[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY]

Ring Closure in the Tetronic Acid Series[1]

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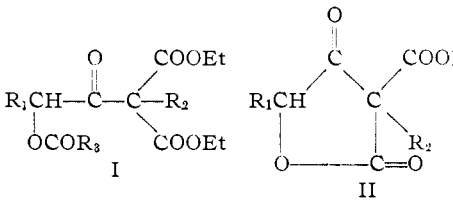
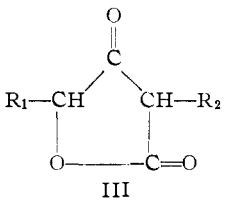
Cyclization of γ-acyloxy-β-ketoesters of type I *via* acyl–oxygen ester fission in 100% sulfuric acid at 5° results in the formation of α-carbethoxy derivatives (II) of various tetronic acids (III) when the solutions are poured onto chopped ice. This procedure very probably proceeds with retention of configuration about the γ-carbon atom. Structural proof is provided for a tetronic acid (III, R_1 = *t*-Bu, R_2 = Me) which fails to give a characteristic coloration with ferric chloride solution.

Tetronic acids (III) were first known in the early literature as synthetic products, but were later found to be formed from glucose by the molds *Penicillium charlesii* G. Smith[4] and *Penicillium terrestre* Jensen.[5] Degradation experiments have been presented as evidence for the structures of the six naturally occurring tetronic acids,[6] all of which show optical activity. The racemic forms of two



I

II



III

R_1	Me	Me	Me	*t*-Bu	*t*-Bu	*t*-Bu
R_2	Me	H	*n*-Bu	H	Me	Me
R_3	Me	Me	Me	Me	Me	2,4,6-Me_3Ph

of these acids, *viz.*, (±)-γ-methyltetronic acid[7] and (±)-carolinic acid,[8] have been synthesized by chemical means, but an attempt by Reuter and Welch[9] to resolve synthetic (±)-α-carbethoxy-γ-methyltetronic acid using strychnine was unsuccessful.

Our concern has been with the development of a method in which the formation of the tetronic acid ring system may be accomplished with retention of configuration about an asymmetric γ-carbon atom. We propose that cyclizations of γ-acyloxy-β-ketoesters in cold 100% sulfuric acid may fulfill this requirement. Experimental evidence will be presented which establishes the acceptability and utility of the sulfuric acid method for the synthesis of tetronic acids.

Among the procedures that are available for the preparation of tetronic acids is the method of Anschütz and Bertram,[10] in which an α-acetoxy acid halide is condensed directly with an excess of sodiomalonic diethyl ester and the cyclization carried out *in situ* to form the tetronic acid. The yields obtained in this manner are generally poor, but in some cases may be improved by using ethoxymagnesiomalonic diethyl ester in place of the usual sodio derivative.[8] Since the carbon-to-oxygen bond at the γ-position of the open chain intermediate probably breaks and forms again in the course of this cyclization, there is doubt as to whether this technique or similar routes in which the γ-position is occupied by halogen[11] would permit the retention of stereochemical integrity. Preservation of the carbon-to-oxygen bond in the γ-acyloxy case will occur when the ester group participates in fission of the acyl–oxygen type prior to, or concomitant with, ring closure. To accomplish this, we have made use of the fact that certain esters are known to undergo acylization upon solvolysis with sulfuric acid.

The synthesis of the neutral compound α,α-dimethyl-β-ketobutyrolactone was accomplished by Koelsch[12] in 86% yield by treating ethyl α,α-dimethyl-γ-acetoxyacetoacetate with ethanolic hydrogen chloride at the boil. This same reaction was later carried out by Reid, Fortenbaugh and Patterson[13] using a technique which forms the basis for the present method. Thus the product is obtained in comparable yield when the open chain ester is dissolved in cold concentrated sulfuric acid and the solution poured onto ice after standing for two days. This synthesis has also been carried out recently by heating the starting material with only a trace of sulfuric acid.[14]

It has now been found that a number of triesters of the type I, when dissolved in cold (5°) 100% sulfuric acid, undergo cyclization with the elimination of R_3COOEt to yield α-carbethoxy derivatives (II) of various tetronic acids (III) when poured onto chopped ice. In the cases R_1 = *t*-Bu, R_2 = Me and R_1 = Me, R_2 = H the intermediates II are not isolated due to spontaneous decarbethoxylation in the reaction medium. Survival of the α-carbethoxy group in 100% sulfuric acid may be explained by assuming that in these cases the esters have undergone simple cationization by way of proton attachment as described by Hantzsch.[15] Sulfuric

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(4) P. W. Clutterbuck W. N. Haworth, H. Raistrick, G. Smith and M. Stacey, *Biochem. J.*, **28**, 94 (1934).

(5) J. H. Birkinshaw and H. Raistrick, *ibid.*, **30**, 2194 (1936).

(6) P. W. Clutterbuck, H. Raistrick and F. Reuter, *ibid.*, **29**, 300 (1935).

(7) E. Benary, *Ber.*, **44**, 1759 (1911).

(8) L. J. Haynes, J. R. Plimmer and A. H. Stanners, *J. Chem. Soc.*, 4661 (1956).

(9) F. Reuter and R. B. Welch, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 120 (1938).

(10) R. Anschütz and W. Bertram, *Ber.*, **36**, 468 (1903).

(11) E. Benary, *ibid.*, **40**, 1079 (1907).

(12) C. F. Koelsch, THIS JOURNAL, **66**, 306 (1944).

(13) E. B. Reid, R. B. Fortenbaugh and H. R. Patterson, *J. Org. Chem.*, **15**, 572 (1950).

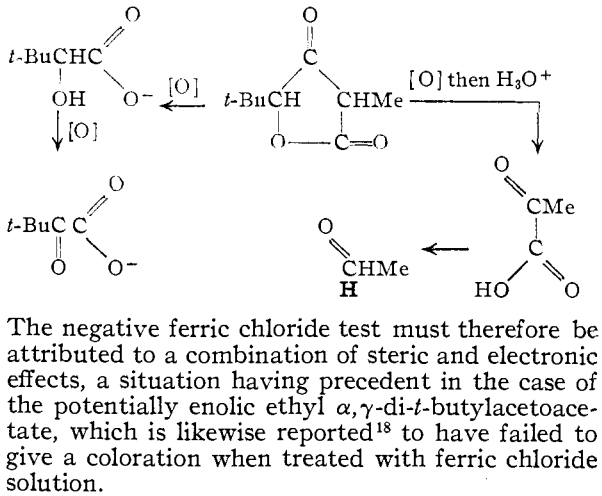
(14) W. N. Cannon and R. G. Jones, *ibid.*, **23**, 126 (1958).

(15) A. Hantzsch, *Z. physik. Chem.*, **61**, 257 (1908).

acid solutions of esters that ionize in this manner yield the unchanged ester when poured onto ice. It is evident from the wide variation in results obtained in the decarbethoxylation step that the mode of ionization of the carbethoxy groups is sensitive to the characteristics of the substituents R_1 and R_2. Removal of the carbethoxy group from compounds of type II is readily accomplished by the use of dilute acid.

Evidence that acyl–oxygen fission does occur at the γ-acyloxy group is provided by the alteration of 2,4,6-trimethylphenyl and methyl for R_3 in the case R_1 = *t*-Bu, R_2 = Me. Cyclization in sulfuric acid yielded the same tetronic acid in both instances. Thus, following the observation that methyl 2,4,6-trimethylbenzoate undergoes acylization upon solvolysis with sulfuric acid,[16] one can conclude that there has been no disruption of the linkage in question during the transformation I to II.

The tetronic acid (III, R_1 = *t*-Bu, R_2 = Me) was previously synthesized by the pyrolysis of ethyl β - keto - γ - bromo - α,δ,δ- trimethylhexanoate.[17] The product is identical with material obtained by the present method, clearly indicating the absence of a neopentyl rearrangement in the earlier experiment. The importance of the structure of this acid to our present argument, along with the anomalous failure of our product to give the coloration with ferric chloride which is typical of all other known tetronic acids, required that the structure of this acid be established beyond question. Confirmation was obtained by means of molecular weight determinations, oxidative degradation under alkaline conditions, bromination, methylation, attempted hydrogenation and attempted ozonolysis. Molecular weight results corresponded to the value for the proposed structure, and oxidation with alkaline permanganate gave the expected products, trimethyllactic acid, trimethylpyruvic acid and acetaldehyde, in accord with the scheme shown below. Bromination and methylation led to the expected product in each case.



The negative ferric chloride test must therefore be attributed to a combination of steric and electronic effects, a situation having precedent in the case of the potentially enolic ethyl α,γ-di-*t*-butylacetoacetate, which is likewise reported[18] to have failed to give a coloration when treated with ferric chloride solution.

(16) H. P. Treffers and L. P. Hammett, THIS JOURNAL, **59**, 1708 (1937).

(17) E. B. Reid and R. B. Fortenbaugh, *J. Org. Chem.*, **16**, 33 (1951).

(18) M. A. Spielman and M. T. Schmidt, THIS JOURNAL, **59**, 2009 (1937).

Experimental

(A) **α,γ-Dimethyltetronic Acid** (III, R_1 = R_2 = Me). (1) **Methyl-(α-acetoxypropionyl)-diethyl Malonate.**—α-Acetoxypropionic acid was prepared from lactic acid and acetyl chloride in 59% yield,[9] b.p. 125–132° (12 mm.), $n^{27}D$ 1.4213, and treated with purified thionyl chloride to give 65% of α-acetoxypropionyl chloride, b.p. 48–50° (10 mm.), $n^{27}D$ 1.4191; anilide m.p. 121–122° (literature[19] b.p. 56° (11 mm.), anilide m.p. 121–122°). To 27.0 grams (0.180 mole) of this acid chloride was added a slurry of 0.197 mole of sodio monomethylmalonic diethyl ester in 150 ml. of dry ether. The reaction mixture was stirred and refluxed for 24 hours, then washed first with 50 ml. of 10% HCl, and then with three 25-ml. portions of 5% $NaHCO_3$ solution. After drying over Na_2SO_4 and removal of the ether, distillation gave 25.3 g. (50%) of the triester, b.p. 125–128° (1.0 mm.), $n^{25.5}D$ 1.4328. *Anal.*[20] Calcd. for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99. Found: C, 54.02; H, 6.85.

(2) **α-Carbethoxy-α,γ-dimethyl-β-ketobutyrolactone.**—In this step, 8.9 g. (30.8 millimoles) of the product from above was added dropwise, with stirring, to 50 g. of 100% sulfuric acid, the temperature of which was maintained below 5° throughout the addition. The mixture was kept cold for four days, during which time bubbling was not observed, then poured onto 75 g. of chopped ice. The distinctive odor of ethyl acetate was detected at this point. The product was continuously extracted with ether for 24 hours. The ether layer was washed with 5% $NaHCO_3$ solution, dried with Na_2SO_4, evaporated, and the residue distilled to give 2.72 g. (44%) of a clear oil, b.p. 77.5–81.0° (0.3 mm.), $n^{25}D$ 1.4421. *Anal.*[20] Calcd. for $C_9H_{12}O_5$: C, 54.00; H, 6.04; OEt, 22.5. Found: C, 54.46; H, 6.39; OEt, 22.4.

(3) **α,γ-Dimethyltetronic Acid.**—Four hundred milligrams (2.0 millimoles) of the above lactone was added dropwise to 3 ml. of 12 *M* sulfuric acid. This was warmed for one hour, then poured onto 10 g. of chopped ice, and extracted with ether to give 170 mg. (67%) of impure crystals. Vacuum sublimation (100° (20 μ)) gave material having m.p. and mixed m.p. with authentic[13] α,γ-dimethyltetronic acid: 122.5–124.5°.

(B) **γ-Methyltetronic Acid.** (1) **α-Acetoxypropionyldiethyl Malonate.**—A slurry consisting of 0.29 mole of sodiomalonic diethyl ester in 200 ml. of dry ether was added to 45 g. (0.30 mole) of α-acetoxypropionyl chloride. This gave 27.7 g. (34%) of product having b.p. 161–165° (0.1 mm.), $n^{25}D$ 1.4540. *Anal.*[20] Calcd. for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.68; H, 6.32.

(2) **γ-Methyltetronic Acid.**—In this experiment vigorous decarbethoxylation prevented the isolation of the known[9] α-carbethoxy intermediate. Ten grams (36.4 millimoles) of α-acetoxypropionyldiethyl malonate was added dropwise to 50 g. of stirred 100% sulfuric acid at 5°. Vigorous effervescence was apparent immediately. After seven days in the cold room the contents of the flask was poured onto 75 g. of chopped ice. This was extracted with ether, after which the ether layer was shaken with 5% $NaHCO_3$ solution. Acidification and extraction of the aqueous layer gave 290 mg. (7%) of a solid, which after sublimation *in vacuo* had m.p. and mixed m.p. with authentic γ-methyltetronic acid[13] of 116–118°.

(C) **α-*n*-Butyl-γ-methyltetronic Acid** (III, R_1 = Me, R_2 = *n*-Bu). (1) ***n*-Butyl-(α-acetoxypropionyl)-diethyl Malonate.**—A slurry of 0.73 mole of sodiomono-*n*-butylmalonic diethyl ester in 400 ml. of dry ether was added dropwise to 110 g. (0.73 mole) of α-acetoxypropionyl chloride. This gave 141 g. (58%) of product having b.p. 118.5–123.0° (0.3 mm.), $n^{25}D$ 1.4408. The analytical sample had b.p. 123° (0.3 mm.), $n^{25}D$ 1.4402.

Anal.[20] Calcd. for $C_{16}H_{26}O_7$: C, 58.16; H, 7.93. Found: C, 58.07; H, 7.77.

(2) **α-Carbethoxy-α-*n*-butyl-γ-methyl-β-ketobutyrolactone.**—One-hundred grams of the triester from above was cyclized in 400 g. of 100% sulfuric acid. After one hour the mixture was poured onto 1 kg. of chopped ice. Extraction with ether and distillation gave 45.3 g. (61%) of the lactone, b.p. 106.0–107.5° (0.11 mm.), $n^{25}D$ 1.4429. The analytical sample had b.p. 106–108° (0.90 mm.), $n^{25}D$ 1.447.

(19) R. Anschütz and W. Bertram, *Ber.*, **37**, 3972 (1904).

(20) Carbon and hydrogen microdetermination by Drs. Weiler and Strauss, Oxford, England.

Anal.[20] Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.71; H, 7.74.

(3) **α-n-Butyl-γ-methyltetronic Acid.**—A portion of the lactone from above weighing 35.2 g. (0.149 mole) was added to 160 g. of 100% sulfuric acid. When addition was complete, enough cracked ice was added to the rapidly stirred solution to bring about effervescence. After three days of mechanical shaking, the solution was poured onto 360 g. of chopped ice and extracted with chloroform. The organic layer was then washed three times with water and extracted with 5% $NaHCO_3$ solution. Acidification and ether extraction gave 14.5 g. (57%) of a white solid. Purification was accomplished by freezing the solid from twice the minimum volume of acetone using a Dry Ice–acetone cooling bath. The product melts at 66–68° and gives a purple coloration with ferric chloride solution.

Anal.[20] Calcd. for $C_9H_{14}O_3$: C, 63.50; H, 8.29. Found: C, 62.40; H, 8.40.

(D) **γ-t-Butyltetronic Acid** (III, R_1 = *t*-Bu, R_2 = H). (1) **Trimethyllactic Acid.**—Seventy-five grams (0.57 mole) of trimethylpyruvic acid, prepared according to Richard,[21] was dissolved in 60 g. of glacial acetic acid and hydrogenated at a pressure of one atmosphere using 0.1 g. of Adams catalyst (PtO_2). The product (80% yield) may be distilled directly (b.p. 134–136° (17 mm.) or crystallized as colorless octahedra from a mixture of four parts of petroleum ether to one part of ether, m.p. 85.5–86.5° (literature[21] m.p. 90°).

(2) **α-Acetoxy-β,β-dimethylbutyric Acid.**—Acetylation of 41.4 g. (0.31 mole) of trimethyllactic acid was accomplished with 67.5 g. (0.86 mole) of acetyl chloride. After standing for one hour, the excess reagent was removed to give a semi-solid mass. A sample of this was purified by recrystallization from petroleum ether. White crystals were obtained, m.p. 70–71°. *Anal.* Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.08, 55.09; H, 8.27, 7.92.

(3) **α-Acetoxy-β,β-dimethylbutyryl Chloride.**—The crude product from above was covered with 125 g. (1.08 moles) of thionyl chloride and refluxed for two hours, after which the excess was removed and the product distilled through a 10-inch Vigreux column, b.p. 68.5–69.5° (6 mm.), yield 67% (based on trimethyllactic acid), $n^{25}D$ 1.4311. *Anal.* Calcd. for $C_8H_{13}O_3Cl$: Cl, 18.41. Found: Cl, 18.10, 18.66.

Five hundred milligrams of the acid chloride was dropped into 10 ml. of water and allowed to hydrolyze spontaneously. White crystals separated after one minute. These were crystallized from petroleum ether: m.p. and mixed m.p. with the parent acid, 70–71°.

(4) **(α-Acetoxy-β,β-dimethylbutyryl)-diethyl malonate.**—Sodiomalonic diethyl ester (0.19 mole) was added to 34.2 g. (0.18 mole) of α-acetoxy-β,β-dimethylbutyryl chloride. Distillation gave 21.9 g. (38%) of material, b.p. 136–181° (0.3–0.6 mm.); analytical sample: b.p. 136–138° (0.30 mm.), $n^{25}D$ 1.4425. *Anal.*[20] Calcd. for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 57.46; H, 7.64.

(5) **α-Carbethoxy-γ-t-butyltetronic Acid.**—A portion of the condensation product from above weighing 13.3 g. (42.0 millimoles) was cyclized in 114 g. of sulfuric acid. After three days the reaction mixture was poured onto 130 g. of chopped ice and allowed to stand in the ice-box for two additional days. A white solid separated (5.8 g., 60%) which was then dissolved in 5% $NaHCO_3$ solution, filtered, and reprecipitated by the dropwise addition of concentrated sulfuric acid. After crystallization from methanol–water the product had a melting point of 108.0–109.0°. A solution of the acid in ethanol gave an orange solid upon treatment with ferric chloride solution. *Anal.*[20] Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.08; OEt, 19.7. Found: C, 57.79; H, 6.90; OEt, 19.9.

(6) **γ-t-Butyltetronic Acid.**—One gram (4.38 millimoles) of the α-carbethoxy compound from above was refluxed for 3.5 hours with 6 ml. of 12 *M* sulfuric acid. Upon cooling and dilution with water 200 mg. (29%) of γ-*t*-butyltetronic acid, m.p. 143–144° (from ethanol–water), was obtained. Zeisel determination showed the absence of alkoxyl groups. With ferric chloride solution a barely perceptible amber coloration was observed. *Anal.*[20] Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.66; H, 7.63.

(E) **α-Methyl-γ-t-butyltetronic Acid** (III, R_1 = *t*-Bu, R_2 = Me). (1) **Synthesis from Tri-ester I Having R_3 = Me.** (a) **Methyl-(α-acetoxy-β,β-dimethylbutyryl)-diethyl Malonate.**—A slurry of 0.19 mole of sodiomonomethylmalonic diethyl ester in 75 ml. of dry ether was added dropwise to 38.6 g. (0.20 mole) of α-acetoxy-β,β-dimethylbutyryl chloride over a period of three hours. After standing overnight, the mixture was refluxed for five hours to bring the reaction to completion. This gave 43.6 g. (68%) of a viscous oil having b.p. 130–137° (2.5 mm.). A small fraction having b.p. 147–148° (4 mm.), $n^{25}D$ 1.4422, was saved for analysis. *Anal.* Calcd. for $C_{16}H_{26}O_7$: C, 58.17; H, 7.93; OEt, 27.3. Found: C, 58.26, 57.88; H, 7.78, 7.81; OEt, 26.9.

(b) **α-Methyl-γ-t-butyltetronic Acid.**—Ten grams of the triester from above was cyclized in 40 g. of sulfuric acid. The gas which was seen to evolve was shown to be carbon dioxide by the fact that it formed a white precipitate when passed through barium hydroxide solution. Upon pouring onto 100 g. of chopped ice a white solid was obtained which was crystallized from chloroform to give 5.0 g. (97%) of a powder. The melting point and mixed melting point with the same acid prepared[13] by the pyrolysis of ethyl β-keto-γ-bromo-α,δ,δ-trimethylhexanoate was 186–187°. *Anal.*[20] Calcd. for $C_9H_{14}O_3$: C, 63.50; H, 8.29; mol. wt., 170.2. Found: C, 63.45; H, 8.32; mol. wt., Rast method,[22] 195, 192, 196 (in camphor); mol. wt., Signer method,[23] 152 (in ethyl acetate using α,γ-dimethyltetronic acid as the control); mol. wt., ebullioscopic,[24] 172.5 (in chloroform).

(2) **Synthesis from Tri-ester I Having R_3 = 2,4,6-Me_3Ph.** (a) **α-Mesitoöxy-β,β-dimethylbutyryl Chloride.**—A portion of α-mesitoöxy-β,β-dimethylbutyric acid,[25] m.p. 130–131° (from boiling ligroin (*Anal.*[26] Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.94. Found: C, 69.07; H, 7.98)) weighing 7.1 g. (0.025 mole) was treated with 6.8 ml. (0.94 mole) of thionyl chloride by refluxing for two hours. The excess reagent was removed *in vacuo* and the product was used in the next step without further purification.

(b) **Methyl-(α-mesitoöxy-β,β-dimethylbutyryl)-diethyl Malonate.**—Sodiomonomethylmalonic diethyl ester (0.04 mole) in 40 ml. of ether was added slowly, with stirring, to the acid chloride from above. After refluxing for seven hours the yield was 9 g. (83% based on the carboxylic acid) of a brownish-yellow oil. Recrystallization from ethanol–water and from petroleum ether gave large white crystals, m.p. 66.0–67.5°. *Anal.* Calcd. for $C_{24}H_{34}O_7$: C, 66.34; H, 7.87; OEt, 20.7. Found: C, 66.50, 67.62; H, 7.74, 7.71; OEt, 20.5.

(c) **α-Methyl-γ-t-butyltetronic Acid.**—Five hundred milligrams of the mesitoate triester was cyclized and decarbethoxylated in 3.6 g. of sulfuric acid. After nine days, pouring onto 9 g. of ice gave 150 mg. (79%) of material which was crystallized first from ethanol–water and then from chloroform. Mixture m.p. showed it to be identical with the material obtained in the previous run where R_3 = Me.

(F) **Proof of Structure for III, R_1 = *t*-Bu, R_2 = Me.** (1) **Oxidative Degradation.**—A sample of the acid weighing 10.0 g. (58.7 millimoles) was dissolved in 133 ml. of 5% $NaHCO_3$ solution and placed in a flask fitted with a tube for sweeping with nitrogen, a dropping funnel, and a Friedrichs condenser, the exit tube of which was arranged so that the effluent gases could be passed through 2,4-dinitrophenylhydrazine reagent.[27]

An oxidizing solution consisting of 36.6 g. of potassium permanganate and 180 g. of sodium carbonate in 1700 ml. of water was added dropwise, while sweeping and stirring, over a 3-hour period. The brown color of manganese dioxide was in evidence from the start. After 24 hours, the derivatizing solution showed no solid, whereupon the suspension in the reaction vessel was filtered and the clear filtrate returned to the reaction flask. Ethanol extraction of the brown solid residue yielded only inorganic material.

The aqueous filtrate was then refluxed, while sweeping with nitrogen for one hour. This led to the formation of an orange solid in the 2,4-dinitrophenylhydrazine reagent. This material, upon recrystallization from aqueous ethanol,

(21) A. Richard, *Ann. chim. phys.*, [8] **21**, 360 (1910).

(22) Determination by Drs. Weiler and Strauss, Oxford, England.

(23) R. Signer, *Ann.*, **478**, 260 (1930). We are indebted to Professor A. H. Corwin for the loan of the apparatus used in this determination.

(24) We are grateful to Dr. J. W. Ogilvie for this determination.

(25) E. B. Reid and A. W. Lutz, Unpublished Work, The Johns Hopkins University.

(26) Microdetermination by Mr. Joseph Walter, The Johns Hopkins University.

(27) C. F. H. Allen, THIS JOURNAL, **52**, 2957 (1930).

gave a melting point and mixed melting point with authentic acetaldehyde 2,4-dinitrophenylhydrazone of 167–168°. The refluxing reaction mixture was allowed to distil slowly at atmospheric pressure into a receiver. The distillate (1830 ml.) was extracted with ether to give 1.2 g. of an oil upon evaporation. This was eventually combined with the main batch of oil obtained below.

The degraded material remaining in the pot was acidified by the dropwise addition, with stirring, of 400 ml. of concentrated hydrochloric acid. Overnight sweeping produced no additional solid in the derivatizing solution. The acidic ether was washed with water, and the washings brought to *p*H 7 and re-extracted. The combined ether layers were dried with Na_2SO_4 and evaporated to give an oil weighing 12.4 g. This oil was combined with that obtained from the extraction of the aqueous distillate above and distilled through a micro-still: cut 1, 1.5 g., b.p. 79–81° (20 mm.), $n^{25}D$ 1.4182; cut 2, 2.2 g., b.p. 81–86° (20 mm.), $n^{25}D$ 1.4172. Values obtained for authentic trimethylpyruvic acid under the same conditions are: b.p. 84–85° (20 mm.), $n^{26}D$ 1.4168. Samples of the fractions solidified when allowed to stand exposed to the atmosphere, as did trimethylpyruvic acid. When heated with 2,4-dinitrophenylhydrazine and sulfuric acid in ethanol, the fractions gave ethyl trimethylpyruvate 2,4-dinitrophenylhydrazone, identical with material obtained under the same conditions from authentic trimethylpyruvic acid: fine canary yellow needles (from alcohol–water), m.p. 163–164°, in agreement with the literature.[28] The distillation pot residue was a brown solid, which upon recrystallization from a 4:1 mixture of petroleum ether–ether was found to be trimethyllactic acid, m.p. and mixed m.p. 86–87°.

(2) **Bromination.** (a) **In Ethanol.**—Two grams (11.8 millimoles) of the same acid examined above was dissolved in 10 ml. of ethanol and monobrominated by the rapid addition of 23.3 ml. of 5% bromine in carbon tetrachloride (11.8 millimoles of Br_2). After 0.5 hour the discharge of the bromine color was almost complete. Solvent removal was accompanied by the evolution of hydrogen bromide, as detected by moist blue litmus paper. The oily residue was distilled: cut 1, 0.9 g., b.p. 78–81° (0.3 mm.); cut 2, 1.1 g., b.p. 81–83° (0.3 mm.). Both fractions solidified upon standing overnight. These were combined and recrystallized from 95% ethanol, m.p. 56–57°. The monobromide is insoluble in water, but dissolves with slight effervescence in 5% $NaHCO_3$ solution. *Anal.*[22] Calcd. for $C_9H_{13}O_3Br$: C, 43.39; H, 5.26; Br, 32.08. Found: C, 43.41; H, 5.17; Br, 32.33.

(b) **In Chloroform.**—One gram (5.9 millimoles) of the acid in 180 ml. of purified chloroform at ice temperature was treated rapidly with 1.0 g. (6.3 millimoles) of bromine in 10 ml. of chloroform. After two days at room temperature the color of the bromine was not discharged. Evaporation without heating gave a solid and a yellow liquid. The solid was sublimed (5 hours, 110°, 50 μ) to give m.p. and mixed m.p. with starting material of 185–187°. The liquid, upon distillation (b.p. 50° (80 μ)), gave four drops of an oil which solidified on standing. Recrystallization from ethanol gave crystals which did not depress the melting point of the monobromide obtained by bromination in ethanol.

(3) **Methylation.**—Slightly moist diazomethane in 50 ml. of ether from 42 millimoles of N-nitrosomethylurea[29] was added to a solution of 2.04 g. (12 millimoles) of the acid in a mixture of 50 ml. of ether and 8 ml. of absolute methanol. After standing for one hour the yellow color had disappeared. The solution was washed with 5% $NaHCO_3$ solution; the washings yielding no solid upon acidification. This was followed by further washing with 10% hydrochloric acid, then with water until the washings were neutral. The average yield of methylated acid from two identical runs was 48%. Distillation gave 1.5 g. of the methyl ether, b.p. 78.6–81.0° (0.16 mm.), $n^{25}D$ 1.4685. *Anal.*[20] Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76; OMe, 16.8. Found: C, 64.39; H, 8.96; OMe, 17.2. The product reverted to starting material after one month as shown by recrystallization and mixed m.p. determination.

For comparison with the above results, α-ethyltetronic acid was methylated. Diazomethane from 0.101 mole of N-nitrosomethylurea in 125 ml. of ether was poured into a cold solution of 4.0 g. (31.2 millimoles) of α-ethyltetronic acid[13] dissolved in a mixture of 50 ml. of ether and 5 ml. of methanol. The color of the diazomethane was discharged after 15 minutes. Extraction and washing as before, followed by distillation, gave 700 mg. (18%) of the methyl ether of α-ethyltetronic acid, b.p. 75–79° (60 μ), $n^{25}D$ 1.4833. *Anal.* Calcd. for $C_7H_{10}O_3$: OMe, 21.9. Found: OMe, 20.1. On standing, a solid was obtained which did not depress the melting point of the parent acid.

(4) **Attempted Hydrogenation.**—No uptake of hydrogen gas was observed in 12 hours at atmospheric pressure when a solution of the acid in glacial acetic acid was shaken with Adams catalyst. Starting material was recovered.

(5) **Attempted Ozonolysis.**—A sample of the methyl ether of the acid was dissolved in ethyl acetate and treated with ozone from a discharge generator for four hours. Attempted hydrogenation of the product at atmospheric pressure using $Pd(OH)_2$ on $CaCO_3$ gave no discernible pressure drop after shaking for 10 hours. Starting material was reclaimed.

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[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN & PHARMACEUTICAL CORP.]

Hypoglycemic Agents. IV.[1–3] N^1,N^5-Alkyl- and Aralkylbiguanides

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A series of N^1,N^5-substituted biguanides have been prepared by condensation of the amine hydrochloride, $R_1R_2NH\cdot HCl$, with the R_3R_4-substituted dicyandiamide. Reversal of the substituents on the initial reactants afforded the same biguanide. A greater bulk or number of substituents on the biguanide was associated with the formation of monopicrates rather than dipicrates and has been interpreted as restricting hydrogen bond formation and failure to afford the cyclic cation I. Hypoglycemic effects with these biguanides are noted, particularly when N^5-methyl or N^5-dimethyl substituents are introduced in physiologically active N^1-substituted biguanides.

In proposing the intramolecular hydrogen-bonded, six-membered ring structure (I)[1,3] for β-phenethylbiguanide and related N^1-substituted biguanides, several assumptions had been made.[4] With N^1,N^5-

(1) S. L. Shapiro, V. A. Parrino and L. Freedman, THIS JOURNAL, **81**, 2220 (1959).

(2) S. L. Shapiro, V. A. Parrino, E. Rogow and L. Freedman, *ibid.*, **81**, 3725 (1959).

(3) S. L. Shapiro, V. A. Parrino and L. Freedman, *ibid.*, **81**, 3996 (1959).

(4) Assuming that within this series, peak hypoglycemic activity would be associated with similar molecular forms of the active species, the noted activity wherein R_1 and R_2 are hydrocarbon radicals requires that the N^2 of the biguanide be an imino nitrogen. Indications for a conjugated double bond system[1] complete the bond distribution pattern as shown for I, with the four hydrogen atoms at the N^4 and N^5