since the acids were destroyed completely under the conditions of the reaction.

Action of Ammonium Sulfide on Tetraiodo-*o*-sulfobenzoic Acid

A concentrated solution of tetraiodo-*o*-sulfobenzoic acid was prepared by boiling 22.4 g. of the corresponding anhydride with 50 cc. of water. Fifty cc. of concentrated aqueous ammonia was then added (causing the neutral ammonium salt to precipitate partially), the solution was saturated with hydrogen sulfide and allowed to stand for twenty-four hours. The white precipitate thus obtained in a yield of 11.5 g. was the neutral ammonium salt of triiodo-*o*-sulfobenzoic acid. It was crystallized from water.

Anal. Calcd. for $C_7H_9O_6I_3N_2S$: I, 62.02; S, 5.22; N, 4.56. Found: I, 61.98; S, 5.26; N, 4.80.

When heated with concentrated sulfuric acid at 160° for one hour, the neutral ammonium salt was converted into the anhydride of triiodo-*o*-sulfobenzoic acid. The cooled sulfuric acid mixture was poured on cracked ice and, after washing with water, the moist yellow solid was dissolved in hot glacial acetic acid. The anhydride was precipitated again by adding acetic anhydride. It is a pale yellow substance, melting at 287–288°, and identical with the 3,5,6-triiodo-*o*-sulfobenzoic anhydride obtained by direct iodination. A mixed melting point with the latter substance did not show a depression.

After the white crystals of the neutral ammonium salt of 3,5,6-triiodo-*o*-sulfobenzoic acid were filtered off, a yellow solution remained. It was evaporated to dryness and extracted with water. The residue consisted of 1.3 g. of sulfur. The evaporated extract yielded 6.4 g. of an alcohol-soluble portion, which was shown to be ammonium iodide. The analysis of the alcohol-insoluble fraction, consisting of 5.7 g. of a white substance, showed it to be the diammonium salt of a diiodo-*o*-sulfobenzoic acid.

Anal. Calcd. for $C_7H_{10}O_6I_2N_2S$: I, 52.02; S, 6.57; N, 5.74. Found: I, 51.78; S, 6.79; N, 5.9.

Treatment with concentrated sulfuric acid at 150° did not produce an anhydride as in the case of the 3,6-diiodo derivative, but a diiodo-*o*-sulfobenzoic anhydride was apparently obtained by refluxing the diammonium salt with thionyl chloride for several hours. It dissolved in the excess of thionyl chloride and was isolated by separating the solution from the precipitate of ammonium chloride and evaporating the thionyl chloride. It was dissolved in water, the solution decolorized with charcoal, and again evaporated to dryness. The residue was treated with acetic anhydride and recrystallized several times from that solvent. In this manner, a diiodo-*o*-sulfobenzoic anhydride was isolated, different from the one obtained by direct iodination. The compound melted at 221–223°. The position of the iodine atoms was not determined.

Anal. Calcd. for $C_7H_2I_2SO_4$: I, 58.23; S, 7.35. Found: I, 57.97; S, 7.27.

Our thanks are due to Mr. Grant Spurrier for carrying out much of the analytical work.

Summary

1. Mono-, di-, tri- and tetrahalogeno substitution products of *o*-sulfobenzoic anhydride were prepared by halogenation in fuming sulfuric acid.

2. The positions of the halogen atoms were determined by eliminating the sulfonic acid group by hydrolysis and identifying the resulting halogenated benzoic acids.

BALTIMORE, MARYLAND
LEXINGTON, VIRGINIA RECEIVED JUNE 1, 1936

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF JOHNS HOPKINS UNIVERSITY]

A Study of Some Substituted Hydroxybenzyl Alcohols[1]

BY BROWN DUNNING, JR., FITZGERALD DUNNING AND E. EMMET REID

As saligenin (*o*-hydroxybenzyl alcohol) has three distinct types of physiological action, anesthetic, antispasmodic, and antiseptic, it seemed desirable to prepare a number of its derivatives in which one or more of these might be accentuated and to study these in connection with the derivatives, homologs and analogs already known to see how these properties are altered by changes of structure and composition. It was also of interest to find out how far the physiological activities of these compounds can be correlated with their physical properties, particularly their solubilities and partition coefficients. Eight new compounds have been prepared and studied along with ten that were already known. These include halogen and alkyl substituted saligenins and halogen substituted *m*- and *p*-hydroxybenzyl alcohols.

The unsubstituted hydroxybenzyl alcohols were made by the reduction of the corresponding hydroxybenzaldehydes through the use of the Adams platinum catalyst.[2] The halogen derivatives of these were prepared by direct halogenation. The alkyl derivatives were synthesized from various

(1) From the Ph.D. dissertation of Brown Dunning, Johns Hopkins University, 1934. Original manuscript received November 26, 1935.

(2) Adams, "Organic Syntheses," Vol. VIII, Wiley and Sons, Inc., New York, 1928.

substituted phenols by means of the well-known Reimer–Tiemann reaction,[3] which gave hydroxyaldehydes which were subsequently reduced. In those cases where the alkyl phenols were not available, they were obtained by reduction of the appropriate hydroxyphenones, using the Clemmensen reduction method.[4]

The partition coefficients were determined indirectly for each compound by dividing the solubility in olive oil by the water solubility.

The water solubility was determined by weighing the residue from evaporation of a known volume of a saturated solution in distilled water. For the oil solutions since the refractive index was found to be practically a straight line function of the concentration for each individual compound, it was possible to determine the concentration of a saturated solution by comparing its refractive index with the refractive indices of solutions of known concentration.

There was found to be a very definite relationship between partition coefficients and bactericidal power in each series, but changing the relative positions of the functioning groups, as in the case of the analogs (*o*-, *m*- and *p*-hydroxybenzyl alcohols) changes the physiological properties without regard to partition coefficients. The pharmacological results, although of necessity only roughly comparative, in most cases support the bacteriological results.

Experimental

The preparation of 5-ethyl-2-hydroxybenzyl alcohol may be taken as an example of the general method of preparing the compounds.

p-Hydroxyacetophenone was reduced by the Clemmensen method[4] using amalgamated zinc and hydrochloric acid. The *p*-ethylphenol obtained was purified by steam distillation and the aldehyde group introduced by treating with sodium hydroxide and chloroform according to the method of Reimer and Tiemann.[3] The 5-ethyl-2-hydroxybenzaldehyde was purified by making the sodium bisulfite addition compound which was washed with alcohol and ether, dried, and decomposed with warm dilute acid to liberate the aldehyde. Yields from most of the Reimer–Tiemann reactions were about 30%.

The purified aldehyde was reduced in alcohol solution by passing in hydrogen under about 500 mm. excess pressure in the presence of 1% of the Adams platinum oxide catalyst[2] while shaking on a mechanical shaker. After removal of the catalyst by filtration, the alcohol was evaporated off on a water-bath and the product of the reduction purified by crystallization from carbon tetrachloride.

(3) Reimer and Tiemann, *Ber.*, **9**, 423, 824 (1876); **10**, 1562 (1877); etc.

(4) Clemmensen, *ibid.*, **46**, 1837 (1913); **47**, 53 (1914).

The purified product of the Reimer–Tiemann reaction on *m*-cresol is a heavy yellow oil which is a mixture of two isomers, 2-hydroxy-4-methyl-benzaldehyde and 6-hydroxy-2-methyl-benzaldehyde. These were separated as suggested by Chuit and Bolsing[5] by steam distilling the mixture with a solution of sodium carbonate from which the former less acidic isomer distils leaving the latter behind. Upon reduction the two corresponding isomeric benzyl alcohols are obtained which melt at 103 and 80°, respectively. These are incidentally isomers of the alcohol obtained by starting with *p*-cresol.

Analyses of the new compounds are included in Table I.

Bacteriological

All the compounds prepared were tested for their bacteriological activity. The organism used was *Staphylococcus aureus*. A modification of the F. D. A. test was employed, which was essentially as follows: 0.5 cc. of a standard twenty-four hour culture was added to 5 cc. of diluted antiseptic. Transfers were made at the end of forty-five minutes with a 4-mm. platinum loop made from No. 23 B. and S. gage wire. The culture media used was a sterile nutrient, beef extract broth, 10 cc. being used in each subculture tube. All dilutions were made with 20% alcohol, the use of which was necessary in order to dissolve some of the compounds. Although the presence of the alcohol has a slight effect on the killing power, it was, however, used throughout all the tests and the results are therefore comparable.

The results of the bacteriological tests are contained in Table I. The figures show the relative bactericidal strengths of equimolar quantities of the respective compounds calculated from their maximum killing dilutions, saligenin being given an index value of 1. In Fig. 1 these are plotted against the partition coefficients for the mono substituted saligenins. Figure 2 shows the same for the di-halogenated compounds. No attempt has been made to compare these two series with each other.

Attention is called to the analogs of saligenin, 3-hydroxy- and 4-hydroxybenzyl alcohol and their respective bromo derivatives. As was expected, the partition coefficient relationship holds between each analog and its derivative, but not between the members of the different series, in which the relative positions of the functioning groups are different.

Pharmacological

Most of the compounds have been tested for anesthetic and antispasmodic action and also for toxicity.

The best method of obtaining comparable values of the anesthetic efficiency was by the frog-skin method in which a 1% hydrochloric acid solution was used as the stimulus on the skin of a pithed frog, both before and after soaking the skin in various concentrations of the anesthetic. The factors taken into consideration in calculating the figures are the time of the normal reflex, the time of immersion in the anesthetic solution, the concentration of the solution, the time of the reflex after anesthesia and the duration of anesthesia. The anesthetic effects on mice and on goldfish were also studied and while they confirm the results of the frog-skin tests, the type of data obtained

(5) Chuit and Bolsing, *Bull. soc. chim.*, [3] **35**, 129, 134 (1906).

TABLE I

Benzyl alcohol derivatives	Solubility in water, %	Solubility in olive oil, %	Partition coefficient	Relative bactericidal strength	Relative anesthetic efficiency	Relative antispasmodic action	M. p., °C.	Analyses	Calcd.	Found
3,5-Diiodo-2-hydroxy-[a]	0.015	9.0	600	91	30	50	107	I,	67.53	67.70
3-Iodo-5-bromo-2-hydroxy-	.05	14.8	296	53			86	I,	38.6	39.2
								Br,	24.3	24.1
3,5-Dibromo-2-hydroxy-[b]	.11	11.4	103	45.4	15	25	89	Br,	56.6	56.4
3-Chloro-5-bromo-2-hydroxy-	.12	7.1	59	34.4			93	Br,	33.6	32.6
								Cl,	14.9	14.5
3,5-Dichloro-2-hydroxy-[c]	.28	10.6	37	15.6	7.5	2.7	83	Cl,	36.75	36.86
5-Propyl-2-hydroxy-	.27	4.1	15.1	16	20	10	73	C,	72.2	71.7
								H,	8.5	8.9
5-Iodo-2-hydroxy-[a]	.11	1.5	13.6	14.1	10	25	138	I,	50.77	50.72
5-Bromo-2-hydroxy-[a]	.70	4.8	6.8	9.8	5	16.5	109	Br,	39.4	39.47
5-Chloro-2-hydroxy-[a]	1.46	7.4	5.0	7.6	2	6	90	Cl,	22.37	22.17
5-Ethyl-2-hydroxy-	0.80	3.0	3.7	4.9	3.4	5	83	C,	71.0	70.5
								H,	7.9	7.7
5-Methyl-2-hydroxy-[d]	.95	1.1	1.1	1.1	2.5	4	105			
2-Hydroxy-[d]	6.0	1.8	0.3	1	1	1	87			
6-Methyl-2-hydroxy-	1.6	3.6	2.2	2.2	0.9	5.5	80	C,	69.5	69.5
								H,	7.3	7.3
4-Methyl-2-hydroxy-	1.5	2.7	1.8	2.2	1.8	6	103	C,	69.5	69.0
								H,	7.3	7.3
6-Bromo-3-hydroxy-	0.78	4.0	5.1	9.8	2	25	124	Br,	39.4	38.8
3-Hydroxy-[e]	43.4	1.1	0.02	0.5	0.2	1.1	71			
3-Bromo-4-hydroxy-	1.0	1.1	1.1	22.9	.8	1.5	128	Br,	39.4	39.8
4-Hydroxy-[c]	2.0	1.0	0.5	0.5	.03	0.75	124			

[a] Visser, *Arch. Pharm.*, **235**, 547 (1897). [b] Auwers and Buttner, *Ann.*, **302**, 131 (1898). [c] Mettler, *Chem. Centr.*, **77**, II, 1790 (1906). [d] Manasse, *Ber.*, **27**, 2411 (1894). [e] Mettler, *ibid.*, **38**, 1752 (1905).

does not well lend itself to comparison on a numerical basis. These results have been in part reported elsewhere.

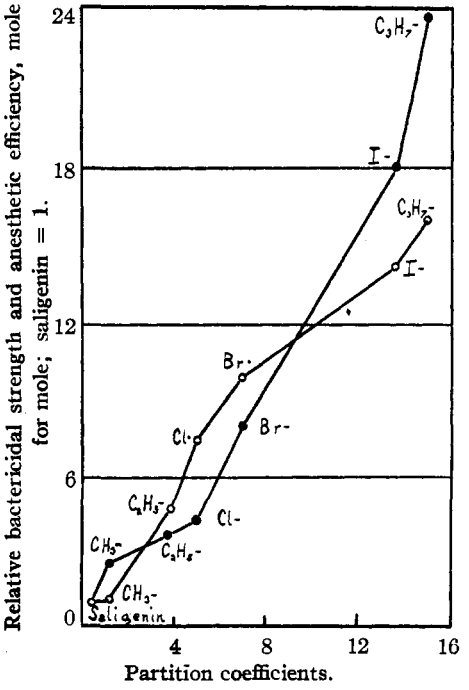

Fig. 1.—Mono-substituted saligenins: ○, relative bactericidal strength; ●, relative anesthetic efficiency.

The figures in Table I represent the relative local anesthetic efficiency of the compounds obtained by the frog-skin method on a weight for weight basis, saligenin being given an index value of 1. It was found that a molecule for molecule comparison would give a relationship more nearly corresponding to the partition coefficients, and a comparison of this kind may be seen in Fig. 1 for the mono substituted saligenins.

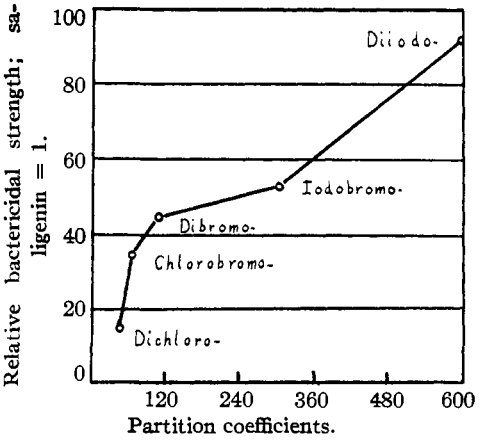

Fig. 2.—Di-halogen derivatives of saligenin.

Also included in Table I are figures for the antispasmodic activity of the compounds. These were calculated from the amounts required to produce antispasmodic action on the smooth muscle of cat's intestine in 50 cc. of Locke's solution oxygenated at 38°, saligenin again being given

an index value of 1. No attempt has been made to relate these figures with the partition coefficients since there is no obvious reason why lipoid solubility should be related to effects of this kind.

The toxicity of the compounds was determined on cats and on the seedlings of lupinus albus. No relationship was expected in these figures, since such an effect as toxicity could hardly be predicted from any one set of physical properties; hence they are not included in this paper.

Discussion

It is felt that from the preceding data it may be stated that there has been demonstrated herein a definite relationship between physical and physiological properties of hydroxybenzyl alcohols. It is interesting to note how the actions of the mono-alkyl and mono-halogen derivatives are related according to their partition coefficients without regard to the great difference in chemical nature of the substituent groups, as may be seen in Fig. 1.

The question of the position of the substituent group in the parent molecule has also been considered in the case of the three isomeric methyl saligenins. It is seen that the bactericidal power depends more on the physical properties of the molecule than on the position of the inert group.

As mentioned previously, shifting the relative positions of the functioning group changes the nature of the molecule, so that there can be no comparison between saligenin and its analogs. It is to be noted, however, that in comparing each analog to its respective derivatives, the relation of physical to physiological properties holds good.

Summary

The partition coefficients between oil and water of a series of derivatives, analogs and homologs, of saligenin (*o*-hydroxybenzyl alcohol) have been determined and compared with the bacteriological and pharmacological properties of the compounds. A definite relationship exists, even in cases where the structures of the inert substituent groups differ greatly.

BALTIMORE, MARYLAND RECEIVED JUNE 4, 1936

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Studies in the Phenanthrene Series. XI. Propanolamines of the Type $C_{14}H_9CHOHCH_2CH_2NR_2$[1]

BY JACOB VAN DE KAMP AND ERICH MOSETTIG

The pharmacological study of a number of amino alcohols in the phenanthrene series[2] has shown that some of these compounds, carrying the side chain $-CHOHCH_2NR_2$ (type I)[3] and $-CHOHCH(CH_3)NR_2$ (type II),[4] exhibit a decided analgesic action. In both types of compounds the nitrogen atom is located in the side chain in the β-position to the phenanthrene nucleus. Through the systematic investigations by Barger and Dale and associates[5] of the amines $Ar(CH_2)_xNH_2$ (Ar being the phenyl, hydroxyphenyl or iminazolyl group), it became evident that almost universally the greatest physiological action (in particular with respect to blood pressure) is exerted by the compounds in which $x = 2$. As Barger points out, compounds of this type occur frequently in nature and are probably in some instances intermediates in the phytosynthesis of isoquinoline derivatives. In the compounds with $x < 2$ or $x > 2$, the physiological action is greatly diminished. It was of interest to determine, by comparison of the phenanthrene alkamines of type I and II[6] on the one hand with the compounds of the type $C_{14}H_9CHOHCH_2CH_2NR_2$ on the other, whether or not a similar regularity may be observed with the phenanthrene derivatives of these series, particularly in respect to their analgesic action.

The propanolamines described in this communication were prepared essentially by the Mannich method,[7] starting from 2-, 3- and 9-acetylphenanthrenes: $C_{14}H_9COCH_3 + CH_2O + HNR_2$.

(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia and the University of Michigan.

(2) Eddy, *J. Pharmacol.*, **55**, 419 (1935).

(3) Mosettig and van de Kamp, THIS JOURNAL, **55**, 3448 (1933).

(4) Mosettig and Czerwin, unpublished results.

(5) Barger, "Some Applications of Organic Chemistry to Biology and Medicine," McGraw-Hill Book Co., Inc., New York City, 1930, pp. 73–100.

(6) The comparison of type I and type II has shown that the compounds of type II are generally slightly weaker analgesics than those of type I.[2]

(7) Mannich, *Arch. Pharm.*, **255**, 261 (1917); Mannich and Braun, *Ber.*, **53**, 1874 (1920); Mannich and Heilner, *ibid.*, **55**, 356 (1922); Mannich and Lammering, *ibid.*, **55**, 3510 (1922).