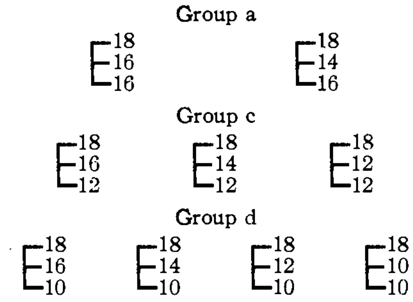
In Fig. 3 are plotted the long-spacing and melting-point data for those glycerides which were crystallized from solvent in the β' phase. The glycerides may be grouped as follows on the basis of the relationships observed in Fig. 3.



Figures 4 and 5 correlate the determined long-spacing values with capillary melting points. A definite relationship seems to exist among the members of the individual groups of glycerides which have been designated as Groups a, b and c of Fig. 1 and a, c and d of Fig. 3, respectively.

Acknowledgments.—The assistance of Miss Gretta L. Scott in obtaining some of the X-ray diffraction data is gratefully acknowledged.

An X-ray diffraction unit, given by the Picker X-Ray Corporation, was used to obtain some of the diffraction patterns.

Summary

The polymorphism of solvent-crystallized synthetic triacid triglycerides has been established by X-ray diffraction data.

Crystallization of the triacid triglycerides from solvent in either the β or β' phase seems to be dependent upon the rate of crystal growth.

Correlations between molecular weights and melting points and molecular weights and long-spacing values have been indicated.

PITTSBURGH, PENN. RECEIVED AUGUST 6, 1945

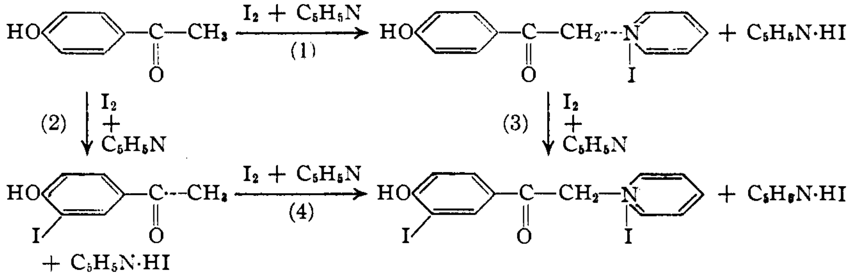
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Reactions of Acetophenols with Iodine and Pyridine and the Preparation of Hydroxybenzoic Acids

BY L. CARROLL KING, MARGARET MCWHIRTER AND DANIEL M. BARTON

In former papers from this Laboratory[1a,b] the reaction of iodine and pyridine with ketones, to give substituted β-ketoalkylpyridinium iodides was reported. This reaction has now been extended to a number of hydroxyacetophenones. *o*-Hydroxyacetophenones and resacetophenone gave the corresponding 1-(hydroxybenzoylmethyl) pyridinium iodides, *p*-hydroxyacetophenones and *m*-hydroxyacetophenone gave a mixture of the corresponding 1-(hydroxybenzoylmethyl)-pyridinium iodide and a 1-(hydroxymonoiodobenzoylmethyl)-pyridinium iodide. In each of the reactions studied approximately half of the iodine used appeared as pyridine hydroiodide. Each of the substituted β-ketoalkylpyridinium iodides produced by the above reactions gave characteristic hydroxy acids when cleaved by means of aqueous alkali.

Since about half of the iodine which enters into the reaction appears as pyridine hydroiodide (Table I), the reaction products can be best explained if it is assumed that one mole of the pyridine hydroiodide is obtained for each mole of iodine that enters the ring, and one mole of it for each mole of iodine which becomes a part of a substituted β-ketoalkylpyridinium iodide group. If *p*-hydroxyacetophenone is used as an example the reactions may be written as



The 1-(hydroxybenzoylmethyl)-pyridinium iodides could result only from reaction 1 but the 1-(hydroxymonoiodobenzoylmethyl)-pyridinium iodides could arise either from reaction 3 or from a combination of (2) and (4). No attempt was made to find in the reaction mixtures hydroxyiodoacetophenones such as might have been produced by reaction (2).

A list of the various pyridinium iodides obtained together with their yields and a list of the hydroxybenzoic acids obtained by alkaline cleavage of the iodides is shown in Table I.

The structures listed for eleven of the pyridinium salts prepared were supported by cleavage of the iodides or perchlorates with aqueous alkali to known substituted benzoic acids according to the general plan described in previous papers.[1a,b] In

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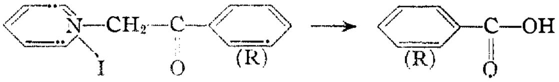
(1) (a) L. C. King, THIS JOURNAL, **66**, 894 (1944); (b) *ibid.*, **66**, 1612 (1944).

TABLE I

FORMATION AND CLEAVAGE OF SUBSTITUTED 1-BENZOYLMETHYLPYRIDINIUM IODIDES



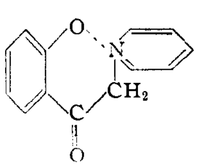
Starting acetophenone[a]	Yield[b] of pyridine hydriodide, g.	1-Benzoylmethylpyridinium iodide formed—substituents on R ring	Cpd. no.	Yield[b] of crude pyridinium iodide, g.	Yield[c] of pure material, g.	Yield of acid[d] from alkaline cleavage, %	M. p. of acid, °C.
o-Hydroxy	17	2-Hydroxy	1	19	0.55	85	156–158
m-Hydroxy	20	3-Hydroxy	2	18	.25	40	197–201
		3-Hydroxy-4-iodo	2a	1.2	.025	95	226–230[e]
p-Hydroxy	20	4-Hydroxy	3	17	.31	98	212–213
		4-Hydroxy-3-iodo	3a	8.7	.18	79	172–175
2-Hydroxy-5-methyl	20	2-Hydroxy-5-methyl	4	29	.69	95	148–150
2-Hydroxy-4-methyl	20	2-Hydroxy-4-methyl	5	23	.48	44	172–174
2-Hydroxy-3-methyl	20	2-Hydroxy-3-methyl	6	24	.47	75	158–160
4-Hydroxy-3-methyl	20	4-Hydroxy-3-methyl	7	29	.19	75	172–174
		4-Hydroxy-5-iodo-3-methyl	7a	2.5	.05	67	216–218[g]
4-Hydroxy-2-methyl	19	4-Hydroxy-2-methyl	8	20	.06	82	177–179
		4-Hydroxy-5-iodo-2-methyl	8a	11	.22	61	210–212[h]
2,4-Dihydroxy	18	2,4-Dihydroxy	9	25	.60	72	218–219

[a] One-tenth mole of the ketone was used for each reaction. [b] These yields are estimated after breaking down the reaction mixture into major fractions and calculated from halogen analysis of these fractions, assuming that the fraction contained only two of the possible components. These yields represent the course of the reaction better than the yields of purified material, since considerable losses were incurred on purification in some instances. [c] Moles of pure product per mole of starting ketone. [d] The acid in every case is a substituted benzoic acid, the substituents being the same as those in the third column of the table. Yields are based on starting pyridinium iodide. [e] This substance changed from needles to a compact mass at about 150–180°. P. H. Beijer [*Rec. Trav. Chim.*, **41**, 701 (1922)] gave the melting point as 226–228°. Analysis of the substance prepared in this Laboratory was as follows: Calcd. for $C_7H_5O_3I$: C, 31.84; H, 1.90. Found: C, 31.41; H, 1.88. [f] The melting point of this material was in good agreement with that reported by Auwers [*Ber.*, **30**, 1473 (1897)] but does not correspond to that reported by Peltzer and Narwa [*Ann.*, **146**, 288 (1868)]. The latter gave 234.5° for the methyl ether of this compound obtained by the iodination of *p*-anisic acid. The present compound formed a methyl ether with melting point of 238–240°. Schall and Dralle [*Ber.*, **17**, 2528 (1884)] reported 234–235° for the compound obtained by oxidation of 2-iodo-4-methylanisole. [g] Calcd. for $C_8H_7O_3I$: C, 34.55; H, 2.53. Found: C, 34.34; H, 2.74. Recrystallized from water and ethyl alcohol. [h] Calcd. for $C_8H_7O_3I$: C, 34.55; H, 2.53. Found: C, 34.55; H, 2.84. Recrystallized from water and ethyl alcohol.

most cases good agreement with the reported physical constants for these acids was obtained. Where discrepancies occur an explanatory footnote is included in Table I.

In the case of the substances described as 1-(4-hydroxy-5-iodo-2-methylbenzoylmethyl)-pyridinium iodide and 1-(4-hydroxy-5-iodo-3-methylbenzoylmethyl)-pyridinium iodide, the acids expected from alkaline cleavage, namely, 4-hydroxy-5-iodo-2-methylbenzoic acid and 4-hydroxy-5-iodo-3-methylbenzoic acid, are unknown. However, the uncertainty, both with respect to the pyridinium compounds and the acids, is restricted to the position of the iodo group in the phenolic ring. The assigned structures are supported by evidence that iodine enters the ortho and para positions when phenols are iodinated in the presence of weak bases such as ammonia,[2] and by the observation that for the other iodinated compounds prepared in this research the one iodine atom entering the ring was invariably ortho to the phenolic hydroxyl group. Of the two ortho positions available in the first of the two compounds, the one chosen is preferred by comparison with the iodinated compound formed from *m*-hydroxyacetophenone, where the iodine substituted only in the less hindered ortho position.

At the beginning of this work the possibility that an *o*-hydroxyacetophenone might react with iodine and excess pyridine to give a structure of the type illustrated below was considered. Under the experimental conditions used there was no evidence for the formation of this sort of substance.



This investigation was partially supported by a grant from the Abbott Fund of Northwestern University.

Experimental

Preparation of the Hydroxyacetophenones.—The *o*- and *p*-hydroxyacetophenones were prepared by means of the Fries rearrangement. In general, the aluminum chloride was added directly to the appropriate ester and the reaction permitted to set its own temperature. In each case after decomposition of the aluminum chloride complex and cooling, most of the para isomer was separated by filtration

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(2) C. R. Harrington and G. Barger, *Biochem. J.*, **21**, 169 (1927); R. L. Datta and N. Prosad, THIS JOURNAL, **39**, 441 (1917).

TABLE II

ANALYSES AND MELTING POINTS OF 1-BENZOYLMETHYLPYRIDINIUM SALTS

		Pyridinium Iodide								Pyridinium Perchlorate[e]					
				Analyses, %[b]								Analyses, %			
				Carbon		Hydrogen		Iodide[d]				Carbon		Hydrogen[b]	
No.	Compound[a]	Formula	M. p., °C.[c]	Calcd.	Found	Calcd.	Found	Calcd.	Found	Formula	M. p., °C.[c]	Calcd.	Found	Calcd.	Found
1	1-(2-Hydroxy-R)-	$C_{13}H_{12}INO_2$	211–215	45.71	45.93	3.51	3.83	37.2	37.6	$C_{13}H_{12}ClNO_6$	193–196	49.77	49.78	3.85	3.98
2	1-(3-Hydroxy-R)-	$C_{13}H_{12}INO_2$	223–228	45.71	45.78	3.51	3.34	37.2	36.5	$C_{13}H_{12}ClNO_6$	224–226	49.77	50.40	3.85	3.84
2a	1-(3-Hydroxy-4-iodo-R)-	$C_{13}H_{11}I_2NO_2$	239–242	33.35	33.64	2.37	2.37	27.1	27.2	$C_{13}H_{11}ClINO_6$	260–203	35.51	36.16	2.52	2.71
3	1-(4-Hydroxy-R)-	$C_{13}H_{12}INO_2$	215–219	45.71	44.61	3.51	4.10	37.2	36.8	$C_{13}H_{12}ClNO_6$	181–183	49.77	50.16	3.85	4.04
3a	1-(4-Hydroxy-3-iodo-R)-	$C_{13}H_{11}I_2NO_2$	235–240	33.35	34.14	2.37	2.47	27.1	27.7	$C_{13}H_{11}ClINO_6$	253–257	35.51	36.62	2.52	2.65
4	1-(2-Hydroxy-5-methyl-R)-	$C_{14}H_{14}INO_2$	180–182	47.33	47.20	3.97	4.03	35.7	36.2	$C_{14}H_{14}ClNO_6$	201–203	51.30	50.62	4.31	4.17
5	1-(2-Hydroxy-4-methyl-R)-	$C_{14}H_{14}INO_2$	215–217	47.33	46.81	3.97	3.86	35.7	35.6	$C_{14}H_{14}ClNO_6$	212–215	51.30	50.23	4.31	4.02
6	1-(2-Hydroxy-3-methyl-R)-	$C_{14}H_{14}INO_2$	217–218	47.33	46.56	3.97	3.72	35.7	34.9	$C_{14}H_{14}ClNO_6$	225–235	51.30	49.70	4.31	4.16
7	1-(4-Hydroxy-3-methyl-R)-	$C_{14}H_{14}INO_2$	220–227	47.33	46.67	3.97	3.89	35.7	35.6	$C_{14}H_{14}ClNO_6$	237–240	51.30	51.13	4.31	4.11
7a	1-(4-Hydroxy-5-iodo-3-methyl-R)-	$C_{14}H_{13}I_2NO_2$	227–232	34.95	35.93	2.72	2.79	26.4	27.2	$C_{14}H_{13}ClINO_6$	239–242	36.98	37.73	2.88	2.86
8	1-(4-Hydroxy-2-methyl-R)-	$C_{14}H_{14}INO_2$	246–248	47.33	46.37	3.97	4.07	35.7	34.8	$C_{14}H_{14}ClNO_6$	195–199	51.30	50.99	4.31	4.35
8a	1-(4-Hydroxy-5-iodo-2-methyl-R)-	$C_{14}H_{13}I_2NO_2$	240–244	34.95	36.66	2.72	2.96	26.4	26.9	$C_{14}H_{13}ClINO_6$	260–266	36.98	37.20	2.88	2.82
9	1-(2,4-Dihydroxy-R)-	$C_{13}H_{12}INO_3$	241–242	43.71	43.81	3.39	3.59	[f]	[f]	$C_{13}H_{12}ClNO_7$	253–255	47.35	47.66	3.66	3.87

[a] R = benzoylmethyl. [b] Carbon and hydrogen analyses by T. S. Ma. [c] All melting points were observed with a Fisher–Jones melting point block and represent the range where the crystalline salt becomes an orange to black liquid. [d] These analyses represent the water soluble iodide only. Analyses were carried out by the Volhard method. [e] From the iodide 80–95% of perchlorate was isolated in each case. [f] This substance gave a red coloration with ferric ion, hence the Volhard method could not be used for iodide determination.

and purified by crystallization; the ortho isomer was purified by distillation. The melting points and boiling points of all the substances prepared were in good agreement with the literature except the melting point of 4-hydroxy-3-methylacetophenone. The melting point of this substance, crystallized from dilute ethyl alcohol, was 108–109°.[3]

***m*-Hydroxyacetophenone.**—This substance was prepared in 48% yield from *m*-aminoacetophenone by diazotization in sulfuric acid solution and subsequent heating of the diazotate.[4] The pure product melted at 94.5–95°.

The *m*-aminoacetophenone was prepared as follows: A mixture of 3.5 moles of stannous chloride dihydrate and 700 cc. of concentrated hydrochloric acid was cooled to 10° and 1 mole of *m*-nitroacetophenone added. The mixture was stirred vigorously and the temperature kept below about 85° until the first vigorous reaction was over. The reaction mixture was heated to reflux temperature and then allowed to cool. The *m*-aminoacetophenone stannichloride was filtered from the cooled reaction mixture and decomposed with 30% sodium hydroxide solution. The amine which floated to the top on cooling was skimmed off and crystallized from water and ethyl alcohol; yield 102 g.; m. p. 96–97°.

Resacetophenone.—This substance was prepared according to the method of Nencki and Sieber.[5] The product melted at 137–140°.

The Reactions of *o*-Hydroxyacetophenones with Iodine and Pyridine: Example.—A mixture of 0.1 mole of *o*-hydroxyacetophenone, 0.1 mole of iodine and 40 g. of pyridine was heated about one hour on the steam-bath and allowed to stand overnight. The reaction mixture thus obtained was thoroughly washed with ether to remove unreacted starting substances and then leached with 50 ml. of cold water to remove pyridine hydroiodide. The solid residue remaining after this treatment consisted mostly of 1-(2-hydroxybenzoylmethyl)-pyridinium iodide. It was purified by crystallization from a mixture of water and ethyl alcohol. Other *o*-hydroxyacetophenones were handled in a similar manner.

The Reactions of *m*-Hydroxyacetophenones or *p*-Hydroxyacetophenones with Iodine and Pyridine: Example.—A mixture of 0.1 mole of *p*-hydroxyacetophenone and 40 g. of pyridine was treated with iodine as in the example above. The reaction mixture was treated in the same way as described above until the pyridine hydroiodide had been removed. At this point the residual solid consisted of a mixture of 1-(4-hydroxybenzoylmethyl)-pyridinium iodide and 1-(4-hydroxy-3-iodobenzoylmethyl)-pyridinium iodide. These substances were separated by taking advantage of the greater solubility of the 1-(4-hydroxybenzoylmethyl)-pyridinium iodide in water or dilute ethyl alcohol solution. The less soluble component was obtained as residue in good yield. It was purified by crystallization from water or dilute alcohol. The more soluble component was obtained from the mother liquors after extended fractional crystallization. Mixtures obtained from other acetophenones were separated in a similar manner. In some cases the complete separation of the two salts proved exceedingly difficult.

Preparation of Perchlorate Salts.—A small amount of the pyridinium iodide was dissolved in water and treated with perchloric acid as previously described.[1a] The perchlorate salt was crystallized from a solution containing a small amount of perchloric acid until no iodide was present in the mother liquors.

Alkaline Cleavage of the Substituted β-Ketoalkylpyridinium Iodides.—About 1 g. of pyridinium iodide was treated with sodium hydroxide solution as previously described.[1a] After the reaction was complete the alkaline solution was decolorized with Norite A and the acid fraction separated and purified.[6] Data for these compounds are given in Table I.

Summary

1. The reactions of nine hydroxyacetophenones with iodine and pyridine were examined. It was found that *o*-hydroxyacetophenones gave 1-(2-hydroxybenzoylmethyl)-pyridinium iodides, while *m*- and *p*-hydroxyacetophenones gave mixtures of the appropriate 1-(hydroxybenzoylmethyl)-pyridinium iodides and 1-(hydroxymonoiodobenzoylmethyl)-pyridinium iodide. Resacetophenone gave 1-(2,4-dihydroxybenzoylmethyl)-pyridinium iodide. In each of the reactions about

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[3] J. Klingel, *Ber.*, **18**, 2699 (1885), and M. Nencki and E. Stoeber, *ibid.*, **30**, 1770 (1897), give 104° as the melting point of this substance.

[4] E. Besthorn, E. Banzhaf and G. Jaegle, *ibid.*, **27**, 3042 (1894); H. Rupe and K. Majewski, *ibid.*, **33**, 3407 (1900).

[5] Nencki and Sieber, *J. prakt. Chem.*, [2] **23**, 147 (1881).

[6] Mixtures of an hydroxybenzoic acid and an hydroxyiodobenzoic acid, obtained from cleavage of mixtures of pyridinium salts, may be conveniently separated by taking advantage of the greater solubility of the hydroxyiodobenzoic acid in benzene or toluene.

half of the halogen added appeared as pyridine hydroiodide.

2. Each of the substituted β-ketoalkylpyridinium iodides was cleaved by action of aqueous alkali into a characteristic hydroxybenzoic acid. The reaction provides a new and efficient method for preparation of hydroxybenzoic acids.

EVANSTON, ILLINOIS RECEIVED JULY 12, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK AND CO., INC.]

Hydrogenation of Compounds Containing Divalent Sulfur

BY RALPH MOZINGO, STANTON A. HARRIS, DONALD E. WOLF, CHARLES E. HOFFHINE, JR., NELSON R. EASTON[1] AND KARL FOLKERS

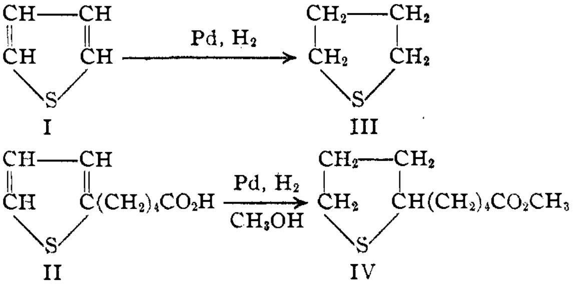
The occurrence of a sulfur atom in many natural products has led us to investigations of the hydrogenation of sulfur-containing compounds which would contain groups or structures representative of those which might be encountered in the synthesis of such natural products.

It became evident, after biotin had been shown to contain sulfur[2] and to be essentially a fully reduced compound,[3] that it might be useful to know catalytic methods for the hydrogenation of carbon to carbon double bonds and the like in sulfur-containing compounds, especially in thiophene derivatives.

The reduction of sulfur-containing compounds has been accomplished in the past largely by chemical reduction rather than catalytic hydrogenation due to the poisoning effect of reduced (divalent) sulfur on the catalysts. However, the catalytic hydrogenation of cystine to cysteine in the presence of hydrochloric acid has been reported.[4] Here the reduction was the hydrogenolysis over palladium of a disulfide to the mercaptan. The hydrogenation of compounds containing oxidized sulfur[5] over platinum or palladium and the reduction of sulfonic acids to mercaptans[6] have been reported. The use of sulfur-active catalysts in the Bergius process is well-known.[7] But practical laboratory methods for the hydrogenation of reducible groups in sulfides, generally applicable to large numbers of compounds, appear not to have been reported. A method for the hydrogenation of carbon to carbon double bonds, carbonyls, and nitro groups and the reduction products of nitro groups, as well as hydrogenolysis of ring halogen, in divalent sulfur compounds has now been found. The method has been applied in the synthesis of biotin in this Laboratory.[8]

The choice of a catalyst for the hydrogenation of sulfur-containing compounds at a few atmospheres pressure[9] was limited, of course, to those catalysts which would cause hydrogenation under these conditions in sulfur-free compounds. Of the common catalysts, the oxide and sulfide catalysts are generally useful only in high pressure reactions, so only the various metal catalysts would be expected to be useful with hydrogen at, or near, atmospheric pressure. It has been shown that nickel removes the sulfur atom from sulfides[10] and for this reason appears to be not generally useful for hydrogenation of these compounds.

When various sulfides were submitted to hydrogenation it was found that palladium on carbon or palladium on barium sulfate is, under some conditions, active in the presence of sulfur-containing compounds. For example, thiophene (I) and 2-thiophenevaleric acid (II) were converted into the corresponding tetrahydro compounds (III and IV) by hydrogen and palladium on carbon. The nitro groups of 2,5-dibromo-3,4-dinitrothiophene (V) were reduced in acid solution to amino groups and at the same time the halogen atoms in this compound underwent hydrogenolysis to give 3,4-diaminothiophene (VI). Because this diamine, as well as its salts, was readily oxidized in the air, it, therefore, was converted into the diacetamido (VII), dibenzamido (VIII) or imidazole (IX) derivative for isolation. Another example of such hydrogenation involving hydrogenolysis of a bromine atom was the reduction



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(1) Present address: Department of Chemistry, University of Illinois, Urbana, Illinois.

(2) Kögl, *Naturwissenschaften*, **25**, 465 (1937).

(3) Hofmann, Melville and du Vigneaud, *J. Biol. Chem.*, **141**, 207 (1941).

(4) Bergmann and Michalis, *Ber.*, **63**, 987 (1930); Kavanagh, THIS JOURNAL, **64**, 2721 (1942).

(5) Roblin and Winnek, *ibid.*, **62**, 1999 (1940).

(6) Lazier and Signaigo, U. S. Patent, 2,221,804; *C. A.*, **35**, 1410 (1941).

(7) Ellis, "Hydrogenation of Organic Substauces," D. Van Nostrand Co., Inc., New York, N. Y., 1930.

(8) Harris, Wolf, Mozingo, Arth, Anderson, Easton and Folkers, THIS JOURNAL, **67**, 2096 (1945).

(9) Because of the general availability of apparatus for low pressure (below 50 lb.) hydrogenation compared to that of stainless-steel apparatus safe to use with sulfur compounds at high pressures, it appeared more desirable to operate in this low pressure region. Accordingly, the entire method has been worked out for this pressure range.

(10) Mozingo, Wolf, Harris and Folkers, *ibid.*, **65**, 1013 (1943).