ciently weakens the force of attraction for the second ion that it ionizes readily. The energy change for this rearrangement must be sufficiently large to more than offset the coulomb energy which would normally make the second sodium ion ionize with much less ease.

On the basis of these facts the following hypothesis is suggested. The two electrons furnished by the two sodium atoms are localized in the ion, on a carbon atom in a quinonoid ring. The two sodium ions are held closely to the negative charge, one on either side of the atom on which the electrons are localized. When one of the sodium ions leaves, the coulomb force of the single sodium ion then becomes too small to cause this localization of the electrons to continue. The pair of electrons then resonates among all of the various quinonoid structures which can be written for the molecule with the result that the effective size of the ion is greatly increased, the coulomb force weakened and the second sodium ionizes as though the salt were a strong electrolyte.

Referring now to the equilibrium data[13] we find what at first glance would appear to be a contradiction. One of the sodium atoms can be removed easily by shaking disodium tri-α-naphthylboron with an amalgam while the other sodium atom is removed only by shaking with a more dilute amalgam. This turns out not to be a contradiction, however, but is quite capable of being explained without modifying the above theory. If we are right in assuming that both electrons are located on the same atom and that they resonate together, then we would expect a large coulomb repulsion term on account of the proximity of the two negative charges. This would account for the difficulty of adding a second sodium atom to monosodium tri-α-naphthylboron. When we consider the process of ionization, however, we are not removing electrons and hence this coulomb term does not enter into the dissociation constants of the ions.

The theory which has just been outlined is in harmony with all of the observations which we have made on these compounds. It is of course desirable to have more data in order to test further the theory.

In a later communication the significance of the temperature coefficient of conductance will be considered. It is not unusual for weak electrolytes in non-aqueous solution to exhibit a negative coefficient.[14]

(13) Bent and Dorfman, *loc. cit.*

Summary

A simple method is described for measuring the specific resistance of non-aqueous solutions. This method has been used for specific resistances up to 5×10^{10} ohms.

The equivalent conductance for sodium triphenylboron and disodium tri-α-naphthylboron in ether solution has been determined at 0 and 25° and from 10^{-1} to 10^{-7} mole per liter.

The bearing of these results on the structure of disodium tri-α-naphthylboron is discussed.

(14) Kraus, "The Properties of Electrically Conducting Systems," Chemical Catalog Co., New York City, 1922, p. 144.

CAMBRIDGE, MASS. RECEIVED JUNE 4, 1935

[CONTRIBUTION OF THE CHEMICAL LABORATORIES OF THE RICE INSTITUTE]

Synthesis of Certain Pyridine Derivatives of Barbituric Acid

BY CARL SELLNER KUHN AND G. HOLMES RICHTER

The discovery of the substituted barbituric acids as hypnotics was followed by their administration in conjunction with various other drugs which enhanced their effectiveness. The analgesics and antipyretics are the most commonly used for this purpose. Since many of these drugs are basic, such as the alkaloids and other heterocyclic nitrogen compounds, they will form very definite "molecular compounds" with the acidic barbituric acid derivatives.

The effectiveness of drugs of this type suggests that the heterocyclic substituted barbituric acids would be interesting compounds. In contrast to the easy preparation of the molecular compounds or salts mentioned above, the introduction of a heterocyclic residue in the 5-position of barbituric acids presents a much more difficult problem, since the active halides and the aldehydes of this class of compounds are limited in number or are difficult to synthesize. A review of the

literature on barbituric acids of this type shows that pyrazole,[1,2,3] imidazole,[4] piperidine,[5] indole,[6] thiazole,[7] furan[8] and tetrahydrofuran[9] rings have been introduced into the molecule.

Our laboratory has succeeded in preparing four new barbituric acids all containing the pyridine nucleus. Pure β-picoline was brominated to give β-picolyl bromide; this was then condensed with a substituted malonic ester to give an alkyl-β-picolylmalonic ester. The malonic ester was then condensed with urea in the usual fashion to give the 5,5-disubstituted barbituric acids.

Several attempts were made to join the pyridine ring directly to malonic ester and barbituric acid. Notwithstanding reported easy reactions of α-bromopyridine with many reagents, we were unable to condense α-bromopyridine with malonic ester. An effort was made to obtain the pyridine malonic ester through a Ladenburg rearrangement by treating pyridine with brominated malonic esters in the presence of catalysts but the easy decomposition of the malonic esters prevented the success of the experiment.

Experimental Part

(1) β-Picoline.—The β-picoline required for the preparation of the β-picolyl bromide was made by the method of P. Schwarz,[10] and gives a product free from the α and γ isomers.

(2) β-Picolyl Bromide.—The preparation of this product by dissolving β-picoline in concentrated hydrochloric acid and brominating with two molecules of bromine at 150° is described by Dehnel.[11] The isolation of the bromide by treating the solution with sulfur dioxide, neutralizing with sodium carbonate, and extracting with ether must be carried out as rapidly as possible since the bromide may react with itself to give high molecular weight tars. β-Picolyl bromide is a lachrymator and a marked irritant for the skin, hence care must be taken in opening the sealed tubes and in handling the product.

(1) A. Meyer, *Compt. rend.*, **152**, 1677 (1911).
(2) A. Sonn and Litten, *Ber.*, **66B**, 1512 (1933).
(3) Räth and Gebauer, German Patent 589,146.
(4) Taggart and Richter, THIS JOURNAL, **55**, 1110 (1933).
(5) French Patent 776,449.
(6) Akabari, *J. Chem. Soc. Japan*, **52**, 601 (1931).
(7) Hooper and Johnston, THIS JOURNAL, **56**, 484 (1934).
(8) Kirner and Richter, *ibid.*, **51**, 3131 (1929).
(9) Dox and Jones, *ibid.*, **50**, 2033 (1928).
(10) Schwarz, *Ber.*, **24**, 1676 (1891).
(11) Dehnel, *ibid.*, **33**, 3496 (1900).

(3) Ethyl β-Picolylalkylmalonates.—β-Picolyl bromide was condensed with ethyl ethylmalonate, ethyl *n*-propylmalonate, ethyl *n*-butylmalonate and ethyl *n*-amylmalonate. Since the method of condensation and purification was the same in all cases it will be described only for ethyl ethylmalonate.

One and six-tenths grams of sodium was dissolved in 22 cc. of absolute alcohol placed in a two-necked 200-cc. flask fitted with a condenser and stirrer. The resulting solution of sodium ethylate was cooled to 50° and 13.2 g. of ethyl ethylmalonate added. The β-picolyl bromide, which must be prepared shortly before each reaction due to its unstable nature, was thoroughly dried over anhydrous magnesium sulfate in ether solution. The ether solution of the bromide was added as rapidly as possible, the ether being distilled off during the addition by heating on the steam-bath. The mixture was heated for an hour on the steam-bath to complete the reaction. At the end of the reaction the remainder of the ether and the alcohol were distilled off.

The oily liquid and sodium bromide were washed with water to remove the salt and the oily layer removed with ether and extracted with 15% hydrochloric acid to remove the picolylmalonic ester. This acid solution was subsequently made alkaline and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and distilled, about 2 g. of a viscous red oil remained which apparently started to boil when the temperature of the bath reached 145–150° but due to the small amount of material and the obvious decomposition, no further attempts were made to distil the product.

(4) 5-(β-Picolyl)-5-ethyl Barbituric Acid.—One and one-half grams of ethyl β-picolylethylmalonate, 0.62 g. of sodium, and 0.775 g. of urea were dissolved in 15 cc. of absolute alcohol in a Pyrex tube. The tube was sealed and heated with steam for twelve hours. At the end of this time the tube was opened and the contents washed in an evaporating dish, and the alcohol was removed on the hot-plate. The aqueous solution was carefully treated, dropwise addition, with 5% hydrochloric acid. At the turning point of congo red no precipitation took place, but when the solution was made slightly more acid an amorphous solid separated out of solution. This was recrystallized from 95% alcohol several times, yield 0.65 g.

The compound is soluble in dilute alkali and concentrated hydrochloric acid and warm alcohol; it is slightly soluble in hot water.

(5) 5-(β-Picolyl)-5-*n*-propylbarbituric Acid.—The synthesis of this material was carried out in the same manner as described for the picolylethylbarbituric acid. Four grams of the β-picolyl-*n*-propyl ethylmalonate gave 0.52 g. of the barbituric acid. It was recrystallized four times from 95% alcohol.

MELTING POINTS AND ANALYSES OF THE PRODUCTS

Name	M. p., °C.	Formula	% C Calcd.	% H Calcd.	% C Found	% H Found
5-(β-Picolyl)-5-ethylbarbituric acid	213–214	$C_{12}H_{13}O_3N_3$	58.28	5.30	58.80	5.71
5-(β-Picolyl)-5-*n*-propyl barbituric acid	250 dec.	$C_{13}H_{15}O_3N_3$	59.74	5.79	59.61	5.77
5-(β-Picolyl)-5-*n*-butyl barbituric acid	218–219	$C_{14}H_{17}O_3N_3$	61.06	6.23	61.73	6.81
5-(β-Picolyl)-5-*i*-amyl barbituric acid	229–230	$C_{15}H_{19}O_3N_3$	62.25	6.62	62.70	6.62

(6) **5-(β-Picolyl)-5-*n*-butylbarbituric Acid.**—The synthesis was essentially the same as for the lower homologs. Two and one-half grams of the substituted malonic ester gave 0.71 g. of the product when recrystallized three times from 95% alcohol.

(7) **5-(β-Picolyl)-5-isoamylbarbituric Acid.**—The method of preparation was the same as above. Four grams of the substituted malonic ester gave 1.4 g. of the product when recrystallized three times from alcohol.

Summary

1. The synthesis of four new heterocyclic derivatives of barbituric acid which contain the β-picolyl group in the 5-position is described.

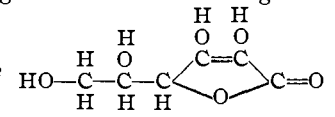
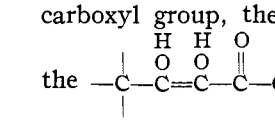
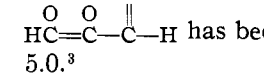
HOUSTON, TEXAS RECEIVED JUNE 22, 1935

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA AND THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

Titration Curves and Dissociation Constants of *l*-Ascorbic Acid (Vitamin C) and Diethyl Dihydroxymaleate

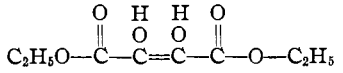
BY W. D. KUMLER AND T. C. DANIELS

Birch and Harris[1] using a micro method found the pK_a values of *l*-ascorbic acid at 16–18° to be pK_{a_1} = 4.17 and pK_{a_2} = 11.57. We have redetermined these constants at 22–23° using a macrohydrogen electrode and find values in agreement with theirs, namely, pK_{a_1} = 4.12 and pK_{a_2} = 11.51.

Although *l*-ascorbic acid is about four times as strong as acetic acid the generally accepted formula[2]  contains no carboxyl group, the acidity being attributed to the  grouping.[2] As evidence that a structure of this type may give rise to relatively strong acid properties the case of reductone (glucose-reductone, gluco-reductone)  has been cited[2] which has a pK_a = 5.0.[3]

Reductone is the enol form of a 1,3-dialdehyde and these compounds like the enol forms of 1,3-diketones are undoubtedly much stronger acids than the enol form of the β-ketonic esters to which type of compound the structure assigned to *l*-ascorbic acid belongs. The enol form of acetylacetone has a $K_{a_{enol.}}$ = 1.3 × 10^{-5} and the enol form of ethyl acetoacetate has a $K_{a_{enol.}}$ = 5 × 10^{-9}.[4] Thus for comparing acid strength reductone is not a correct analog of *l*-ascorbic acid.

We have measured the pK_a values of a β ketonic ester, diethyldihydroxymaleate



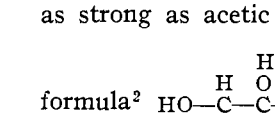
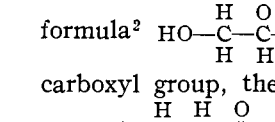
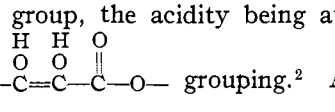
which contains the grouping  to which the acidity of *l*-ascorbic acid has been attributed[2] . Since the negativity of the  group is considerably greater than that of the  group and the ester has two equivalent hydrogens it should actually be a stronger acid than *l*-ascorbic. However, from the pK_a values in Table I it is seen that *l*-ascorbic is much the stronger acid, its first dissociation constant being 1000 times as great as that of the other compound.

TABLE I

ALCOHOL–WATER SOLUTION

	pK_{a_1}	pK_{a_2}
l-Ascorbic acid	4.85	12.0
Diethyl dihydroxymaleate	7.88	12.3
Dimethyl dihydroxymaleate	7.85	12.3
WATER		
l-Ascorbic acid	4.12	11.51

The second dissociation constants have very nearly the same value, and in both cases are un-

(1) Birch and Harris, *Biochem. J.*, **27**, 595 (1933).

(2) Herbert, Hirst, Percival, Reynolds, Smith, *J. Chem. Soc.*, 1270 (1933).

(3) Von Euler and Martins, *Ann.*, **505**, 73 (1933).

(4) Acetylacetone $K_a \approx 1.5 \times 10^{-6}$, ethyl acetoacetate $K_a = 2 \times 10^{-11}$ (Landolt–Börnstein), acetylacetone $K_{enolization} = 0.132$, ethyl-acetoacetate $K_{enolization} = 0.004$ (Rice, "Mechanism of Homogeneous Organic Reactions," Chemical Catalog Co., p. 92). The $K_{a_{enol.}}$ constants were calculated from the above K_a's by use of the equation

$$K_{a_{enol.}} = K_a \frac{(K_{enolization} + 1)}{K_{enolization}}$$