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Studies on N-Substituted Barbituric Acid Derivatives. I

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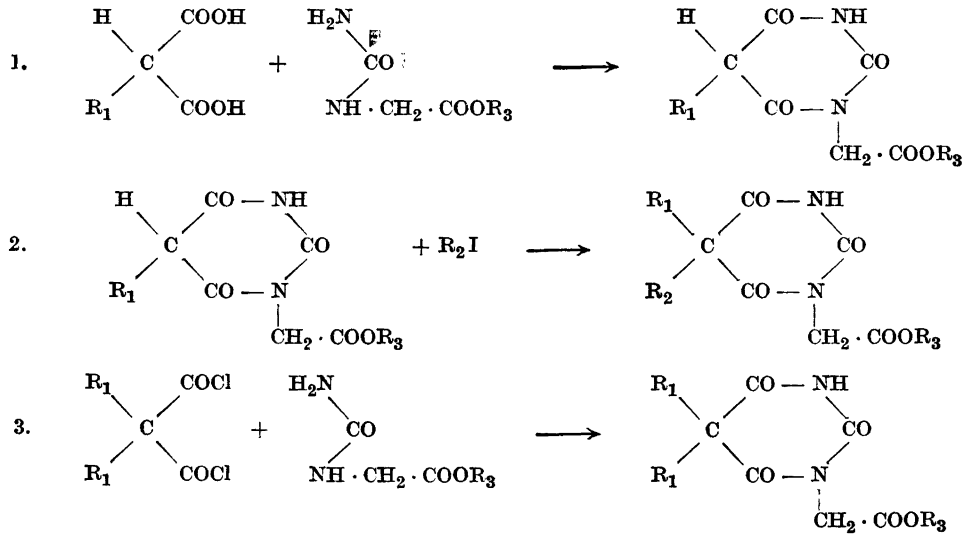
The pharmacological properties of a series of 1-carbethoxymethyl-5 : 5-dialkyl-substituted barbiturates have been described by Sandberg [1].

The syntheses and chemical properties of these derivatives and their parent compounds are described in the present paper.

The syntheses of the required substances were achieved according to the following scheme:



where R_1 = H, alkyl radicals with 1 to 5 C-atoms, or the phenyl group,
R_2 = allyl radical,
R_3 = alkyl radical with 1 to 3 C-atoms.

Part I of this paper deals with reaction 1 and some by-products, and Part II with reactions 2 and 3 and the final products.

EXPERIMENTAL

Syntheses

Malonic acid was condensed with hydantoic acid alkyl ester in the presence of $POCl_3$, on a water-bath (30 min), according to Rosén [2] to yield 1-carbomethox ymethyl-barbituric acid and its homologues (substances 1—3 in Table 1).

These compounds are soluble in hot water and alcohol, less soluble in benzene, and sparingly soluble in ether. Since they react as monobasic acids, their equivalent weights could be determined by titration with 0.1 *N* sodium hydroxide. Table 1 gives the equivalent weights and melting points.

1-Carbomethoxymethyl-barbituric acid (1) Found: N 14.01 per cent; $C_7H_8O_5N_2$ requires N 14.00 per cent.

1-Carbisopropoxymethyl-barbituric acid (3) Found: N 12.21 per cent; $C_9H_{12}O_5N_2$ requires N 12.28 per cent.

A few points concerning this synthesis are worthy of note. It was observed that if ten times or more of the usual quantities (0.05 moles of malonic acid, 0.10 moles of hydantoic acid alkyl ester and 0.055 moles of $POCl_3$) were used, the substances 1—3 were obtained only to a very small extent, and the main product was 1-carbomethoxymethyl-5-acetyl-barbituric acid and its homologues (derivatives 15—17 in Table 2).

If, on the other hand, equivalents of malonic acid and hydantoic acid alkyl ester were condensed, the compounds 15—17 were obtained as the main products, regardless of the quantities used.

In this case the yellow reaction mixture, after cooling, was a hard mass. This was crushed, washed with cold water and dried at room temperature. 5 g of this product was mixed with 50 ml of water. On heating to 70—80° C, an almost clear solution was obtained. After some minutes at this temperature, CO_2 was liberated, the solution became turbid, and a light-yellow precipitate appeared. This was filtered off and dissolved in alcohol, and the alcoholic solution was treated with charcoal. Repeated crystallizations from alcohol or benzene gave the pure substances 15—17.

These derivatives are insoluble in cold water, sparingly soluble in boiling water, and easily soluble in hot alcohol, benzene, and ether. As they are acids, the equivalent weights were determined by titration with 0.1 *N* sodium hydroxide (phenolphthalein as indicator). The equivalent weights and melting points are given in Table 2.

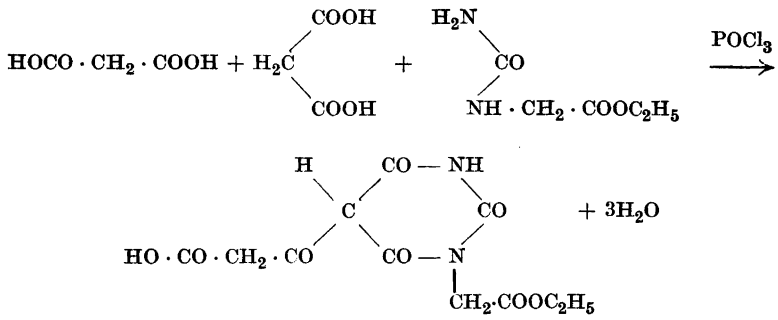
1-Carbomethoxymethyl-5-acetyl-barbituric acid (15). Found: N 11.54 per cent; $C_9H_{14}O_6N_2$ requires N 11.57 per cent.

1-Carbethoxymethyl-5-acetyl-barbituric acid (16). Found: C 46.70; H 4.74; N 10.95 per cent; $C_{10}H_{16}O_6N_2$ requires C 46.88; H 4.72; N 10.94 per cent. With 2:4-dinitrophenylhydrazine it gave a hydrazone melting at 247° C.

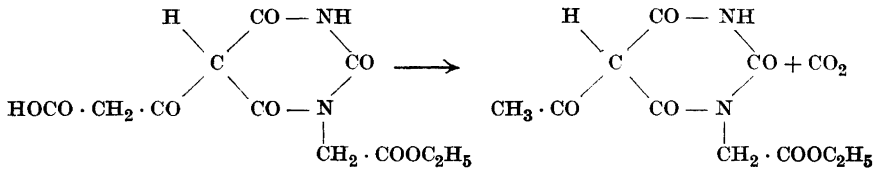
1-Carbisopropoxymethyl-5-acetyl-barbituric acid (17). Found: N 10.33 per cent; $C_{11}H_{18}O_6N_2$ requires N 10.37 per cent.

These compounds show an exceptional stability. They are not decomposed by boiling in water for one hour, and on acidification of their alkaline solutions (many hours old) they reprecipitate. These properties and the formation of a hydrazone indicate the 5-position of the acetyl group.

The first step in the formation of the 5-acetyl derivatives might be:



As mentioned earlier, this intermediate product is decomposed in water solution at about 80° C as follows:



The 5-acetyl derivatives were also obtained by the condensation of 1-carbomethoxymethyl-barbituric acid and its homologues with malonic acid in the presence of $POCl_3$.

These results are analogous with the findings of Conrad and Guthzeit [3], who obtained 5-acetyl-barbituric acid as a by-product in the synthesis of barbituric acid from malonic acid, urea, and $POCl_3$.

The structure of the substances 15—17 will be discussed again in connection with their ultra-violet absorption spectra.

The condensation of monoalkyl-substituted malonic acid with hydantoic acid alkyl ester was achieved by the two methods given by Rosén [2]:

1. Condensation in the presence of acetic anhydride at 60—70° C for 4 hours.
2. Condensation in the presence of $POCl_3$ on a water-bath for half an hour.

Table 1.

No.	Derivatives	M. p. uncorr.	Equiv. wt.		In 0.1 *N* NaOH	
			found	calc.	ε_{max}	Å
1	1-Carbomethoxymethyl-barbituric acid	168—169°	201.0	200.1	17 230	2 600
2	1-Carbethoxymethyl- » » *	137—138°	214.5	214.1	16 530	2 600
3	1-Carbisopropoxymethyl- » »	123—124°	229.3	228.1	16 100	2 600

* This substance is described by Rosén [2].

Table 2.

No.	Derivatives	M. p. uncorr.	Equiv. wt.		In 0.1 *N* NaOH	
			found	calc.	ε_{max}	Å
4	1-Carbethoxymethyl-5-methyl- barbituric acid *	137—138°	228.6	228.1	18 120	2 700
5	1-Carbomethoxymethyl-5-ethyl- » »	94— 95°	228.1	228.1	18 140	2 700
6	1-Carbethoxymethyl-5-ethyl- » » *	97— 98°	242.0	242.1	17 500	2 700
7	1-Carbisopropoxymethyl-5-ethyl- » »	95— 96°	257.0	256.1	16 300	2 700
8	1-Carbethoxymethyl-5-*n*-propyl- » »	138—139°	257.0	256.1	4 950	2 700
9	1- » -5-*iso*propyl- » »	80°	255.6	256.1	18 250	2 700
10	1- » -5-*n*-butyl- » »	124—125°	271.9	270.1	4 040	2 700
11	1- » -5-*sec*-butyl- » »	107—108°	272.4	270.1	—	—
12	1- » -5-*iso*-butyl- » »	100—101°	272.0	270.1	16 960	2 710
13	1- » -5-*iso*-amyl- » »	119—120°	285.8	284.1	4 140	2 700
14	1- » -5-phenyl- » »	142°	291.3	290.1	17 160	2 680
15	1-Carbomethoxymethyl-5-acetyl- » »	146—147°	241.1	242.1	13 700	2 810
16	1-Carbethoxymethyl-5-acetyl- » »	142—143°	256.7	256.1	12 900	2 810
17	1-Carbisopropoxymethyl-5-acetyl- » »	166—168°	271.8	270.1	11 700	2 810
18	1-Carbethoxymethyl-5-allyl- » »	oil	—	254.1	—	—
19	1-Carbethoxymethyl-3-acetyl-5-ethyl- » » *	184—187°	—	—	19 550	2 700
20	1-Carbethoxymethyl-3-acetyl-5-*n*-propyl- »	159—161°	—	—	18 400	2 700

* This substance is described by Rosén [2].

Derivatives 4—14 and 18 were obtained by both methods. Their melting points and equivalent weights are given in Table 2.

These compounds were crystallized from alcohol or benzene. They are also soluble in ether but only very slightly soluble in water. Difficulties were encountered in the crystallization of the higher homologues, but all but one were finally obtained in a crystalline form.

The following comments may be made on certain of the preparations involved. In synthesizing derivative 9, 1-carbethoxymethyl-5-isopropyl-barbituric acid, a by-product was obtained using the $POCl_3$-method. This proved to be: *2-methyl-buturyl-hydantoic acid ethyl ester,* $CH_3 \cdot \underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}} \cdot CH_2 \cdot CO \cdot NH \cdot CO \cdot NH \cdot CH_2 \cdot COOC_2H_5$

Found: C 52.3; H 7.81; N 12.05 per cent; $C_{10}H_{18}O_4N_2$ requires: C 52.2; H 7.89; N 12.17 per cent.

Crystallized from aqueous alcohol (30 per cent), the ester gave glistening plates, m. p. 125 to 127° C. It is also soluble in benzene and ether, and slightly soluble in boiling water.

It is obvious that in this case the *iso*propyl-malonic acid had been partly decomposed, giving an aliphatic compound on condensation with hydantoic acid ethyl ester.

Recrystallization of 1-carbethoxymethyl-5-phenyl-barbituric acid (14) from benzene sometimes gave a substance melting at about 100° C. This, however, was easily converted into the form melting at 142° C.

1-Carbethoxymethyl-5-allyl-barbituric acid (18) occurred as a viscous oil, which failed to crystallize. The product obtained has not been further investigated.

In the preparation of the derivatives 6 and 8 according to the acetic anhydride method, their corresponding 3-acetyl derivatives (19—20) were obtained as by-products.

As the substances 19 and 20 are insoluble in ether, they could easily be separated from their ether-soluble parent compounds. They were crystallized from alcohol or benzene. They are also soluble in alkali with decomposition.

1-Carbethoxymethyl-3-acetyl-5-n-propyl-barbituric acid (20)

Found: N 9.37 per cent; $C_{13}H_{18}O_6N_2$ requires N 9.38 per cent.

We have not succeeded in isolating the higher homologues of these 3-acetyl derivatives, although they were probably formed.

To obtain the sodium salts of compounds 2, 9, 12, and 13, the acids were dissolved in equivalent quantities of alcoholic sodium hydroxide. The sodium salts were precipitated on adding a considerable excess of ether. The sodium salts, however, deliquesced in the atmosphere.

Ultra-violet absorption spectra

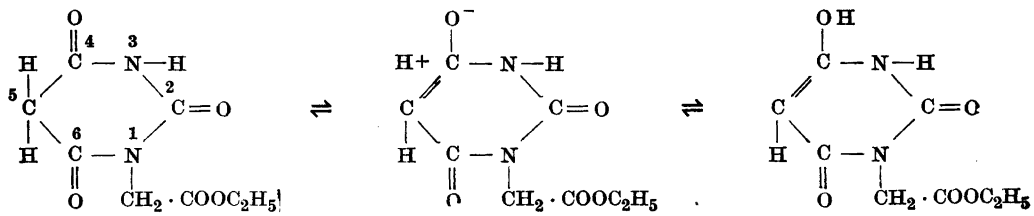
Measurements were made with a Beckman quartz Spectrophotometer. The molecular extinction coefficient ε is defined by the relation $\log I_0/I = \varepsilon \cdot c \cdot l$, where c is the molar concentration and l is the length of the tube in cm. In making the solutions, recently distilled, carbon dioxide-free water was used, and the solutions were examined immediately against blanks.

DISCUSSION

Fig. 1 shows the absorption spectra (in water) of 1-carbethoxymethyl-barbituric acid (2) under varying conditions. The concentration of all solutions is $4.324.10^{-5}$ molar.

The carbonyl groups in the molecule will act as chromophores and produce a small absorption. Tautomerism, however, producing an enolized structure with an olefinic linkage, would cause a much larger absorption than that due to the carbonyl groups.

From the absorption curves in Fig. 1 and the findings of Fredholm [4] and Stuckey [5] on the tautomerism of 1-methyl-barbituric acid, it can be concluded that the following mechanism is operative:



I ⇌ II ⇌ III

where only the hydrogen of the active methylene group in the 5-position is involved in the keto-enol tautomerism.

Two small peaks of low extinction value (approx. 1850) at 2750 Å and 2580 Å and a notable end-absorption are present in solutions of 0.1 *N* hydrochloric

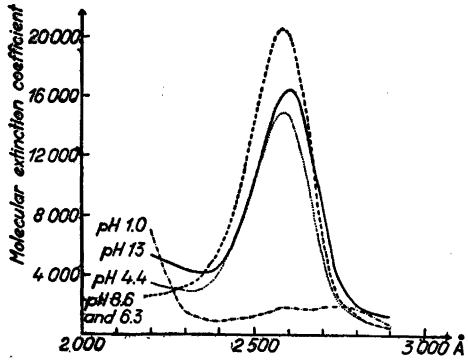


Fig. 1. Absorption spectra of 4.324 · 10^{-5} molar solutions of 1-carbethoxymethyl-barbituric acid at varying pH.
pH 1 : In 0.1 N hydrochloric acid.
pH 4.4: Pure aqueous solution.
pH 6.3: Two equivalents of sodium hydroxide added.
pH 8.6: Three equivalents of sodium hydroxide added.
pH 13 : In 0.1 N sodium hydroxide.

acid. The pure aqueous solution (pH 4.4) shows a marked increase in absorption, producing a peak at 2580 Å (ε_{max} = 15 000). The curve for the solution with one equivalent of NaOH added (pH 5.5), *i. e.* corresponding to a solution of the monosodium salt, shows a further augmentation of absorption, ε_{max} being 19 200 at 2580 Å (this curve is not drawn in Fig. 1). The addition of two and three equivalents of NaOH to the solution (pH 6.3 and 8.6) — which would correspond to the disodium and trisodium salts, if these exist — gave the same curve, the highest extinction coefficient figure being 20 600 at 2580 Å. In 0.1 *N* sodium hydroxide the absorption is decreased to ε_{max} = 16 500 at 2600 Å.

This shift of the band to a longer wave-length in strong alkaline solution might be due to the asymmetrical structure of the molecule, which is probably accompanied by a pronounced electro-asymmetry.

The interpretation of these curves may be the following: The strong band at 2580 Å is necessarily due to the ion II. At pH 1, the equilibrium has shifted and the keto-form I is mainly present (represented by the peak at 2750 Å), but the ion II is still present to a lesser extent (the peak at 2580 Å). In aqueous solution (pH 4.4), an intermediate equilibrium position is found where the enol-form II predominates. In slight alkaline solution (pH 8.6), the enolization rises to its maximum.

The decrease in absorption at pH 13 is due to the formation, to a certain extent, of the compound III as the sodium salt. This involves the assumption that the absorption of the undissociated sodium salt is less than that of the enolic ion II.

Reference to Table 1 shows that in 0.1 *N* sodium hydroxide the derivatives 1—3 all have the selective absorption at 2600 Å, the molecular extinction coefficient being decreased as the number of C-atoms in the side-chain in the 1-position increases.

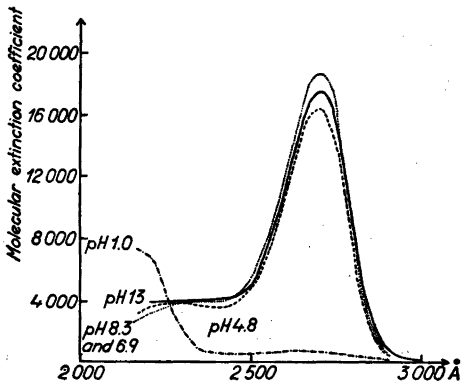
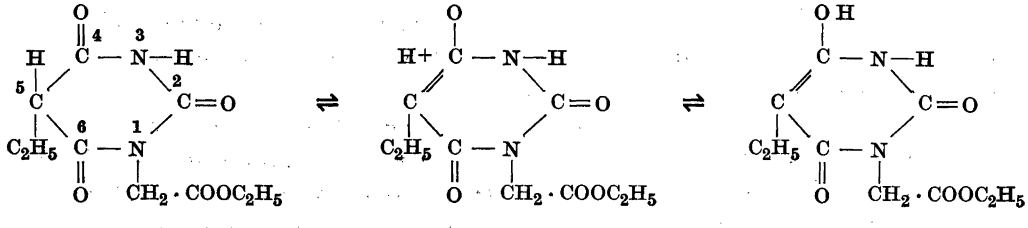


Fig. 2. Absorption spectra of 4.482 · 10^{-5} molar solutions of 1-carbethoxymethyl-5-ethyl-barbituric acid at varying pH.
pH 1 : In 0.1 N hydrochloric acid.
pH 4.8: Pure aqueous solution.
pH 6.9: One equivalent of sodium hydroxide added.
pH 8.3: Two equivalents of sodium hydroxide added.
pH 13: In 0.1 N sodium hydroxide.

5-Monosubstituted derivatives were next studied. These compounds still have a free hydrogen in the 5-position, and it is very probable that this will also undergo enolization.

Fig. 2 shows the absorption spectra of $4.482.10^{-5}$ molar solutions of 1-carbethoxymethyl-5-ethyl-barbituric acid (5) at varying pH. Examination of the curves shown in Fig. 2 reveals striking similarities with those in Fig. 1. From the close resemblance of the absorption spectra of the two derivatives at varying pH, it can be concluded that a similar tautomerism occurs, namely:



The enolic ion V gives a strong band at 2700 Å, ε_{max} being 18 600 at pH 8.3 (the curve at pH 6.9 not being measurably different from that of the absorption at pH 8.3). At pH 13, the compound VI is formed to a certain extent (ε_{max} = 17 500 at 2700 Å). A small peak at 2650 Å indicates the presence of the keto-form IV at pH 1, and the absorption in aqueous solution (pH 4.8) shows an intermediate equilibrium position (ε_{max} = 16 300 at 2700 Å) between IV and V.

The 5-monosubstituted derivatives in Table 2 (with the exception of 15—17: see the following) all have a peak at approximately 2700 Å. In the compounds 5—7, ε_{max} is diminished when the number of C-atoms in the sidechain

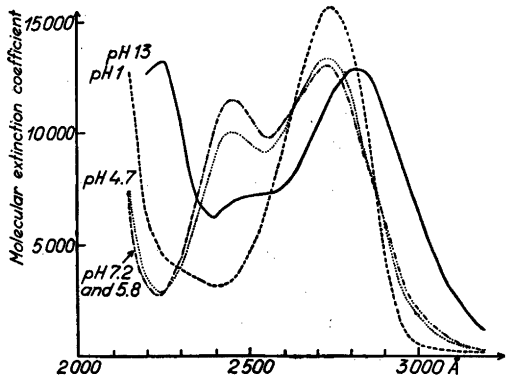


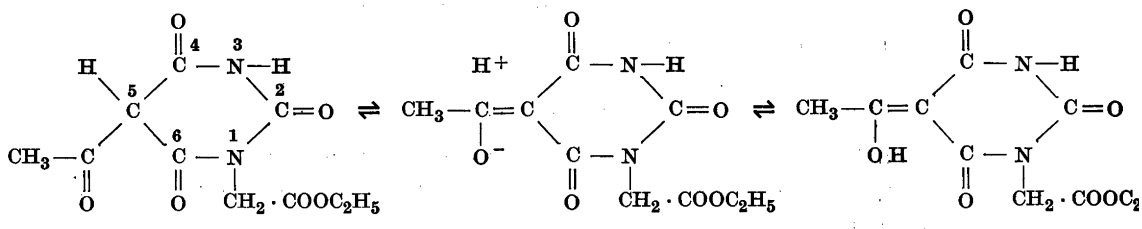
Fig. 3. Absorption spectra of 3.237 · 10⁻⁵ molar solutions of 1-carbethoxymethyl-5-acetyl-barbituric acid at varying pH.
pH 1: In 0.1 N hydrochloric acid.
pH 4.7: Pure aqueous solution.
pH 5.8: One equivalent of sodium hydroxide added.
pH 7.2: Two equivalents of sodium hydroxide added.
pH 13: In 0.1 N sodium hydroxide.

in the 1- position increases (*cf.* derivatives 1—3). It is further worth noticing that there is a remarkable decrease in the value of ε_{max} for some of the higher homologues.

As a representative of the three homologous compounds 15—17, the absorption spectra of 1-carbethoxymethyl-5-acetyl-barbituric acid (16) at varying pH are shown in Fig. 3. The concentration of all solutions is $3.237.10^{-5}$ molar.

The general pattern of the curves in Fig. 3 is in sharp contrast to those in Fig. 2. Thus, a similar tautomerism is excluded.

The following mechanisms are, then, possible:



At pH 1 there is a peak absorption (ε_{max} = 15 700) at 2730 Å, which is due to the compound VII. This band is diminished to a value of ε_{max} = 13 400 in the aqueous solution (pH 4.7), and a new strong band appears at 2450 Å (ε_{max} = 10 100).

The curves of the absorption at pH 5.8 and 7.2 (corresponding to the monosodium and disodium salts) are almost the same and show a further decrease in the band at 2730 Å (ε_{max} = 13 100) and an augmentation of the band at 2450 Å (ε_{max} = 11 500).

The two strong bands indicate the presence of two chromophores in the ion VIII, one of which is the double bond between the C-atom in the 5-position and the C-atom in the sidechain.

It is thus possible that tautomerism has occurred, affecting the hydrogen atom attached to the nitrogen in the 3-position, producing either a conjugated system with the double bond in the 3 : 4-position or a form with the double bond in the 2 : 3-position. This tautomerism (which is not marked in the above scheme) must then be most pronounced in VII and least in IX, a rather astonishing conclusion.

The absorption curve at pH 13 shows two peaks: one at 2810 Å (ε_{max} = 12 900) and the other at 2250 Å (ε_{max} = 13 300) and are referred to IX.

The above scheme is borne out to some extent by the following two facts:

In strongly acid solution, this derivative can be condensed with 2 : 4-dinitrophenolhydrazine forming a hydrazone, indicating the ketonic structure of the side-chain in the 5-position (VII).

In alkaline solution it was not possible (as will be reported in Part II of this paper) to substitute the free hydrogen atom in the 5-position with an allyl radical, thus showing that there is no free hydrogen owing to the formulae VIII and IX.

The pattern of the curves for the three 5-acetyl derivatives (15—17) is exactly the same in all details, and in 0.1 *N* sodium hydroxide solution ε_{max} decreases as the number of C-atoms in the side chain in the 1-position increases (*cf.* derivatives 1—3 and 5—7).

Further investigations on the tautomerism of the 5-acetyl derivatives will be carried out and published later.

SUMMARY.

1-Carbomethoxymethyl-barbituric acid, 1-carbethoxymethyl-5-methyl-barbituric acid, 1-carbomethoxymethyl-5-acetyl-barbituric acid, and some of their homologues have been prepared and their chemical properties and ultraviolet absorption spectra are reported.

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