appear. However, solutions of benzylamine, glucose and acetic acid become colored more rapidly than corresponding blanks.

Four alcoholic solutions were made up to contain in 50 cc.: (1) 1.5 g. of glucose, 0.89 g. of benzylamine and 0.5 g. of acetic acid, (2) a comparable solution of glucose and benzylamine, (3) of benzylamine and acetic acid, (4) of benzylamine alone. They were left at room temperature, 24–25°. Solution 1 had a tinge of yellow in one day, orange in four and a red-brown in ten days; Solution 2 acquired a slight tinge of yellow in ten days, but in 125 days it was still yellow. In 245 days Solution 3 was a faint yellow but Solution 4 was still colorless.

After 75 days the colored material of Solution 1 was precipitated by dilution with water to 300 cc. The precipitate was washed with water and dried in a vacuum. It weighed 0.10 g., was a sandy-brown in color, blackened at 98° and melted at about 135°. Except to discover that the precipitate was soluble in alcohol and a portion was insoluble in ether, the investigation was left until later.

Summary

The coloration produced in solutions of glucose, aniline and acetic acid is not due to any peculiar property of the amine, as *o*- and *p*-toluidine behave in a similar manner, nor is it due to acetic acid as such, for potassium dihydrogen phosphate can be used as the acid component. As solutions of glucose, aniline and acetic acid show a reactive condition and as glucose has little effect on the coloration of methylaniline solutions, it is held that the glucose-anilide is changed to a more reactive form, probably the aldehyde isomer. The coloration may, in part, be due to oxidation of the aniline in presence of glucose, but only in part, as benzylamine, which is difficult to oxidize, in the presence of glucose and acetic acid rapidly becomes colored.

SASKATOON, SASKATCHEWAN, CANADA

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

SOME ACETOPHENONYL DERIVATIVES OF BARBITURIC ACID[1]

BY DEWITT T. KEACH AND ARTHUR J. HILL

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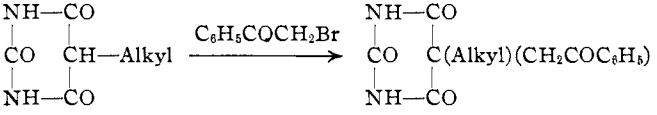
It is well known that the ketone carbonyl group confers hypnotic properties on many organic compounds, a notable case being that of acetophenone, or "Hypnone." In view of this fact it would seem quite probable that the presence of a ketonyl group, particularly acetophenonyl, together with a suitable alkyl group, on the 5-position of the barbituric acid nucleus, would produce a compound having desirable hypnotic properties.

[1] This investigation has been conducted in coöperation with the National Research Council, Sub-Committee on Hypnotics.

Very little work has been done in connection with the preparation of such compounds. While this investigation was in progress, Dox and Houston[2] published a paper on acetonyl-barbituric acid and certain of its derivatives. The introduction of the acetonyl group was shown by these investigators to diminish hypnotic activity.

In the investigations reported in this paper the writers have introduced the acetophenonyl group, using bromo-acetophenone, into the following 5-substituted barbituric acids, namely, ethyl-, *n*-propyl-, allyl-, *n*-butyl-, and *iso*butylbarbituric acid.



The physiological properties[3] of these new compounds are unpromising. They are quite toxic and, excepting the ethyl derivative, lack hypnotic properties. The latter is fairly hypnotic in its action, but possesses undesirable toxicity.

Experimental Part

The writers experienced considerable difficulty in alkylating mono-substituted malonic esters with bromo-acetophenone.[4] The reaction appeared not to be a simple one, and the frequently used malonic ester-urea condensation method was abandoned in favor of direct alkylation of the barbituric acids with bromo-acetophenone.

The following procedure was used in all cases. One molecular proportion of the appropriate alkyl barbituric acid was dissolved in 75% alcohol by gentle heating in a flask fitted with a reflux condenser. An alcoholic solution of one and one-half molecular proportions of acetophenone bromide and two molecular proportions of crystallized sodium acetate was then added and the reaction mixture digested for two hours. In the preparation

TABLE I

PROPERTIES AND ANALYSES OF THE ACETOPHENONYL-BARBITURIC ACIDS

Compound -5-acetophenonyl-barbituric acid	Yield, %	M. p., °C.	Sol. in.	Analyses Calcd. %	Found %	Found %
5-Ethyl-	50	248–249	H_2O and alcohol	10.22	10.04	9.98
5-*n*-Propyl-	33	299–300	H_2O and alcohol	9.72	9.58	9.56
5-Allyl-	75	270–271	H_2O and alcohol	9.79	9.61	9.64
5-*iso*Butyl-	50	286–287	H_2O and alcohol	9.27	9.03	8.99
5-*n*-Butyl-	53	294–295	Abs. alc.	9.27	9.15	9.30

[2] Dox and Houston, THIS JOURNAL, **46**, 252 (1924).

[3] The writers are indebted to Drs. Underhill, Gross and Allison, of the Yale Department of Pharmacology, for their coöperation in determining the physiological properties of these compounds. A detailed pharmacological report will be published elsewhere.

[4] This reaction is being studied.

of 5-*n*-butyl-5-acetophenonyl-barbituric acid, precipitation occurred during the heating period; with all the others, the reaction product crystallized only after removal of part of the solvent, and cooling.

The compounds are colorless, and crystallize from alcohol or water in characteristic plates. Other data are given in Table I.

Summary

1. Acetophenonyl-substituted barbituric acids have been prepared by the action of bromo-acetophenone on certain 5-alkyl-substituted barbituric acids.

2. In contrast to acetophenone, these new substances, with the exception of the ethyl derivative, are surprisingly lacking in hypnotic properties, and all are moderately toxic.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE RICE INSTITUTE]

THE EFFECT OF STRUCTURE OF ORGANIC HALIDES ON THEIR RATE OF REACTION WITH INORGANIC HALIDES. I. THE EFFECT OF THE HYDROXYL, PHENOXYL AND BENZOXYL GROUPS

BY W. R. KIRNER

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Introduction

The influence of the benzoyl, carbethoxyl, phenyl and acetoxyl groups upon the reactivity of a chlorine atom placed at various distances from the functional group in a typical series such as ACl, ACH_2Cl, ACH_2CH_2Cl, $ACH_2CH_2CH_2Cl$, etc., has already been determined.[1]

The purpose of this paper is to extend the list of these groups, which now includes the effect of the hydroxyl, phenoxyl and benzoxyl groups. The results obtained are in general agreement with those already published; that is, in the new series that have been studied it has again been found that there are indications of an alternation in the reactivity of the chlorine atom as the distance between A and Cl is regularly increased by the insertion of methylene groups. The degree and extent of this alternation in reactivity is a function of the character of the group A; in the case of certain groups the alternation is well defined, in other cases it is feeble. This is brought out by a study of Table I which contains a summary of the results.

From a consideration of this table together with summarizing tables previously published[1a,2] one may arrange the groups in the following order of decreasing activity: $C_6H_5CO—$, > $C_2H_5OCO—$, > $CH_3COO—$, > $HO—$,

[1] (a) Conant and Kirner, THIS JOURNAL, **46**, 232 (1924). (b) Conant, Kirner and Hussey, *ibid.*, **47**, 488 (1925).

[2] Conant and Hussey, *ibid.*, **47**, 477 (1925). Ref. 1 b, pp. 489, 494.