ethyl alcohol in mg. per 1000 g."—Alexander O. Gettler.

Mass, Zahl und Gewicht in der Chemie der Vergangenheit. Ein Kapitel aus der Vorgeschichte des sogenannten Quantitativen Zeitalters der Chemie. By Paul Walden.

Page 1700. In paragraph one, lines 7 and 8, for "appear as our Troy and avoirdupois pounds of today," read "appear as the older Dutch Troy pound and our avoirdupois pound of today."—Arthur B. Lamb.