was made approximately 5%, and the buffer solutions for producing the acid and alkaline forms of the indicator had P_H values of about 6.65 and 10.65. The comparison of the solutions to be evaluated with the standards was made as soon as the standards were prepared.

Summary

1. 1-Naphthol-2-sodium sulfonate indophenol is relatively unstable in aqueous solutions but is stable in absolute alcohol.

2. The dissociation of the dye follows the normal course of a monobasic acid.

3. The apparent dissociation constant is 8.63 in aqueous solutions containing 5% of alcohol.

4. Data are supplied for the application of the indicator in the determination of hydrogen-ion exponents by the spectrophotometric and drop-ratio methods.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

ALKYL-ALLYL-BARBITURIC ACIDS[1]

BY ERNEST H. VOLWILER

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Of the numerous types of compounds that have been found to have hypnotic action, none has attained such extensive use as the derivatives of barbituric acid, or malonyl urea. This is due to the relatively greater ease of preparation, higher efficiency and lower toxicity of these compounds. These barbituric acid derivatives, in which the substituent groups are both attached to the 5 carbon atom, were introduced into therapeutic use by Fischer and von Mering[2] who, however, investigated only a limited number of the many possible derivatives. While di-*n*-propyl-barbituric acid is twice as active an hypnotic as the diethyl derivative (Barbital) the efficiencies of the di-*iso*butyl and di-*iso*-amyl derivatives show a drop again; from this observation, Fischer apparently concluded that the optimum activity in this homologous series of derivatives resides in the *n*-propyl compound.

The recent availability of higher alcohols has again stimulated investigation in the field, and as a result the series of simple and mixed dialkyl derivatives up to the ethyl-nonyl compound has been rather thoroughly investigated. The 5,5-di-*n*-butyl-barbituric acid[3] was found to be slightly

[1] Presented at the 69th Meeting of the American Chemical Society at Baltimore, April 10, 1925.

[2] Fischer and von Mering, *Med. Klinik*, **1**, 1327 (1904–5).

[3] Kamm and Volwiler, U. S. pat. 1,331,712 (1920).

more effective than the corresponding diethyl derivative, but the *n*-butyl-ethyl compound proved to be much more effective than either.[4]

Carnot and Tiffeneau[5] studied a number of dialkyl barbituric acids from ethyl-methyl to ethyl-heptyl, and found the *n*-butyl-ethyl derivative to be the most efficient hypnotic of the series. Shonle and Moment[6] state that the ethyl-*iso*-amyl is the most effective of the series from ethyl-methyl to ethyl-*iso*-amyl, when injected subcutaneously into rabbits. Dox[7] has found the ethyl-*n*-hexyl derivative to be an efficient hypnotic, when tested on white mice.

It seemed to be of interest to compare the hypnotic activity and toxicity of the members of the barbituric acid series in which one of the alkyl groups should be replaced by an allyl group. The following 5,5-alkyl-allyl-barbituric acids were prepared: ethyl-allyl, *n*-propyl-allyl, *iso*propyl-allyl, *n*-butyl-allyl, *iso*butyl-allyl, *sec.*-butyl-allyl, and *iso*-amyl-allyl; in addition, the diallyl compound was prepared and compared with the others.

The allyl group attached to simple radicals seems to be highly toxic; allyl alcohol is said to be 50 times as toxic as propyl alcohol;[8] which is three times as toxic as ethyl alcohol; allyl amine is intensely irritating to mucous membranes and has heart depressant and other toxic effects; allyl formate, allyl isothiocyanate (oil of mustard) and allyl norcodeine all have deleterious effects on the tissues or organs of animals. On the other hand, the introduction of allyl groups into certain other types of compounds causes little, if any, increase in toxicity, and at the same time it frequently markedly enhances the therapeutic activity. The allyl ether of *p*-aceto-aminophenol is a stronger antipyretic than the corresponding ethyl ether (acetophenetidine), and is a narcotic, but it is also more toxic.[9] A number of allyl derivatives in other series have recently been suggested as therapeutically superior to the alkyl compounds. Diallyl-hydantoin is therapeutically inactive, but diallyl-barbituric acid is a strong hypnotic. Some anesthetics of the procaine type derived from alkyl-allyl amines are more efficient than the corresponding dialkyl compounds.[10]

An attempt has been made to explain the hypnotic activity of dialkyl-barbituric acids by assuming that the heterocyclic ring is decomposed in

[4] Volwiler, paper presented before the Division of Chemistry of Medicinal Products, American Chemical Society, St. Louis, April, 1920. Dox and Yoder, THIS JOURNAL, **44**, 1578 (1922). Tiffeneau, *J. Pharm. Chim.* [7] **25**, 153 (1922).

[5] Carnot and Tiffeneau, *Compt. rend.*, **175**, 242 (1922).

[6] Shonle and Moment, THIS JOURNAL, **45**, 243 (1923).

[7] Dox, *ibid.*, **46**, 1707 (1924).

[8] Fraenkel, "Die Arzneimittel Synthese," Julius Springer, Berlin, 5th ed. 1921, p. 110.

[9] Uhlmann, *Schweiz. med. Wochenschr.*, **50**, 171 (1920). Juliusberger, *Deutsch. med. Wochenschr.*, **46**, 1335 (1920).

[10] v. Braun and Braunsdorf, *Ber.*, **54B**, 2081 (1921). Volwiler and Adams, U. S. pat. 1,476,934 (1923).

such a manner that the alkyl groups are free to function in the brain cells. In view of the fact that in the case of the allyl-barbituric acids this should give rise to very toxic and irritating allyl compounds, whereas since that does not seem to occur, this theory must be abandoned along with all other theories that have attempted to give a satisfactory explanation of narcosis.

The allyl-alkyl-barbituric acids were tested for efficiency and toxicity by subcutaneous injection of solutions of the sodium salts into white rats.[11] The concentration used for the toxicity tests was 2%, and for the efficiency tests 1%, the volume of solution injected being kept within the limits of 0.5 to 2 cc. For the sake of comparison, a number of dialkyl-barbituric acids were similarly tested. To keep the volumes of solution within the specified limits, it was necessary in the cases of the diethyl- and the di-*n*-butyl-barbituric acids to use 4% solutions for the toxicity tests, and 2% for the efficiency tests.

The lower the figure obtained by dividing the minimum effective dose by the minimum lethal dose, the more desirable the compound should be, other factors being equal. The order of decreasing desirability on this basis is as follows: *n*-butyl-allyl, *iso*butyl-allyl, diallyl, *n*-propyl-allyl, *iso*propyl-allyl or *sec.*-butyl-allyl, *iso*-amyl-allyl, ethyl-allyl.

These pharmacological data are to be regarded as applying rigidly only to white rats, for results in higher animals or in human therapy may alter the order somewhat.

Experimental Part

The mono-alkyl-barbituric acids were prepared by the Fischer-Dilthey synthesis[12] by the reaction of the mono-alkyl malonic esters with urea at 80–85°, in the presence of sodium ethylate. The products were purified by recrystallization from alcohol or water.

In preparing the alkyl-allyl-barbituric acids, advantage was taken of the reactivity of the allyl group, and the fact that the second substituent is introduced with greater ease than the first on the 5 carbon atom of barbituric acid. The method of preparation was similar to that used by Preiswerk.[13] The mono-alkyl-barbituric acid was dissolved in 1 molecular equivalent of 30% sodium hydroxide solution, filtered, and 1.1 equivalents of allyl bromide was added; the mixture was stirred for 48 hours at room temperature. Crystals began to form within a few hours, and in most cases the allyl bromide had disappeared and the reaction was practically complete in 24 hours or less. In the case of mono-*n*-propyl-barbituric acid, a 15% solution of sodium hydroxide was employed, due to the lower solubility of the sodium salt obtained. The solid alkyl-allyl-barbituric acid obtained

[11] The pharmacological work on these compounds was done by Mr. J. A. Higgins, of the Abbott Laboratories, and will be published elsewhere.

[12] Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

[13] Preiswerk, U. S. pat., 1,444,802 (1923).

in each case was filtered off and recrystallized from water or dil. alcohol; usually 35% alcohol was quite satisfactory. Since the primary object of the work was to obtain the pure compounds for physiological tests, no attempt was made to find the conditions for obtaining the optimum yields.

All melting and boiling points given are corrected.

TABLE I

ANALYSES

Allyl-barbituric acid	Empirical formula	Subs. G.	Vol. of 0.1 *N* acid Cc.	%N Calcd.	%N Found (Kjeldahl)
5,5-Ethyl-	$C_9H_{12}O_3N_2$	0.2135	21.41	14.28	14.05
5,5-*n*-Propyl-	$C_{10}H_{14}O_3N_2$	.2112	19.77	13.33	13.11
5,5-*iso*Propyl-	$C_{10}H_{14}O_3N_2$	.2009	19.04	13.33	13.28
5,5-*n*-Butyl-	$C_{11}H_{16}O_3N_2$	.2063	18.11	12.50	12.3
5,5-*iso*Butyl-	$C_{11}H_{16}O_3N_2$	.2106	18.90	12.50	12.57
5,5-*sec.*-Butyl-	$C_{11}H_{16}O_3N_2$	.2004	17.93	12.50	12.53
5,5-*iso*-Amyl-	$C_{12}H_{18}O_3N_2$	.2010	16.43	11.76	11.45

TABLE II

YIELDS AND CONSTANTS OF MALONIC ESTER DERIVATIVES AND OF SUBSTITUTED BARBITURIC ACIDS

Malonic ester derivative	B. p. °C.	% yield	Barbituric acid derivative	M. p. °C.	% Yield	Alkyl-allyl-barbituric acid	M. p. °C.	% Yield
Mono-ethyl	207–9 (755)	80	Mono-ethyl	193–4	80	Ethyl-allyl	158–9.5	75
Mono-*n*-propyl	222–7 (750)	75	Mono-*n*-propyl	204.5–5.5	70	*n*-Propyl-allyl	133–4.5	72.5
Mono-*iso*propyl	215–7 (748)	60	Mono-*iso*propyl	214–4.5	50	*iso*Propyl-allyl	137.5–8.5	82
Mono-*n*-butyl	242–5 (745)	70	Mono-*n*-butyl	208–9	60	*n*-Butyl-allyl[a]	128	75
Mono-*iso*butyl	217–27 (750)	55	Mono-*iso*butyl	235–6	50	*iso*Butyl-allyl	137–8.5	82
Mono-*sec.*-butyl	239–40 (762)	68	Mono-*sec.*-butyl	197–9	70	*sec.*-Butyl-allyl	108–10	72
Mono-*iso*-amyl	245–50 (747)	75	Mono-*iso*-amyl	242	45	*iso*-Amyl-allyl	118–9.5	66

[a] Layraud, French pat. 541,997 (1922), gives m. p. 118°.

TABLE III

SOLUTIONS OF THE SODIUM SALTS INJECTED SUBCUTANEOUSLY INTO WHITE RATS, EXPRESSED IN MILLIGRAMS OF THE BARBITURIC ACID PER KILOGRAM OF BODYWEIGHT

Barbituric acid derivative	Minimum lethal dose	Minimum effective dose (not awakened when inner ear is tickled with a straw)	Ratio $\frac{\text{M.E.D.}}{\text{M.L.D.}}$
Diallyl	150	60	0.40
Ethyl-allyl	180	102	.57
n-Propyl-allyl	175	72	.41
*iso*Propyl-allyl	125	52.5	.42
n-Butyl-allyl	270	75	.27
*iso*Butyl-allyl	175	52.5	.30
sec.-Butyl-allyl	90	37.5	.42
iso-Amyl-allyl	170	85	.50
Diethyl	310	225	.72
n-Butyl-ethyl	190	62.5	.33
*iso*Propyl-ethyl	110	90	.82
iso-Amyl-ethyl	140	57.5	.41
n-Butyl-*iso*propyl	160	72.5	.45
Di-*n*-butyl	380	200	.53
Phenyl-ethyl	140	110	.78

Summary

1. The following barbituric acid derivatives have been prepared: diallyl, ethyl-allyl, *n*-propyl-allyl, *iso*propyl-allyl, *n*-butyl-allyl, *iso*butyl-allyl, *sec.*-butyl-allyl, *iso*-amyl-allyl. Their physiological actions have been compared with those of known dialkyl-barbituric acids.

2. Tests on white rats show that the alkyl-allyl-barbituric acids fall in the following order of decreasing desirability as hypnotics, based upon their efficiency and toxicity: *n*-butyl-allyl, *iso*butyl-allyl, diallyl, *n*-propyl-allyl, *iso*propyl-allyl or *sec.*-butyl-allyl, *iso*-amyl-allyl, ethyl-allyl.

3. The replacement of an alkyl group in 5,5-dialkyl-barbituric acids by an allyl group frequently leads to an increase in effectiveness, together with a lower degree of increase in toxicity.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

BENZOYLHYDROPEROXIDE: PREPARATION AND APPLICATION TO ORGANIC SYNTHESIS[1,2]

BY HAROLD HIBBERT AND C. PAULINE BURT

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The use of benzoylhydroperoxide for the synthesis of organic oxides and glycols[3] from unsaturated derivatives offers many advantages over that of permanganates, hypochlorous acid, halogens, etc., due to the fact that the oxide formation is carried out in the absence of water and in a neutral, organic medium from which the reaction products can be easily isolated.

For these reasons it is particularly applicable to syntheses relating to studies on carbohydrates and polysaccharides.[3b] Unfortunately there is no detailed description available in the literature regarding the preparation of benzoylhydroperoxide from benzoylperoxide[4] and this has proved to

[1] This paper is constructed from part of a dissertation presented by C. Pauline Burt in June, 1925, to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy.

[2] Communicated to the Organic Division of the American Chemical Society at Baltimore, April, 1925.

[3] (a) Prileschajew, *Ber.*, **42**, 4811 (1909); *J. Russ. Phys.-Chem. Soc.*, **42**, 1387 (1910); **43**, 609 (1911); **44**, 613 (1912). (b) Bergmann and others, *Ber.*, **54**, 440 (1921); **56**, 2255 (1923); *Ann.*, **432**, 333 (1923). (c) Derx, *Rec. trav. chim.*, **40**, 524 (1921); **41**, 332 (1922). (d) Böeseken and Blumberger, *ibid.*, **44**, 90 (1925).

[4] Baeyer and Villiger, *Ber.*, **33**, 1569 (1900). Ref. 3 a. Also in the work of Derx (Ref. 3 c) and in the recent paper of Böeseken and Blumberger (Ref. 3 d), published after the completion of the present investigation, the details are still lacking. The last-named authors find that benzoylhydroperoxide, as prepared by them, shows a somewhat "capricious behavior" towards unsaturated hydrocarbons, the "rate of oxide formation" being greatly influenced by the presence of small traces of other products. A freshly-prepared solution of the hydroperoxide is stated to be less active than one that has stood for 24 hours at 15°; and the latter is more active than one kept at 0°.