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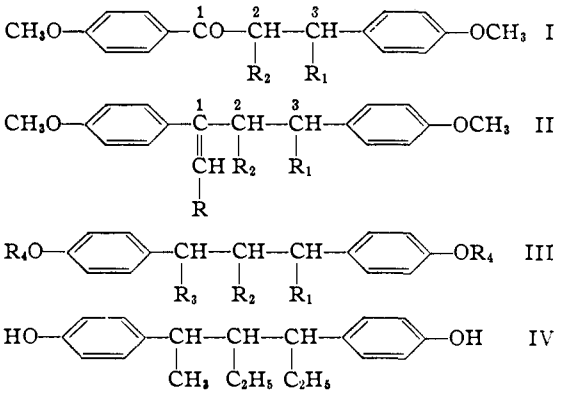
Synthetic Estrogenic Compounds. III. Trialkyl Derivatives of 1,3-Di-(*p*-hydroxyphenyl)-propane. Benzestrol

BY ALFRED H. STUART, ANTHONY J. SHUKIS, RALPH C. TALLMAN, CECILIA MCCANN AND GINO R. TREVES

As part of a continuing search for better synthetic estrogens, a rather extensive investigation of compounds with a 1,3-di-(*p*-hydroxyphenyl)-propane nucleus has been carried out in this Laboratory in order to observe the variations in estrogenic activity with changes in structure. Several compounds which can be considered as derived from 1,3-di-(*p*-hydroxyphenyl)-propane by substitution of one or two alkyl groups in the propane chain were described in previous reports.[1,2] Introduction of one alkyl substituent did not enhance the activity of the parent substance to any appreciable extent. There was, however, a considerable variation in the estrogenic activity of the various 1,2- and 1,3-dialkyl derivatives reported, though none approached the range of clinical usefulness. However, since the most active members of this series were some 200 to 300 times as effective as the unsubstituted parent compound, the positive effect of such structure changes was well established and the desirability of extending the study to include trialkyl derivatives was apparent. The still greater range of activities which might be expected has appeared in this series of compounds (III, R_4 = H), a maximum being reached with a substance having a potency of the same order of magnitude as that of the natural estrogenic hormones.

Practical considerations have limited the number of compounds which could be prepared. As in the previous paper,[2] only methyl, ethyl and *n*-propyl groups have been employed, since there is little evidence to favor the use of larger radicals. Even so, the number of isomeric forms of each particular structure to be expected (one racemic



and two meso forms in the cases where $R_1 = R_3$, and four racemic forms for each of the unsymmetrical compounds) prohibits consideration of any attempt to cover the proposed series in its entirety. However, certain further limitations are imposed by inaccessability of intermediates and others are suggested by the relation of structure to activity in the dialkyl series. Thus the number of compounds to be synthesized has been reduced to a reasonable figure.

The group of 1,3-di-(*p*-methoxyphenyl)-2-alkyl ketones (I) described in the previous paper[2] served as starting materials. These were reacted with Grignard reagents in refluxing ether. The primary reaction products were dehydrated by heating, usually with a trace of acid as catalyst, giving unsaturated compounds represented by formula II. The position of the double bond in these products was evidenced by oxidation to the starting ketone by means of chromic acid-acetic acid mixtures. All the unsaturated ethers prepared seemed to adopt the structure indicated

(1) Stuart and Tallman, THIS JOURNAL, **65**, 1579 (1943).
(2) Stuart, Shukis and Tallman, *ibid.*, **67**, 1475 (1945).

even when the reactant was methylmagnesium iodide. None of the compounds oxidized gave the splitting products which would result if the double bond were established between carbon atoms 1 and 2. This was fortunate, since it meant that introduction of the third alkyl group would probably not change the relative spatial relationship of the groups about carbon atoms 2 and 3.

The unsaturated ethers were readily hydrogenated with either platinum or nickel catalysts. The resulting products (III, $R_4 = CH_3$) were demethylated by acid or alkaline hydrolysis and phenols of the desired structure (III, $R_4 = H$) obtained. Every effort has been made to obtain individual racemic or meso forms for testing. (Resolution of racemic mixtures into optical antipodes will not be considered in this paper.) As reported in the previous paper,[2] each of the dialkyl ketones (I) had been separated into the two isomeric racemic forms; hence each isomer could be reacted in turn with the desired Grignard reagent. Thus the spatial arrangement of the groups about carbon atoms 1 and 2 was fixed and the final phenolic products obtained should be mixtures of only two racemic or meso forms. In some instances no further separation could be effected. In most others, only one crystalline isomer was isolated from each resinous reaction product. In such cases, the crude product, as well as the purified substance, was assayed for estrogenic activity in order to be certain that more active material was not being discarded in the filtrates. With only two of the compounds has complete separation of all isomers been effected.

Estrogenic activities of the various substances, as determined in this Laboratory by Dr. E. W. Blanchard, are recorded in Table III. The designation of isomers should be explained. The letters A and B correspond to the similarly identified isomers of the ketones (I) from which these products are derived. Thus an A isomer has been obtained by introduction of the R_3 group into the A isomer of the ketone (I) which contains the R_1 and R_2 groups indicated. When no further identification is given, the phenolic product in question has been obtained only as a resinous mixture which may contain two isomeric forms. If the two forms were separated, the lower-melting, more soluble compound was labeled 1 and the other product 2. When only one pure crystalline isomer was isolated, this was arbitrarily assumed to be the less soluble of the two possible forms and has been designated A-2 or B-2. The possibility that the most active isomer of any given structure might never be formed in these syntheses has not been excluded, but seems rather unlikely. It might be pointed out that in the cases where there is an appreciable difference between isomeric forms, isomer B-2 is usually the most potent.

Certain generalities as to gross structure are also apparent. In the 1,2-dialkyl series it was seen that the presence of a methyl group at R_2 resulted in very low activities. The first three compounds in the table show that this relationship is maintained in the trialkyl derivatives. For the remaining compounds ethyl and propyl groups have been used as R_1 and R_2 substituents and in this group the importance of having R_3 = methyl is indicated.

Attempts to derive a more fundamental relation between the structure and estrogenic activity of these compounds have not been fruitful. It is not possible to show any such resemblance of the carbon skeleton of these substances to estradiol as has frequently been pointed out in the case of diethylstilbestrol. Whether or not the assumption that the estrogenic activity of the latter stems from this coincidence of carbon skeleton arrangements is valid,[3] it can be seen from the compounds reported here that such resemblance is not essential for high activity. The interesting suggestion has been made[4] that the structure of greatest activity (IV) can be arranged to coincide with that of 9,10-dimethyl-1,2-benzanthracene, and also of cholanthrene. Here again it is difficult to judge the value of such comparisons, but the potentialities warrant further investigation.

The structure IV represents the maximum estrogenic activity found in this series of compounds. Syntheses and separations of the various isomeric racemic forms of this substance are described in the experimental section. Isomer A-1 has been obtained only as a resin; the other three forms are crystalline solids. Comparative assays show the minimum activity of isomer B-2 to be midway between that of estrone and estradiol. This compound is called benzestrol[5] and is in clinical use.[6] It is an effective substitute for the natural hormones and is said to be relatively free from the various toxic manifestations which frequently accompany the use of other synthetic estrogens. Various physiological studies on benzestrol have been reported elsewhere.[7]

Experimental[8]

Grignard Reactions on 1,3-Di-(*p*-methoxyphenyl) Ketones.—Ether solutions of individual racemic forms of the various ketones (*cf.* ref. 2, Table IV, page 1477) were added to ether solutions of two molecular equivalents of the proper Grignard reagent (methylmagnesium iodide, ethyl- or propylmagnesium bromide) and the mixtures refluxed for five hours. After decomposing and extracting in the usual manner, the ether solution of the product was washed with dilute sodium carbonate and sodium thio-

(3) *Cf.* the recent review by Dodds in "Vitamins and Hormones," Vol. III, Academic Press, Inc., New York, N. Y., 1945, p. 229.

(4) Martin, *Chemistry and Industry*, 94 (1944).

(5) Benzestrol has been recognized as the non-proprietary name of this compound and it is now uniformly so designated; *cf. J. Am. Med. Assoc.*, **126**, 1085 (1944). In some of the earlier clinical reports it was called Octofollin.

(6) Freed, Eisin and Greenhill, *J. Clin. Endocrinol.*, **2**, 213 (1942); Murphy, *Am. J. Obstet. Gynecol.*, **46**, 146 (1943); Talisman, *ibid.*, **46**, 534 (1943); Hufford, *J. Am. Med. Assoc.*, **123**, 259 (1943).

(7) Blanchard and Stebbins, *Endocrinology*, **36**, 207 (1945); Stebbins and Blanchard, *ibid.*, 305 (1945).

(8) Semimicro analyses carried out in this Laboratory by Beatrice M. Stuart.

TABLE I

UNSATURATED ETHERS (II)

R_1	R_2	R	Isomer	B. p., °C., 1 mm.	$n^{20}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_2H_5	CH_3	H	B	175–177	1.5651	81.25	80.77	8.44	8.27
C_2H_5	CH_3	CH_3	A	175	1.5662	81.44	80.98	8.70	8.22
			B	187	1.5582	81.44	81.14	8.70	8.88
C_2H_5	C_2H_5	C_2H_5	A	190	1.5592	81.77	81.26	9.15	8.41
			B	190	1.5559	81.77	81.66	9.15	9.46
C_2H_5	C_3H_7	CH_3	A	185	1.5541	81.77	81.32	9.15	8.80
			B	174–177	1.5504	81.77	81.58	9.15	9.52
C_2H_5	C_2H_5	CH_3	A	178	1.5570	81.61	81.89	8.93	9.02
			B	190	1.5559	81.61	81.16	8.93	9.16
C_3H_7	C_2H_5	H	A	185	1.5568	81.61	81.19	8.93	8.39
			B	187	1.5578	81.61	81.31	8.93	8.93
C_2H_5	C_3H_7	H	A	186–188	1.5566	81.61	81.74	8.93	8.87
			B	185	1.5575	81.61	81.46	8.93	9.38
C_2H_5	C_2H_5	H	A	174–176	1.5630	81.44	81.22	8.70	8.69
			B	M. p., 44		81.44	81.66	8.70	8.90

TABLE II

SATURATED ETHERS (III, $R_4 = CH_3$)

R_1	R_2	R_3	Isomer	B. p., °C. (1 mm.)	$n^{20}D$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_2H_5	CH_3	CH_3	B	175–180	1.5549	80.73	80.81	9.03	9.22
C_2H_5	CH_3	C_2H_5	A	165	1.5534	80.93	80.96	9.26	9.26
			B	175	1.5500	80.93	80.80	9.26	9.10
C_2H_5	C_2H_5	C_3H_7	A	180	1.5460	81.31	81.07	9.67	9.67
			B	185–190 (2)	1.5402	81.31	81.42	9.67	9.45
C_2H_5	C_3H_7	C_2H_5	A°	168–170	1.5450	81.31	81.25	9.67	9.69
			B	183–185	1.5412	81.31	81.07	9.67	9.00
C_2H_5	C_2H_5	C_2H_5	A	182–183	1.5450	81.13	81.03	9.47	9.18
			B	190 (2)	1.5472	81.13	81.42	9.47	9.37
C_3H_7	C_2H_5	CH_3	A[a]	175–180	1.5400	81.13	81.28	9.47	9.24
			B	190–192 (2)	1.5459	81.13	81.40	9.47	8.73
C_2H_5	C_3H_7	CH_3	A[a]	165–168	1.5468	81.13	81.26	9.47	9.23
			B	165–168	1.5438	81.13	81.12	9.47	9.84
C_2H_5	C_2H_5	CH_3	A	168–170	1.5493	80.93	80.74	9.26	9.36
			B-1	M. p. 61		80.93	80.88	9.26	9.06
			B-2	M. p. 56		80.93	81.00	9.26	9.46

[a] Prepared with platinum catalyst.

sulfate solutions, dried and the ether distilled off. The oily residues were heated carefully under water-pump vacuum. If evolution of water did not occur spontaneously below 200°, the flask was cooled and a small drop of concentrated hydrochloric acid added. Renewed application of heat usually brought about the desired splitting. The water evolved was collected in a cooled receiver, the amount obtained giving a measure of the completeness of the reaction. The unsaturated ethers distilled at 1 to 2 mm. as colorless to pale yellow oils. Yields averaged about 80%. Properties are listed in Table I. Designations of isomers (A or B) refer only to the corresponding forms of the ketones used as starting materials.

The carbinols were quite sensitive to the presence of various impurities. Attempts to catalyze the dehydration with sulfuric, hydrobromic or hydriodic acids, or iodine, resulted in extensive decomposition with production of low-boiling fission products. The presence of the latter two substances was particularly damaging and considerable care had to be exercised to remove all traces of both from the reaction products obtained with methyl magnesium iodide.

Oxidations.—The unsaturated ethers were surprisingly resistant to permanganate oxidation, being recovered unchanged after refluxing with aqueous or dilute acetone solutions of potassium permanganate. Ozonization was attempted in one case, but the results were inconclusive. Chromic acid–acetic acid solutions, however, proved effective. A typical oxidation procedure follows: A solution of 2 g. of chromium trioxide in 40 cc. of 80% acetic acid was added dropwise to a stirred solution of 2 g. of isomer B of 2,4-di-(*p*-methoxyphenyl)-3-ethyl-heptene-1 (II, $R_1 = R_2 = C_2H_5$, R = H) in 100 cc. of glacial acetic acid. The temperature was maintained below 20°. After standing overnight the mixture was diluted and extracted thoroughly with ether. The ether solution was washed with dilute potassium hydroxide solution. Acidification of the alkaline extract gave only a slight turbidity. The oily ether residue was taken up in ethanol from which 0.8 g. of solid product crystallized. After recrystallization, this proved to be identical in m. p. and mixed m. p. (82°) with isomer B of 1,3-di-(*p*-methoxyphenyl)-2-ethyl-pentanone.

Hydrogenations.—The double bond in the above unsaturated ethers was readily reduced with Adams catalyst in glacial acetic acid at room temperature and atmospheric pressure, or with Raney catalyst in ethanol at 100° and 100 to 150 atmospheres. It was found, after hydrolysis and purification of the final phenolic products, that the use of nickel catalyst tended to give largely a single isomeric form, while the use of platinum seemed to give a mix-

TABLE III

PHENOLS (III, R_4 = H)

R_1	R_2	R_3	Isomer	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Estrogenic activity Allen-Doisy rat unit, mg.
C_2H_5	CH_3	CH_3	B-2	141–143	80.24	79.82	8.51	8.60	0.50
C_2H_5	CH_3	C_2H_5	A	Resin	80.49	79.93	8.78	8.64	1.0
			B-2	126–127	80.49	80.18	8.78	8.82	5.0
C_2H_5	C_2H_5	C_3H_7	A-2	102	80.93	80.30	9.26	9.61	2.0
			B-2	143–144	80.93	80.83	9.26	9.06	2.0
C_2H_5	C_3H_7	C_2H_5	A	Resin	80.93	80.99	9.26	9.24	0.60
			B	Resin	80.93	80.36	9.26	8.78	1.0
C_2H_5	C_2H_5	C_2H_5	A-2	144	80.73	80.50	9.03	9.13	1.0
			B-1	138–139	80.73	80.71	9.03	8.58	0.50
			B-2	154–155	80.73	80.90	9.03	8.86	0.10
C_3H_7	C_2H_5	CH_3	A-2	132	80.73	80.55	9.03	9.13	0.40
			B-2	155	80.73	80.71	9.03	8.97	0.013
C_2H_5	C_3H_7	CH_3	A-2	68–72	80.73	80.06	9.03	9.23	0.10
			B-2	121–122	80.73	80.20	9.03	8.75	0.005
C_2H_5	C_2H_5	CH_3	A-1	Resin	80.49	80.30	8.78	8.68	0.010
			A-2	75	80.49	80.30	8.78	8.67	0.005
			B-1	144	80.49	80.08	8.78	8.71	0.035
			B-2	162	80.49	80.70	8.78	8.97	0.0008

ture of the two possible isomers in roughly equivalent amounts. It was possible to separate the two isomeric racemic forms of compound 221B in crystalline form, as explained below. Separation of isomers was not attempted with the other saturated ethers, which were obtained as colorless oils, after purification by vacuum distillation. Properties are listed in Table II. The properties listed are for products obtained from hydrogenations with Raney catalyst except as otherwise noted.

Hydrolysis.—Each of the above ethers was hydrolyzed to the corresponding phenol in the usual manner by treatment with potassium hydroxide in ethanol for sixteen to eighteen hours at 200° in an autoclave. A preliminary purification of the crude phenolic products was effected by distillation under oil-pump vacuum in a short-path sublimation tube. At this point the compounds were light yellow glassy resins. Further purification, where possible, was effected by crystallizations and fractional crystallizations from benzene or ethylene dichloride. The phenols are listed in Table III.

Isomers of 2,4-Di-(*p*-hydroxyphenyl)-3-ethylhexane (IV).—Further details of the separation of individual racemic forms of IV will be described, since this series has been the most extensively investigated.

(A) After hydrolysis of the ether groups of liquid (A) ether isomer, the crude A phenol distilled in a sublimation tube as a pale yellow glass. This was dissolved in ethylene dichloride, from which solution colorless crystals of the A-2 isomer (m. p. 75°) crystallized readily.

After as much of the A-2 isomer as possible had been separated by crystallization, the filtrates were evaporated and the residue again distilled. The distilled phenols were converted to dibenzoates by reaction with benzoyl chloride, using a drop of concentrated sulfuric acid as catalyst. From an alcohol solution of the resulting dibenzoates, a crystalline product separated. This proved to be the dibenzoate of the above A-2 isomer; m. p. 76°.

Anal. Calcd. for $C_{34}H_{34}O_4$: C, 80.60; H, 6.77. Found: C, 80.51; H, 6.85.

The total amount of A-2 isomer thus isolated represented about 80% of the reaction product.

The filtrate from the dibenzoate separation would not yield any further crystalline material. The oily ester which remained was saponified and the phenol again distilled. This material has been considered as isomer A-1, though its purity may be open to question, as neither the phenol nor any of its derivatives has been obtained in crystalline form.

(B) Ten grams of the crystalline (B) isomer of 2,4-di-(*p*-methoxyphenyl)-3-ethyl-hexene-1 was mixed with 50 cc. of ethanol and 0.5 cc. of Raney catalyst and hydrogenated at room temperature and 100 atm. pressure for eighteen hours. The catalyst was then filtered off and the solution cooled. The product crystallized readily, giving a yield of 8.5 g. of a pure isomer, m. p. 56°. This proved to be the dimethyl ether of benzestrol (isomer B-2). When larger batches or less pure samples of the hexene were to be reduced, the hydrogenation was run at 100° to insure completeness. Yields in such cases averaged 70–75% of pure benzestrol dimethyl ether.

The hexene could also be reduced readily by means of Adams catalyst in glacial acetic acid at atmospheric pressure. In a test run, 10 g. of hexene was hydrogenated with 0.15 g. of platinum oxide and 75 cc. of acetic acid. Hydrogen absorption reached the calculated volume within thirty minutes. After filtration of the catalyst and removal of the acetic acid, the reduced product was taken up in ethanol, seeded with benzestrol dimethyl ether, and cooled. The material which crystallized readily was filtered off. This proved to be 5 g. of the benzestrol derivative, melting at 53–55°. From the filtrates on further seeding and cooling, another 4 g. of crystalline material separated. This had a m. p. of 56–58°. A mixture with the benzestrol ether melted at 40–48°. Further crystallizations raised the m. p. of the second ether to 61°. This was the dimethyl ether of isomer B-1.

Each of the above ethers could be hydrolyzed to the free phenol in excellent yields by reaction with alcoholic potassium hydroxide at 200° in an autoclave. The phenols solidified readily and could be purified by high-vacuum distillation and crystallization from benzene or ethylene dichloride. It was also possible to hydrolyze a crude mixture of B-1 and B-2 dimethyl ethers and separate the mixture of phenol isomers thus obtained. Pure benzestrol could be readily separated from such a mixture by crystallization from a suitable solvent, but isolation of isomer B-1 in pure form from the filtrates required many fractionations from benzene.

Summary

A number of 1,2,3-trialkyl derivatives of 1,3-di-(*p*-hydroxyphenyl)-propane have been prepared and tested for estrogenic activity.

There is a wide variation in the estrogenic activity of the various compounds, a maximum

being reached with one of the isomeric racemic forms of 2,4-di-(*p*-hydroxyphenyl)-3-ethylhexane, which is known as benzestrol.

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Antibacterial Action of an Oxidation Product of Sulfanilamide[1a,b]

BY GEORG BARKAN AND LEONTINE GOLDSMITH

An early theory, now largely abandoned, explained the antibacterial action of the sulfonamide drugs on the basis of the formation *in vivo* of an oxidation product, with enhanced bacteriostatic effect. The history of this theory, and the evidence leading to its present disrepute, may be found in full detail in the monograph by Henry.[2] Barkan[3] observed in 1939 that when molecular oxygen was bubbled through concentrated solutions (0.015 *M*) of sulfanilamide in the presence of traces of copper sulfate, hydrogen peroxide appeared, demonstrable by the phenolphthalein test of Schales,[4] and a blue color developed, which disappeared with the addition of certain reducing agents (sodium hydrosulfite or ascorbic acid) and which returned on reoxidation by shaking with air.

Ottenberg and Fox[5] had previously obtained a similar colored oxidation product by ultraviolet irradiation of sulfanilamide in the presence of oxygen. In 1940 Barkan[6] reported the formation of an apparently identical blue oxidation product by the similar treatment of arsanilic acid. The identity of the products led to the conclusion that the side chains were removed during the oxidation process. Rosenthal and Bauer[7] had previously postulated the loss of the sulfonamide group from sulfanilamide as a result of similar oxidative changes.

In a short note in 1944, Barkan[8] announced the isolation, purification and analysis of the blue oxidation product, stating that the substance possesses high antibacterial activity. Since Dr. Barkan's death (March 7, 1945), this paper has been prepared to present the data upon which these statements were based.

Experimental

Preparation of the Oxidation Product.—To 200 ml. of 0.03 *M* (0.5%) aqueous solution of sulfanilamide is added an equal volume of 2% sodium carbonate, then approximately 100 mg. of solid hydrazine sulfate. After this is dissolved, 4 ml. of freshly-prepared 0.01 *M* cupric sulfate will develop a faint blue color. One hundred ml. of benzene (thiophene-free) is added at this stage and oxygen passed through the mixture for ten minutes.

The product, which is blue in aqueous solutions, enters the benzene layer, which is separated, washed with water, and dried over anhydrous sodium sulfate. It is then separated by chromatographic adsorption on aluminum oxide (Alorco activated, chromatographic, mesh minus 80, partially deactivated by exposure to cool, moist air).[9] The adsorbed material is dark blue in color; no color is left in the benzene. After washing away the benzene with petroleum ether, the substance is eluted with ether (peroxide-free), yielding a red solution. The solvent is removed by distillation on a water-bath in an atmosphere of nitrogen. About 4 mg. of blue-black amorphous product is obtained from the above procedure.

Properties of the Oxidation Product.—The product is a blue-black amorphous solid; m. p. about 118° with decomposition; soluble and stable in pure organic solvents; soluble in water up to about 40 mg. per 100 ml., and unstable in that it cannot be recovered completely by extraction; reducible by ascorbic acid or sodium hydrosulfite to a colorless compound, which can be reoxidized by air; in butanol solution, maximal light absorption at 590 millimicrons; $E^{1\%}_{1\,cm.}$ ranges from 820 to 1028, mean

TABLE I

SUMMARY OF ANTIBACTERIAL ACTIONS OF THE OXIDATION PRODUCT

Original inoculum	Minimal bacteriostatic concn. (oxidized form), micrograms/ml.	Minimal bactericidal concn. (oxidized form), micrograms/ml.	Minimal bacteriostatic concn. (reduced form), micrograms/ml.
Strep. hemolyticus			
17 organisms per ml.	0.5	1.8	0.5
65		1.8	
170	1		0.5
8 (serum 1:1)	4	8	
25 (serum 1:1)	4		
35 (serum 1:1)	1.5		1.5
143 (serum 1:1)	3		
Staph. aureus			
275 organisms per ml.	2		
30 (serum 1:1)	8		
150 (serum 1:1)	8		
750 (serum 1:1)	6		
Pneumococcus Type I			
2250 organisms per ml.		1.5	
2250 (serum 1:1)	3		
7500 (serum 1:1)	3		

(1) (a) This paper was compiled from Dr. Barkan's data by Burnham S. Walker, with the assistance of Dr. Goldsmith. (b) This work was aided by a grant from the Johnson & Johnson Research Foundation.

(2) R. J. Henry, "The Mode of Action of Sulfonamides," Josiah Macy, Jr., Foundation Review Series, **2**, No. 1 (1944).

(3) G. Barkan, *Proc. Soc. Exp. Biol. Med.*, **41**, 535 (1939).

(4) O. Schales, *Ber.*, **71**, 447 (1938).

(5) R. Ottenberg and C. L. Fox, Jr., *Proc. Soc. Exp. Biol. and Med.*, **38**, 479 (1938).

(6) G. Barkan, *Science*, **92**, 107 (1940).

(7) S. M. Rosenthal and H. Bauer, *ibid.*, **91**, 509 (1940).

(8) G. Barkan, *Federation Proc.*, **3**, 65 (1944).

(9) H. Brockman and H. Schadder, *Ber.*, **74**, 74 (1941).