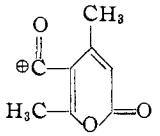
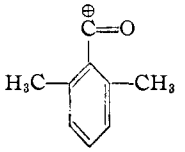
The fact that ethyl isodehydroacetate is not rapidly hydrolyzed and the acid not rapidly esterified in concentrated sulfuric acid provides an interesting basis for a preliminary comparison of the degree of resonance stabilization in the ion I with that in the 2,6-dimethylbenzoyl carbonium ion, II. 2,6-Di-



I



II

methylbenzoic acid is known to have a van't Hoff *i* factor of more than three in sulfuric acid[6] and this fact has been interpreted as due to partial dissociation into ions stabilized by resonance through electron-releasing characteristics of the two, one is not enough, ortho methyl groups. This effect has been used to explain the van't Hoff factor of nearly four in concentrated sulfuric acid and the ease of hydrolysis of ethyl 2,4,6-trimethylbenzoate in 100% sulfuric acid. That this effect is not necessarily steric is indicated by the fact that 2,4,6-tribromobenzoic acid is not rapidly esterified as is the corresponding trimethyl derivative.[7]

Apparently, the two ortho methyl groups in the pyrone do not contribute sufficiently to the resonance stabilization of the ion I to promote facile esterification and hydrolysis as observed in the 2,4-6-trimethylbenzoate types but one would not predict that the two methyl groups of the pyrone would produce the same ease of hydrolysis observed with ethyl trimethylbenzoate. Precise data are unavailable for comparing ease of hydrolysis or esterification or van't Hoff *i* factors of the *o,o'*-dimethyl-1,2-pyrone and the 2,6-dimethylbenzenecarboxylic acids. It appears likely, however, that such data will provide the basis for a quantitative comparison of the degree of resonance stabilization of the benzene and pyrone rings in concentrated sulfuric acid although it is recognized that the pyrone may exist as a conjugate acid or perhaps even undergoes reversible ring opening under these conditions. These, as well as data relating other heterocyclic types, are being obtained and will be reported in following papers.

Along with these studies, we have confirmed the saponification of isodehydroacetic ester to β-methylglutaconic acid[2,8] in 88% yield and observed that hydrolysis of ethyl 3-bromoisodehydroacetate is accompanied by decarboxylation with resultant formation of 3-bromo-4,6-dimethylpyrone and that hydrolysis of ethyl 3-nitroisodehydroacetate is accompanied by extensive decomposition.

Experimental

All melting points and boiling points are uncorrected.

Preparation of Isodehydroacetic Acid and Ester.—The general procedure previously described[3] was followed for the sulfuric acid condensation of ethyl acetoacetate to isodehydroacetic acid. Variations of this procedure are given in Tables I, II and III. The yields indicated therein are for isodehydroacetic acid, m.p. 155°, and ethyl isodehydroacetate boiling over a 5° range under reduced pressure except as noted. The following is a brief description of the procedure.

The sulfuric acid was cooled in an ice-bath and the acetoacetic ester added at a temperature of 10–15°. The reaction mixture was protected from atmospheric moisture and allowed to stand at the times and temperatures indicated. After pouring on ice, the products were extracted with ether and the isodehydroacetic acid separated by extracting the ether with sodium carbonate solution. Acidification with excess hydrochloric acid precipitated the crude acid, which was recrystallized from water. The ester was distilled under reduced pressure, after removal of the ether.

Attempts to use other acidic catalysts gave smaller yields of the condensation products. Using aluminum chloride, a 27.5% yield of ethyl isodehydroacetate alone was obtained, while boron trifluoride–etherate gave only a 20% yield of the ester.

Hydrolysis of Ethyl Isodehydroacetate.—The isodehydroacetic ester was hydrolyzed to isodehydroacetic acid by heating with 5 times its weight of concentrated sulfuric acid on a steam-bath for 4 to 5 hours. This was worked up to give a 40–50% yield of isodehydroacetic acid and a 20–30% recovery of the original ester. When the ester was dissolved in 100% sulfuric acid and poured onto ice after standing at room temperature, the original ester was recovered. No isodehydroacetic acid was detected.

Acid hydrolysis of 3-bromoisodehydroacetic acid ethyl ester,[2] produced a mixture consisting of 3-bromo-4,6-dimethylpyrone, m.p. 105°,[2] in 27% yield and 3-bromoisodehydroacetic acid, m.p. 160–2°,[9] in 11% yield. 3-Nitroisodehydroacetic ester under similar conditions underwent extensive decomposition from which no identifiable products were obtained.

Attempted Esterification and Hydrolysis at Room Temperature.—In order to determine whether the acid was formed from the ester or *vice versa*, in conditions used in the condensation, attempts to hydrolyze the ester at room temperature and to esterify the acid in concentrated sulfuric acid were made. When the ester was allowed to stand for 3 days in sulfuric acid at room temperature, 92% of the original ester was recovered and no acid detected. From a mixture of isodehydroacetic acid, ethanol and sulfuric acid there was obtained an 81% recovery of the acid and no ester.

(6) H. P. Treffers and L. P. Hammett, THIS JOURNAL, **59**, 1711 (1937).

(7) M. S. Newman, *ibid.*, **63**, 2432 (1941).

(8) R. P. Linstead and A. F. Millidge, *J. Chem. Soc.*, 486 (1936).

(9) F. Feist, *Ber.*, **26**, 754 (1893).

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Preparation of Acetyl-L-leucine and Acetyl-L-glutamic Acid

BY HANS WOLFF AND ARTHUR BERGER

The use of ketene as acetylating agent for α-amino acids was proposed by Bergmann and Stern,[1] who prepared N-acetyl-*dl*-leucine from *dl*-leucine by treating its water solution with ketene and N-acetyl-*l*-glutamic acid by passing ketene through an aqueous solution of sodium *l*-glutamate. Cahill and Burton[2] have claimed that acetylation of the active amino acids *l*-leucine and *l*-glutamic acid with ketene leads to complete racemization when carried out under acid conditions but that no racemization occurs as long as the solution is kept alkaline. The acidity obtained by the generation of acetic acid from ketene and water in excess of the alkali added to the reaction mixture was found to be sufficient to cause rapid racemization. Racemization occurs on acetylating α-amino acids with excess acetic anhydride in glacial acetic acid as reported by Bergmann and Zervas[3] and confirmed in our experiments.

(1) Bergmann and Stern, *Ber.*, **63**, 437 (1930).

(2) Cahill and Burton, *J. Biol. Chem.*, **132**, 161 (1940).

(3) Bergmann and Zervas, *Biochem. Z.*, **203**, 280 (1928).

We observed, however, that *l*-leucine and *l*-glutamic acid can be acetylated with ketene even under acid conditions and at reflux temperatures without causing complete racemization. These two amino acids can also be acetylated with acetic anhydride in aqueous acetic acid to give the active acetyl amino acids. These procedures appear practical for the preparation of acetyl-*l*-leucine and acetyl-*l*-glutamic acid since they eliminate a separation of salts from the acetylated amino acids and give yields of about 50% of the pure acetylated compounds. The purity of the compounds was proved by de-acetylating them with dilute hydrochloric acid to the original amino acids of unchanged rotation. This method cannot be considered generally applicable to all active amino acids since it was found that *l*-arginine racemizes completely and *l*-cystine decomposes as observed previously (3) when treated with ketene in water solution.

Experimental

N-Acetyl-l-leucine.—Pure *l*-leucine was prepared by recrystallization of its nasylate[4] until it had a constant melting point of 189–191° and a constant rotation of $[\alpha]^{25}D$ +12.84 (4% in ethanol). On decomposing the leucine nasylate in ethanol solution with ethanolamine, *l*-leucine was obtained which was recrystallized from water to a constant rotation of $[\alpha]^{25}D$ +14.7 (9% solution in 4.5 *N* hydrochloric acid); reported $[\alpha]^{24}D$ +15.33 (4), $[\alpha]^{21}D$ +16.5 in 20% HCl (2), $[\alpha]^{25}D$ +13.91 (9.075% in 4.5 *N* HCl).[5] A stream of ketene (0.44 mole/hr.) was passed through a solution of 19 g. of *l*-leucine in 1 l. of water until a Van Slyke determination showed practically no amino nitrogen (about 9 hours were required). The solution reached a temperature of 40–50° during the passage of the ketene. The *p*H of the final solution was 3.0, and titration showed the solution to have an acidity equal to 4 *N* acetic acid. After carbon treatment the solution was concentrated *in vacuo* with repeated additions of water to drive off acetic acid. A white precipitate was obtained, weighing 16 g. after washing and drying. This material on recrystallization from ethanol yielded 10.6 g. (44% of theoretical) of acetyl-*l*-leucine, m.p. 183–184°, $[\alpha]^{25}D$ −23.3 (3% in ethanol); reported $[\alpha]^{29}D$ −21.0 (3% in ethanol)[2] and $[\alpha]D^{29}$ −16.99.[6]

Anal. Calcd. for $C_8H_{15}O_3N$: N, 8.1; neut. equiv., 173.2. Found: N, 8.1; neut. equiv., 174.8.

Passing ketene into a water solution of *l*-leucine under reflux gave similar results. Hydrolysis with 5 *N* hydrochloric acid gave *l*-leucine hydrochloride from which *l*-leucine was obtained in 70% yield $[\alpha]^{25}D$ +14.8. Addition of 100 g. of acetic anhydride to 19 g. of *l*-leucine in 500 g. of 40% acetic acid with stirring at 60° and isolating as described above gave 16.2 g. (65% yield) of acetyl-*l*-leucine, $[\alpha]^{25}D$ −22.9. Repeating the acetylation as described above in the absence of water gave racemized acetylleucine.

N-Acetyl-l-glutamic Acid.—*l*-Glutamic acid, $[\alpha]^{25}D$ +31.6 (5% solution in 10% hydrochloric acid) was treated in aqueous solution with ketene as described for *l*-leucine. N-Acetyl-*l*-glutamic acid was isolated in 47% yield, m.p. 194–195°, $[\alpha]^{25}D$ −15.7 (3% in water), $[\alpha]^{25}D$ +3.97 (2% in 1 *N* sodium hydroxide); reported m.p. 198–199°,[1,2] 195°,[7] 195–197°[8] and $[\alpha]^{24.5}D$ +3.9 resp. 3.83 (2% solution in 1 *N* NaOH)[2,3] and $[\alpha]D$ −22.7 (in water).[8]

Anal. Calcd. for $C_7H_{11}O_5N$: N, 7.4; neut. equiv., 94.6. Found: N, 7.3; neut. equiv., 95.5.

Hydrolysis with 5 *N* hydrochloric acid gave 80% yield of *l*-glutamic acid $[\alpha]^{25}D$ +31.7 (5% solution in 10% hydrochloric acid). Acetylating 20 g. of *l*-glutamic acid in 500 ml. of 40% acetic acid with 100 ml. of acetic anhydride gave 14 g. (55%) of acetyl-*l*-glutamic acid of $[\alpha]^{25}D$ −15.4 (3% in water).

l-Arginine.—A solution of *l*-arginine in water was completely racemized after a stream of ketene was passed through the solution for several hours.

l-Cystine.—On passing ketene through a water solution of *l*-cystine a fine precipitate of sulfur was obtained.

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(4) Bergmann and Stein, *J. Biol. Chem.*, **129**, 609 (1939).
(5) Dunn and Rockland, *Advances in Protein Chem.*, **III**, 354 (1947).
(6) Cherbuliez, Plattner and Ariel, *Helv. Chim. Acta*, **13**, 1390 (1930).
(7) Karrer, Escher and Widmer, *Helv. Chim. Acta*, **9**, 301 (1926).
(8) Knoop and Oesterlin, *Hoppe-Seylers Z.*, **170**, 186 (1927).

The Preparation of Some Dialkylaminoalkylaldehydes

BY MILDRED YANDIK AND A. A. LARSEN

In the course of investigating compounds for analgesic activity two aminoaldehydes were prepared for screening. These compounds, 4-dimethylamino-2,2-diphenyl entanal and 4-dimethylamino-2,2-diphenyl-3-methylbutanal were obtained from the corresponding nitriles[1] by reduction with lithium aluminum hydride.[2] Isolation was somewhat complicated by the presence of the basic amino group in the molecule and in addition by the fact that distillation was of no benefit since the nitrile and aldehyde distill at the same temperature under reduced pressure. The presence of the quaternary carbon atom adjacent to the carbonyl group does not allow for the preparation of the more common aldehyde derivatives. Catalytic hydrogenation of the aldehydes resulted in the uptake of one mole of hydrogen and isolation of the corresponding alcohols.

Bockmühl[3] reported that 2,2-diphenyl-4-piperidinobutanal, prepared by Rosenmund reduction of the acid chloride hydrochloride, has about one-third the analgesic activity of methadone. Tests performed in this Laboratory under the direction of Dr. J. R. Lewis showed that 4-dimethylamino-2,2-diphenylpentanal has about one-fifth the activity of methadone, whereas 4-dimethylamino-2,2-diphenyl 3-methylbutanal is less active as an analgesic.

Experimental

4-Dimethylamino-2,2-diphenylpentanal Hydrochloride.—To a solution of 139 g. (0.5 mole) of 4-dimethylamino-2,2-diphenylbutanenitrile in 90 ml. of dry ether was added portionwise with stirring 5.5 g. (0.145 mole) of lithium aluminum hydride. After addition was complete the mixture was refluxed for four hours and left to stand overnight. After the addition of water, the gelatinous solid was removed by filtration and the ether layer extracted with dilute hydrochloric acid. The acid extract was washed with ether, made ammonical with concentrated ammonia and the free base extracted with ether. After drying, the ether solution was treated with alcoholic hydrogen chloride and the resultant oily solid was recrystallized from acetone–methanol to give 47 g. of aldehyde hydrochloride monohydrate, m.p. 122–124°. When dried in the vacuum oven at 100° for 96 hours the anhydrous hydrochloride was obtained, m.p. 187–189°.

Anal. Calcd. for $C_{19}H_{23}NO\cdot HCl$: C, 71.81; H, 7.61; N, 4.40; Cl, 11.15. Found: C, 71.74; H, 7.37; N, 4.41; Cl, 10.93.

Low pressure catalytic hydrogenation using platinum oxide, 1 g. of catalyst to 10 g. of aldehyde, gave 4-dimethylamino-2,2-diphenylpentanol hydrochloride,[4] m.p. 214–216°.

(1) E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL, **69**, 2456 (1947).
(2) L. Friedman, Abstracts 116th Meeting American Chemical Society, Atlantic City, N. J., 1949, p. 5M.
(3) M. Bockmühl and G. Ehrhart, *Ann.*, **561**, 75 (1948).
(4) M. E. Speeter, W. M. Byrd, L. C. Cheney and S. B. Binkley, THIS JOURNAL, **71**, 57 (1949).