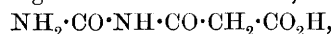


CXI.—*The Constitution of the Salts of Barbituric Acid.*

By JOHN KERFOOT WOOD and EMMA ALEXANDER ANDERSON.

IT has been shown by one of us (Wood, *Trans.*, 1906, **89**, 1831), and also by Trübsbach (*Zeitsch. physikal. Chem.*, 1895, **16**, 711) and Hantzsch and Voegelen (*Ber.*, 1902, **35**, 1006), that barbituric acid is an acid considerably stronger than acetic acid. Such a value for the dissociation constant would be exceedingly high were the acidity to be due simply to the hydrogen of one of the imino-groups, but it was shown by Wood (*loc. cit.*) that most of the acidity was to be traced to the methylene group, the *C*-dialkylbarbituric acids having dissociation constants less than one-thousandth of that of the parent substance. Hantzsch and Voegelen (*loc. cit.*), from determinations of the electrical conductivity of solutions of barbituric acid in aqueous alcohol, had previously drawn the conclusion that barbituric acid is a pseudo-acid, but were unable to decide whether the acid, when in solution, had the formula $\text{NH} \left\langle \begin{array}{l} \text{CO} \cdot \text{CH}_2 \\ \text{CO} \text{---} \text{N} \end{array} \right\rangle \text{C} \cdot \text{OH}$ or $\text{NH} \left\langle \begin{array}{l} \text{C}(\text{OH}) \cdot \text{CH} \\ \text{CO} \text{---} \text{NH} \end{array} \right\rangle \text{CO}$. Taking the results obtained by Wood (*loc. cit.*) into account, and neglecting the slight acidity due to the imino-group, the second of these formulæ would be the correct one for the acid in solution, and the salts would have analogous formulæ, the hydrogen of the hydroxyl group being replaced by metals.

An alternative view to explain the high dissociation constant of barbituric acid would be that the ring might be broken by the action of water, giving rise to a ureido-acid,



in the same way that parabanic acid is decomposed with the formation of oxaluric acid. Such a rupture of the ring is, however, very unlikely in the case of barbituric acid; rather would the ureido-acid containing a chain of six carbon and nitrogen atoms have a tendency to pass into barbituric acid, the conditions being favourable to ring formation. Further, it is exceedingly improbable that replacement of the hydrogens of the methylene group by alkyl groups would prevent the rupture of the ring, assuming it to take place in the case of barbituric acid, but some such effect would be necessary to account for the great discrepancy between the values of the dissociation constants of barbituric acid and its *C*-dialkyl derivatives. Finally, were rupture of the ring to take place, the salts of barbituric acid would be salts of the new ureido-acid, and on analysis would show a molecule of water more than would be the case were there no rupture. The fact that some of the salts are anhydrous and have compositions agreeing

with the ring formula, shows that this alternative explanation is inadmissible.

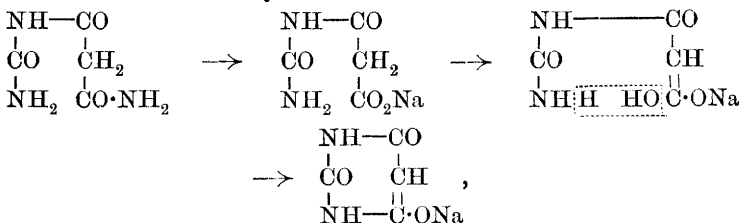
From its intimate connexion with barbituric acid, it was considered that it would be of interest to prepare the above-mentioned ureido-malonic acid and to study its properties. Various attempts were made by the authors to prepare the compound by the hydrolysis of cyanoacetylcarbamide, but all of these, no matter what hydrolysing agent was used, were unsuccessful.

Attempts were then made to condense together malonic acid and carbamide, and from these substances, using acetic anhydride as the condensing agent, the amide of the desired acid was ultimately obtained. This amide, on treatment with sodium hydroxide, yielded a sodium salt, the composition of which agreed with that of sodium barbiturate, and, on being acidified, it yielded barbituric acid and not the ureido-acid. Such behaviour is in agreement with the observation of Boehringer and Söhne (D.R.-P. 193447), that the ethyl ester of ureidomalonic acid, on saponification, is converted into sodium barbiturate.

These results show that it is impossible to prepare and isolate the ureido-acid, since, owing to the tendency to ring-formation, it immediately loses water and passes into barbituric acid.

The formation of sodium barbiturate by the action of sodium hydroxide on the amide and ethyl ester of ureidomalonic acid shows conclusively that the salts of barbituric acid must have the constitution $\text{NH} \left\langle \begin{array}{l} \text{C(OM):CH} \\ \text{CO—NH} \end{array} \right\rangle \text{CO}$, where M represents a univalent metal.

This action of sodium hydroxide on the amide is shown as follows:



it being taken for granted that the nitrogen of the amido-group is removed, rather than that contained in the carbamide portion of the molecule.

EXPERIMENTAL.

Preliminary Experiments with Cyanoacetylcarbamide.—It has been shown by Traube (*Ber.*, 1900, **33**, 1381) that cyanoacetylcarbamide, on treatment with sodium hydroxide, yields the sodium salt of 4-amino-2:6-dihydropyrimidine. In face of this result, alkalis appeared out of the question for the conversion of cyanoacetylcarb-

amide into ureidomalonic acid, but it was thought the cyanogen group might be hydrolysed by using some other agent. Hydrochloric acid was first tried, but without success, the only apparent result being to decompose the cyanoacetylcarbamide into cyanoacetic acid and carbamide. It was then attempted to hydrolyse the substance by heating it with water under pressure. Several grams were heated with water in a sealed tube to 120° for about eight hours. On opening the tube there was an escape of gas, and the liquid possessed a strong ammoniacal odour. A portion of the liquid, on treatment with hydrochloric acid, effervesced vigorously, owing to the escape of carbon dioxide. The liquid was at first slightly cloudy, but, on standing, a precipitate gradually formed. This was collected and dried; on analysis it proved to be 4-amino-2:6-dihydroxypyrimidine, its behaviour when dissolved in sodium hydroxide and treated with sodium nitrite and sulphuric acid supporting this conclusion. The liquid from which the pyrimidine had been precipitated was extracted with ether, and from the ethereal extract a small quantity of a solid acid was obtained; this substance possessed all the properties of cyanoacetic acid. It appears evident, therefore, that when cyanoacetylcarbamide is heated with water under pressure, part is converted into the isomeric 4-amino-2:6-dihydroxypyrimidine, whilst the rest is decomposed, forming eventually cyanoacetic acid, ammonia, and carbon dioxide, the latter two substances existing partly as ammonium carbonate. In view of these results no further attempts to prepare the ureido-acid from cyanoacetylcarbamide were made.

Attempts to Prepare Ureidomalonic Acid from Carbamide and Malonic Acid.

Grimaux (*Bull. Soc. chim.*, 1876, [ii], 31, 146) first synthesised barbituric acid by the action of phosphoryl chloride on a mixture of carbamide and malonic acid. The authors considered that by using some other condensing agent it might be possible to attack only one of the carboxyl groups of the acid. A preliminary experiment was made in which a mixture of carbamide, malonic acid, and acetic anhydride, in equimolecular proportions, was heated on the water-bath. The mixture first melted, forming a clear yellow liquid, which soon burst into vigorous effervescence and deposited a yellow solid. When all apparent action was over, water was added to the mixture and the solid collected and dried. The percentage of nitrogen in the small amount of product obtained from this preliminary experiment suggested that the substance might possibly be malonylbiuret, and accordingly, in repeating the experiment on a larger scale, the proportions in which the original substances were mixed were

such as would most favour the production of that compound, namely, two molecules each of carbamide and acetic anhydride and one molecule of malonic acid. This mixture, when heated on the water-bath, behaved as already described. On attempting to purify the product, it was found that it was not a single substance, as had been concluded from the preliminary experiment, but a mixture. The only liquid with any appreciable solvent action was water, and the mixture was accordingly submitted to fractional crystallisation from that liquid. The mixture was in this way resolved into three components, the most soluble of which was proved on analysis to consist of barbituric acid.

The third or least soluble component of the original product was a white powder, almost insoluble in boiling water, from which liquid it separated in fine needles:

0.1163 gave 0.1419 CO_2 and 0.0501 H_2O . C = 33.27; H = 4.78.

0.1147 ,, 28.0 c.c. N_2 (moist) at 12.5° and 760 mm. N = 28.92.

$\text{C}_4\text{H}_7\text{O}_3\text{N}_3$ requires C = 33.10; H = 4.82; N = 28.96 per cent.

This result would agree with either ammonium barbiturate or the amide of ureidomalonic acid. From the fact that on grinding the substance in a mortar with soda-lime and a little water no ammonia was evolved, and that ammonia was only evolved very slowly on boiling the substance with a solution of sodium hydroxide, the former alternative appears to be impossible. It must be concluded, therefore, that one of the products formed by the action of acetic anhydride on a mixture of carbamide and malonic acid is the amide of ureidomalonic acid.

The amide, when dissolved in sodium hydroxide solution and then treated with sodium nitrite and dilute sulphuric acid, gave a deep magenta colour similar to that given by barbituric acid when treated in a similar manner.

Action of Sodium Hydroxide on Ureidomalonomide.—The compound on being boiled with a 2*N*-solution of sodium hydroxide wholly dissolved, and slowly evolved ammonia. No sodium salt separated from the liquid on cooling, but on the addition of alcohol a white precipitate, consisting of a sodium salt, was obtained. This was collected, washed with alcohol, and dried, first in the air and afterwards by heating to 120° :

0.2877 gave 0.1423 Na_2SO_4 . Na = 16.02.

Sodium barbiturate requires Na = 15.33; sodium ureidomalonate requires Na = 13.6 per cent.

The sodium salt was dissolved in water and concentrated hydrochloric acid added. The solution, on keeping, deposited small crystals, which were collected, washed with water, and dried. The crystals

melted and decomposed at 250—260°; a behaviour similar to that of barbituric acid :

0·1002 gave 19·3 c.c. N₂ (moist) at 11° and 742 mm. N = 22·46.

Barbituric acid requires N = 21·87; ureidomalonic acid requires N = 19·19 per cent.

It is evident, therefore, that ureidomalonamide is converted by sodium hydroxide into a salt of barbituric acid.

Examination of Second Fraction of Original Product.—This substance was less soluble than barbituric acid, but more soluble than the ureidomalonamide. It possessed a pale yellow colour, and readily evolved ammonia on treatment with a solution of sodium hydroxide. When dissolved in sodium hydroxide and mixed with sodium nitrite and sulphuric acid, no magenta colour was obtained, but a yellow, flocculent precipitate was produced when the sulphuric acid was added in excess; if the sodium nitrite were omitted, a similar precipitate was obtained when sulphuric acid was added to the alkaline solution :

0·1002 gave 0·1442 CO₂ and 0·0334 H₂O. C = 39·24; H = 3·70.

0·1035 ,, 19·2 c.c. N₂ (moist) at 11·5° and 765 mm. N = 22·23.

This result would agree fairly well with a substance having the formula C₆H₇O₄N₃, which requires C = 38·91, H = 3·78, N = 22·70 per cent. It being difficult to account for the formation of a compound having the above empirical formula, attempts were made to purify the substance by further treatment with boiling water. The results of analysis after this further treatment were slightly different from those given above, namely, C = 39·33, H = 4·14, N = 21·77; these results would point to the substance being much more complex than was indicated by the first analysis, the simplest formula with which they are in agreement being C₂₁H₂₆O₁₄N₁₀.

An attempt was made to determine the molecular weight of the compound by the ebullioscopic method, using water as solvent. The value obtained for the molecular weight was, however, only 61, and even allowing for the possibility of dissociation, this result was far too low to agree with any of the possible formulæ. It was noticed that the solutions obtained were never perfectly clear, but always more or less opalescent, and it was therefore thought possible that the solution formed was of a colloidal nature. If such were the case it would account for the result obtained in the molecular-weight determination, and this view was supported by the fact that on the addition of ammonium sulphate to the solution an immediate precipitate was obtained, similar in character to those given by solutions of proteins.

The substance formed by the addition of sulphuric acid to the alkaline solution of the original compound also appeared to be

of a complex nature, the results of its analysis agreeing with an empirical formula of $C_9H_{13}O_9N_5$.

No suggestion as to the constitution of these substances can be given, as further experiments were rendered impossible by lack of material. It appears probable, however, that the substance composing the second fraction of the original product is a much more complex compound than those forming the other two fractions.

UNIVERSITY COLLEGE,
DUNDEE.
