Summary

The dissociation constant of ammonia has been determined at intervals of 5° from 0 to 50° by electromotive force measurements of the extent of hydrolysis of the salt formed from ammonia and the weak acid potassium *p*-phenolsulfonate. The results were in good agreement with those obtained previously by another electromotive force method.

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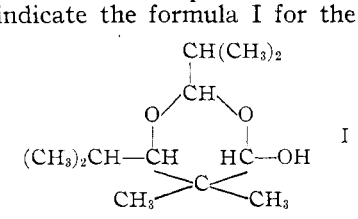
NOTES

The Trimer of Isobutyraldehyde

BY ELLIOT R. ALEXANDER AND ELLIOT N. MARVELL[1]

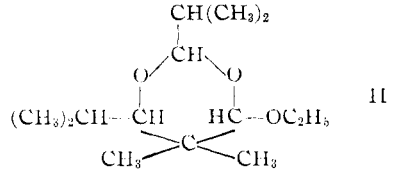
In an earlier communication,[2] Saunders, Murray and Cleveland have pointed out that Raman spectra indicate the formula I for the trimer of



I

isobutyraldehyde which is usually obtained by attempted aldolization. We have obtained additional chemical evidence in support of this formulation.

When the pure trimer was treated with ethyl orthoformate, a homogeneous product was obtained in good yield which did not react with metallic sodium and which did not discolor potassium permanganate or bromine in carbon tetrachloride solution. On long standing the liquid produced a weak color with a Fuchsin reagent but it gave negative tests with Fehling or Tollens solutions. Infrared analysis indicated that oxygen was present only in the form of ether linkages. These data, together with the correct analysis for carbon, hydrogen, ethoxyl groups, molecular weight and molecular refractivity, are in agreement with the formula II for our product.



II

Experimental[3]

Reaction of the Trimer of Isobutyraldehyde with Ethyl Orthoformate.—By the procedure used for the reaction of hydroxypivaldehyde with ethyl orthoformate,[4] 48.1 g. (0.222 mole) of the trimer of isobutyraldehyde[1] (b.p. 80° (1.0 mm.); $n^{20}D$ 1.4487) was treated with 45.0 g. (0.31 mole) of ethyl orthoformate. After distillation through an eight inch electrically heated column packed with glass helices, the product (42.0 g., 78%) was obtained as a homogeneous colorless liquid, b.p. 61° (1.5 mm.); $n^{20}D$ 1.4321; d^{20}_{20} 0.9162. This material did not react with metallic sodium, potassium permanganate or bromine in carbon tetrachloride solution. Fehling and Tollens tests were also negative. On long standing, the liquid produced a weak color with fuchsin reagent. Infrared analysis indicated that oxygen was present only in the form of ether linkages.[5] These properties are those to be expected of 2,4-diisopropyl-5,5-dimethyl-6-ethoxy-1,3-dioxane (II).

Anal.[6] Calcd. for $C_{14}H_{28}O_3$: C, 68.82; H, 11.53; ethoxyl, 18.40; mol. wt., 244; $M^{20}D$, 69.60. Found: C, 68.97; H, 11.56; ethoxyl, 18.59; mol. wt., 238; $M^{20}D$, 69.23.

(1) Present address: Oregon State College, Corvallis, Oregon.

(2) Saunders, Murray and Cleveland, THIS JOURNAL, **65**, 1714 (1943).

(3) All melting points and boiling points are uncorrected.

(4) Alexander and Marvell, THIS JOURNAL, **71**, 15 (1949).

(5) We are indebted to Dr. Foil A. Miller and Mrs. J. L. Johnson for the determination and interpretation of these spectra.

(6) The microanalyses were performed by Miss Theta Spoor and the Howard Clark Microanalytical Laboratories, Urbana, Illinois.

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Preparation of N-Acetyl-DL-amino Acids

BY NOEL F. ALBERTSON

It has been shown that acid hydrolysis of an alkylacetamidomalonic ester gives the amino acid as the end-product of the reaction, whereas hydrolysis with excess sodium hydroxide leads to the formation of the sodium salt of the alkylacetamidomalonic acid.[1,2] In the case of alkylacetamidocyanoacetic ester the end-product is the amino acid with either acid or caustic hydrolysis.[2,3] It has now been found that hydrolysis of an alkylacetamidomalonic ester with aqueous sodium carbonate leads directly to the sodium salt of the acetyl-DL-amino acid. The same results are obtained with the alkylacetamidocyanoacetic esters although the reaction time is longer. The method should prove generally useful for the preparation of N-acetyl-DL-amino acids. This procedure also affords a means of degrading alkylacetamidoma-

(1) Snyder and Smith, THIS JOURNAL, **66**, 350 (1944).

(2) Albertson, *ibid.*, **68**, 450 (1946).

(3) Albertson and Tullar, *ibid.*, **67**, 502 (1945).

lonic esters in basic media which may be of value with acid-sensitive intermediates.[4]

Experimental

Diethyl Isopropylacetamidomalonate.—This compound was prepared in 17% yield[5] by the usual alkylation procedure[2]; m.p. 74.5° from aqueous ethanol.

Anal. Calcd. for $C_{12}H_{21}NO_5$: N, 5.40. Found: N, 5.42.

Diethyl Thenylacetamidomalonate.—This compound has been reported by Dittmer, Herz and Chambers.[6] It was prepared independently in these laboratories.

Anal. Calcd. for $C_{14}H_{19}NO_5S$: S, 10.23. Found: S, 10.25.

Hydrolysis with aqueous sodium hydroxide and acidification with hydrochloric acid gave a 79% yield of the acetamidomalonic acid, m.p. 143.5–145° dec. The crude reaction product was analyzed after drying.

Anal. Calcd. for $C_{10}H_{11}NO_5S$: S, 12.46; neut. equiv., 257. Found: S, 12.48; neut. equiv., 253.

Hydrolysis of the malonic acid with dilute (1:10) hydrochloric acid gave a 60% yield of β-2-thienylalanine, m.p. 265.6–266.9° cor. (lit.,[6] m.p. 273°).

Anal. Calcd. for $C_7H_9NO_2S$: N, 8.18; S, 18.73. Found: N, 8.15; S, 18.88.

General Procedure for Hydrolysis.—The alkylacetamidomalonic esters were refluxed overnight (about sixteen hours) with an equal weight of sodium carbonate dissolved in ten volumes of water. The alkylacetamidocyanoacetic esters were refluxed until evolution of ammonia had practically ceased (usually about sixty hours). The solution was then cooled and acidified to congo paper with hydrochloric acid. The acetyl-DL-amino acid was collected by filtration and recrystallized from water or aqueous alcohol. The lower molecular weight compounds had a tendency to form supersaturated solutions and it was found advisable to obtain seeds from a small portion of the solution before acidifying all of the reaction product. The relatively low yield (52%) for acetyl-DL-norleucine was due to partial hydrolysis to the amino acid in the acidic solution before crystallization could be induced.

***n*-Butyl 2-Acetamido-4-pentenoate.**—Allylacetamidomalonate[2] (15.5 g.) was refluxed with sodium carbonate solution and acidified with hydrochloric acid according to the above procedure. The resulting solution was extracted several times with butanol, dried with sodium sulfate, filtered and distilled to give 9.0 g. of butyl ester; b.p. 118° at 1.1 mm. (70% over-all yield).

Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 60.61; H, 8.98; N, 6.58. Found: C, 60,76; H, 9.20; N, 6.53.

***n*-Propylacetamidomalonic Acid.**—In preparing a sample of N-acetyl-DL-norvaline for mixed m.p., the procedure of Snyder, Shekleton and Lewis[7] was followed, except that the acidified solution was cooled and filtered to give the malonic acid, m.p. 125–126° (dec.).

Anal. Calcd. for $C_8H_{13}NO_5$: neut. equiv., 102. Found: neut. equiv., 106.

Starting material RR′C(NHAc)COOEt R	R″	M. p. of acetyl-DL-amino acid, °C.	Yield, %	N Anal., % Calcd.	Obsd.
Isopropyl	COOEt	146[a]	72		
2-Methyl allyl[2]	COOEt	160	67	8.18	8.03[b]
n-Amyl[2]	COOEt	106	77	7.48	7.21
Benzyl[c]	COOEt	152[a]	75		
2-Thenyl[6]	COOEt	121	80	6.57	6.45[d]
n-Propyl[2]	CN	114[a]	69		
n-Butyl[2]	CN	104[e]	52		
n-Octyl[2]	CN	105	72	6.08	5.80
3-Indolemethyl[3]	CN	200[a]	81		

[a] Identity confirmed by mixed m.p. [b] *Anal.* Calcd. for $C_8H_{13}NO_5$: C, 56.12; H, 7.65. Found: C, 56.29; H, 7.48. [c] Albertson and Archer, THIS JOURNAL, 67, 308 (1945). [d] *Anal.* Calcd. for $C_9H_{11}NO_3S$: neut. equiv., 213. Found: neut. equiv., 212. [e] Identity confirmed by m.p. and analogy.

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(4) Herz, Dittmer and Cristol, *J. Biol. Chem.*, **171**, 383 (1947), report that furfuryl acetamidomalonate could not be hydrolyzed to β-2-furylalanine because of the instability of the intermediates to acids. In this case, carbonate hydrolysis followed by caustic hydrolysis would probably give the amino acid.

(5) It will be noted that although acetamidomalonic ester gives low yields on alkylation with secondary halides, acetamidocyanoacetic ester gives just as good results with secondary as with primary halides; *cf.* ref. 3.

(6) Dittmer, Herz and Chambers, *J. Biol. Chem.*, **166**, 541 (1946).

(7) Snyder, Shekleton and Lewis, THIS JOURNAL, **67**, 311 (1945).

Unsymmetrical Azo Compounds from Diazotized Amines

BY EDWARD R. ATKINSON, DONALD N. REYNOLDS AND DONALD M. MURPHY

The reduction of a mixture of diazotized anthranilic acid and diazotized 3,5-dichloro-2-aminobenzoic acid by cupro-ammonia ion produces the unsymmetrical biaryl 4,6-dichlorodiphenic acid along with the expected symmetrical biaryls.[1]

We have now examined the reduction of a mixture of diazotized anthranilic acid and diazotized aniline and find that in addition to the expected symmetrical products, diphenic acid and azobenzene, the only unsymmetrical product is an azo compound, azobenzene-2-carboxylic acid. It is apparent that the tendency to form an azo compound, which diazotized aniline exhibits, predominates over the tendency to form a biaryl shown by diazotized anthranilic acid. As in the earlier work the reaction is of no great interest as a synthetic method but again demonstrates that whatever the intermediates may be, they possess the ability of reacting with one another.

Experimental Part

Solutions of diazotized aniline and diazotized anthranilic acid were prepared, mixed and reduced by the general procedure previously described[1]; identical results were obtained from mixtures reduced immediately after preparation or after standing at 0° overnight.

Azobenzene was filtered from the ammoniacal reaction mixture and purified by steam distillation. The procedure used for the separation of the acidic products, diphenic acid and azobenzene-2-carboxylic acid, depended on their relative quantities. In cases where the quantity of diphenic acid was not too great, the ammoniacal reaction mixture was slowly acidified at 90° with hydrochloric acid. The azo acid collected as an oil which was removed mechanically while the diphenic acid was obtained by further acidification and cooling overnight. This process took advantage of the tendency of diphenic acid to form supersaturated solutions in water. In other cases it was necessary to obtain a mixture of crude acidic products by acidification with excess acid, dissolve the crude in dilute bicarbonate solution at room temperature, filter free from entrained copper salts and then slowly acidify the bicarbonate solution.

(1) Atkinson, Morgan, Warren and Manning, THIS JOURNAL, **67**, 1513 (1945).