[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

THE OXIDATION OF TETRONIC ACIDS. II. ABSENCE OF REARRANGEMENT IN THE NEOPENTYL SYSTEM DURING DECARBOXYLATION

EVANS B. REID AND ROBERT B. FORTENBAUGH[1]

Received June 28, 1950

It was established in a previous communication (1) that acid oxidation of tetronic acids which are monosubstituted at the 3-position (I) gives rise to α-diketones (III), in accordance with the rule that oxidation occurs at the 3-position and reduction at the 5-position, with simultaneous decarboxylation. Circumstantial evidence was presented (1) which pointed to the intermediacy of a 3-hydroxytetronic acid (II) in this oxidation reaction. The problem which thus arises concerns the mechanism whereby carbon dioxide is eliminated from this 3-hydroxytetronic acid (II), with formation of the α-diketone (III).

Three mechanisms are possible, and these may be adumbrated as follows. First, decarboxylation may occur through an intermediate diradical (IV), which, by hydrogen exchange with water molecules, would lead to the diketone (III). Second, an *ionic* intermediate (V) might be involved, and this could undergo decarboxylation by two paths. Path A represents a heterolytic bond rupture to form VI, which, on loss of carbon dioxide would furnish VII. The latter, by isomerization to VIII, followed by proton elimination would generate IX, which is the enolic form of III. Path B is the electronic opposite of path A, and loss of carbon dioxide by X would lead directly to VIII. These steps are set forth in Figure 1.

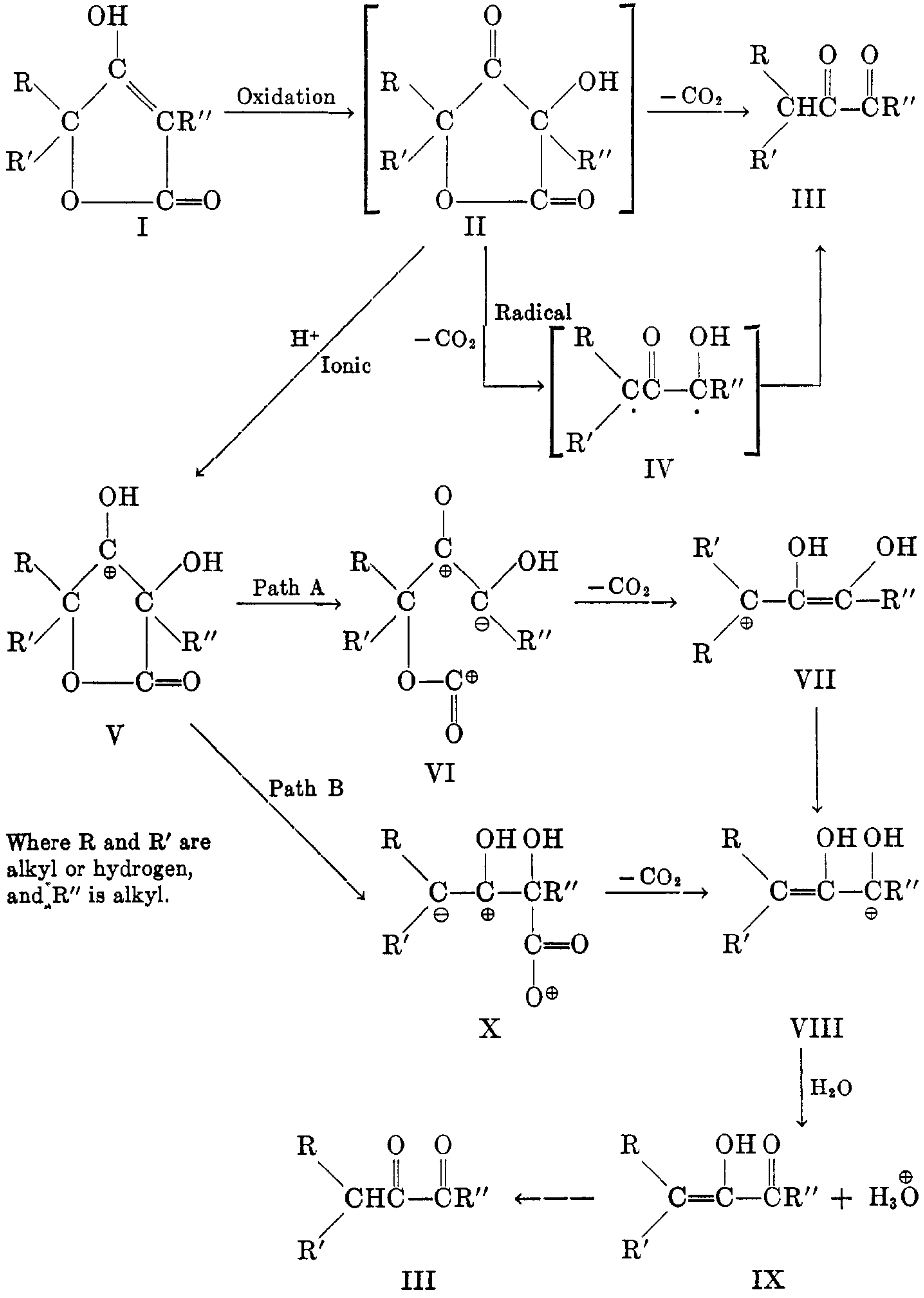
A third possibility exists, and this involves hydrolysis of the lactone ring of II *prior* to decarboxylation. In this circumstance the β-ketoacid, XI, would be the source of the carbon dioxide eliminated, and the ketodiol, XIII, (formed through XII) would be the source of the α-diketone, which would have to form by a dehydration of the pinacol-type. The three routes by which the ketodiol, XIII, could form are set forth in Figure 2.

The S_E1 and S_E2 paths (2) may be considered for the decarboxylation of acetoacetic acid; they differ according to decarboxylation before or after interaction with protons. However, the chelation mechanism (3) represents an internal process which is self sufficient, as is also the radical mechanism, Fig. 1. It is clear that paths A and B, Fig. 1, involve carbonium ions, and are hence different from the S_E1 mechanism, which proceeds through a carbanion.

To decide between those mechanisms which require *carbonium* ion intermediates and those which do not, we have made use of the fact that the neopentyl rearrangement is operative in carbonium ion systems (4, 5, 6), and inoperative in carbanion (7, 8), and radical (9) mechanisms. For this purpose two tetronic acids of unique structures were synthesized, *viz:* 3-methyl-5-*tert*-butyl-

---

[1] From the doctoral dissertation of Robert B. Fortenbaugh, The Johns Hopkins University, 1949. Grateful acknowledgment is here made for a grant-in-aid from the Hynson, Westcott, and Dunning Fund for the pursuance of this research.



Where R and R′ are alkyl or hydrogen, and R″ is alkyl.

FIGURE 1

tetronic acid (XIX) and 3-*tert*-butyltetronic acid (XXIV). These acids contain appropriate *neopentyl systems*, so that if either path A or path B obtains during the oxidation-decarboxylation reaction, the neopentyl rearrangement should intervene.

Several important theoretical steps are involved in the syntheses of these two tetronic acids, and these are illustrated in Figure 3, together with their oxidation products.

For the synthesis of 3-methyl-5-*tert*-butyltetronic acid (XIX), ethyl β-keto-δ,δ-dimethylhexanoate (XV) was prepared in the known manner (10), and alkylated by sodium ethoxide and methyl iodide. Treatment of the alkylated ester (XVI) with bromine formed the *non-enolic* α-bromo-compound (XVII), which was allowed to undergo the α-γ rearrangement in the presence of hydrogen bromide (11). The product was the strongly enolic γ-bromo-ester (XVIII), since catalytic hydrogen regenerated the parent alkyl ester (XVI). This is the first time that the α-γ rearrangement of α-bromoacetoacetic esters has been applied to a neopentyl system, and the fact that it occasioned no skeletal rearrangement furnishes strong support for the radical mechanism advanced by Kharasch, *et al.* (12).

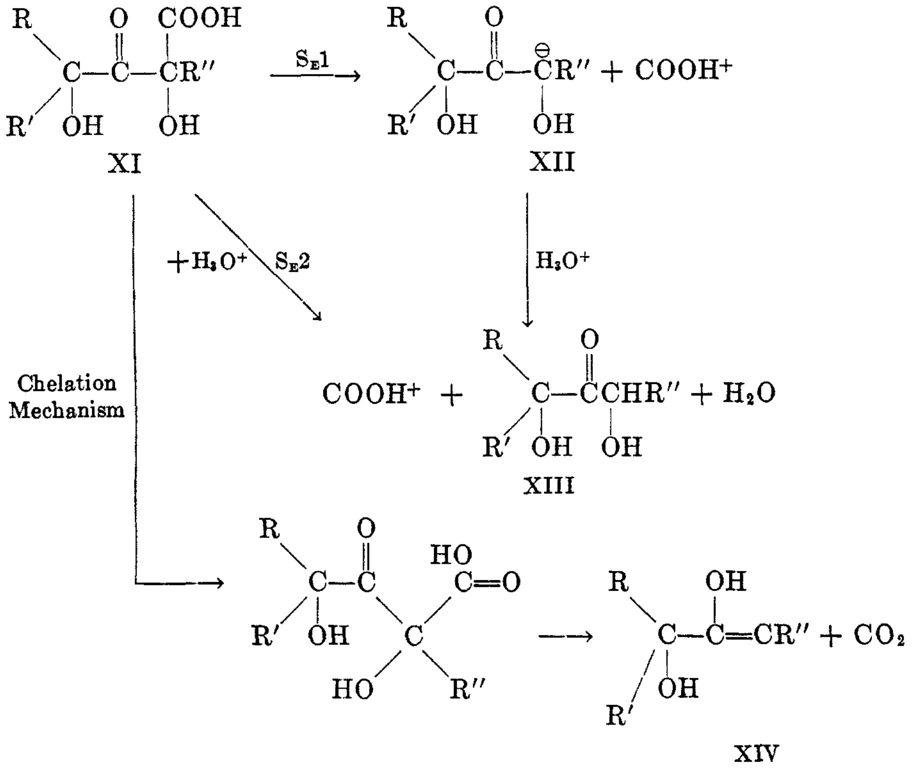


FIGURE 2

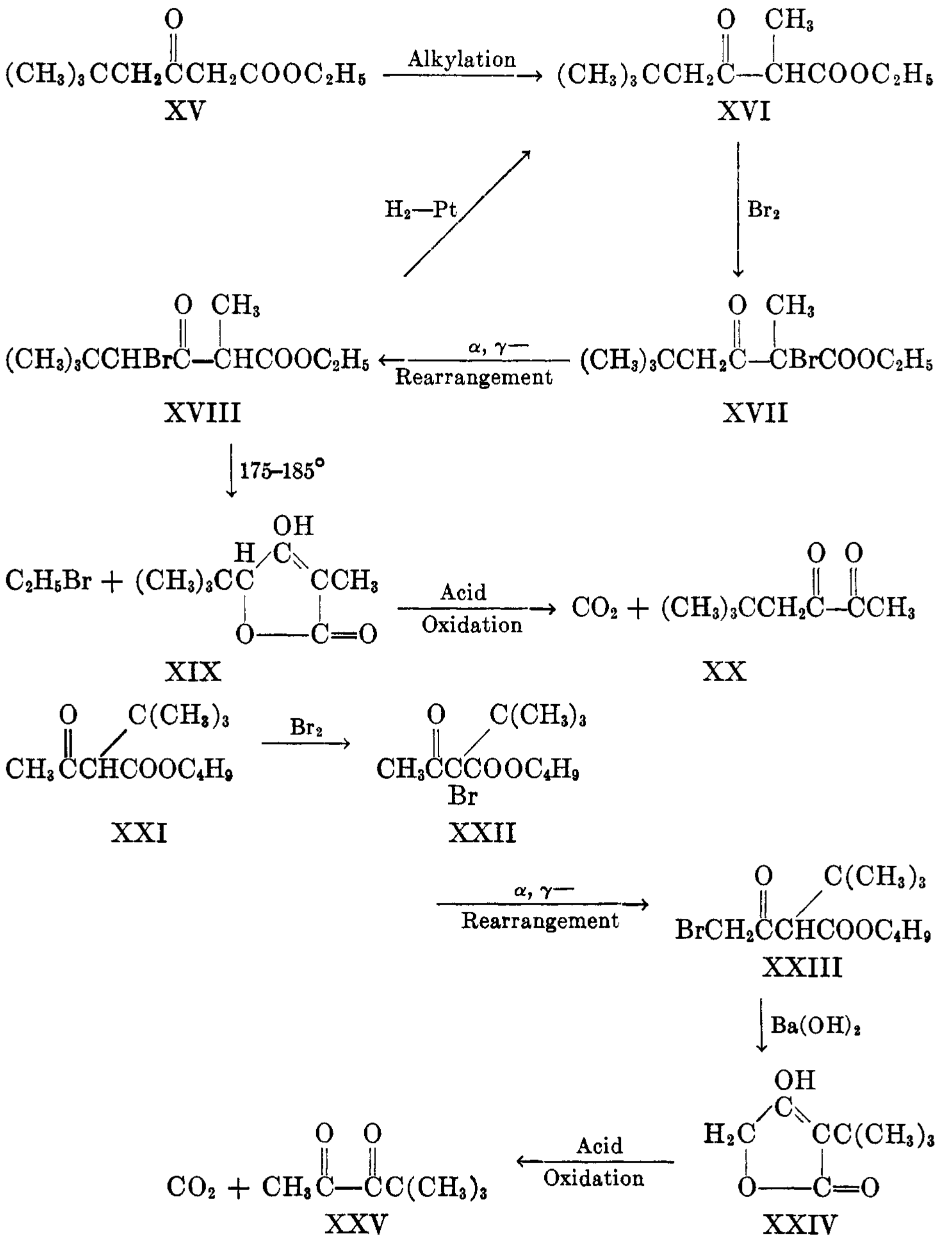

XV
Alkylation
XVI
H_2—Pt
Br_2
XVIII
α, γ— Rearrangement
XVII
175–185°
C_2H_5Br
XIX
Acid Oxidation
CO_2
XX
XXI
Br_2
XXII
α, γ— Rearrangement
XXIII
$Ba(OH)_2$
XXV
Acid Oxidation
XXIV

FIGURE 3

The γ-bromoester (XVIII) failed to cyclize to the tetronic acid when treated with barium hydroxide, but the desired product, together with ethyl bromide, was obtained by the usual gentle pyrolysis (18). The tetronic acid proved to be exceedingly stable to hydrolytic action, so that attempts to prove its structure were not completely successful. However, stability of the molecule is, *prima facie*, evidence for the assigned structure, and this is supported by other data (see experimental part). Moreover, the infrared spectrogram of this acid shows great similarity to those of 3-*tert*-butyltetronic and 3-ethyltetronic acids.[2] These curves are reproduced in Figure 4, and were obtained from samples ground in mineral oil. The bands at 3.3–3.4, 6.8–6.9, and 7.2–7.3 μ are characteristic of the mineral oil used.

Despite the complexity of these spectrograms, certain conclusions seem warranted. The wide and poorly resolved band at about 3.6 μ appears to be due to the OH vibration, since it is present in other enolized tetronic acids.[3] As such it corresponds to the 3.7 μ band observed by Rasmussen, *et al.* (13) for the OH group in acetylacetone. Consistent with this is the slight band (inflection) at about 5.85 μ which corresponds to the normal unconjugated carbonyl absorption (13), indicating almost complete enolization. The relative intensities of these bands in the spectrogram of 3-methyl-5-*tert*-butyltetronic acid (curve III) are reversed, and in point of fact the ferric chloride test for the latter compound is less strong. In all three curves a wide, poorly resolved band occurs, falling across the 6.2 μ region. This band includes the 6.1–6.5 μ range ascribed to the carbonyl

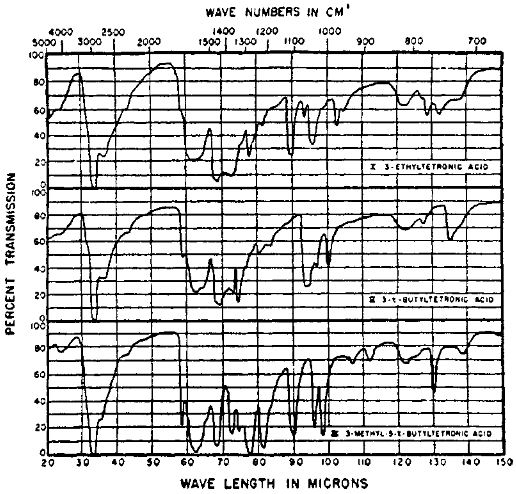


FIGURE 4. INFRARED SPECTRA OF TETRONIC ACIDS

---

[2] We are deeply indebted to Dr. Lester P. Kuhn of the Ballistics Research Laboratories, Aberdeen Proving Grounds, Md., for these determinations. The measurements were made on dry samples mulled in mineral oil. The instrument used was a Baird Associates double-beam infrared spectrophotometer.

[3] Unpublished results from this laboratory.

vibration of a conjugated chelated structure, and it also covers the wave length (6.23 μ) of the OH vibration where external hydrogen bonding is involved (13).

The synthesis of 3-*tert*-butyltetronic acid (XXIV) was accomplished by rearrangement of the α-bromoester (XXII), obtained from *tert*-butyl-α-*tert*-butylacetoacetate (XXI) (13), to the γ-isomer (XXIII), which was cyclized by means of barium hydroxide.

Acid oxidation of 3-methyl-5-*tert*-butyltetronic acid (XIX) formed 5,5-dimethyl-2,3-hexanedione (XX), while from 3-*tert*-butyltetronic acid was obtained 4,4-dimethyl-2,3-pentanedione (XXV). The structures of these diketones rest upon their oxidation with basic hydrogen peroxide, to form known acids. No evidence was obatined which might indicate the intervention of a neopentyl-type rearrangement during the tetronic acid oxidations, and it seems safe to conclude, therefore, that the formation of α-diketones by oxidation of tetronic acids does not involve carbonium ions.

This leaves for consideration only the radical mechanism, (Fig. 1), and those mechanisms shown in Fig. 2. From the evidence at hand it is difficult to reach a decision between these possibilities. It is well established that dihydroxyacetone undergoes dehydration in hot acid to form pyruvic aldehyde (14, 15), but this seems to be a very slow reaction. Moreover, derivatives of pyruvic aldehyde form from dihydroxyacetone in *basic* solution (16), while the diketones described in this and the preceding paper are formed only in acid solution. Evidence bearing upon this question will form the basis of a further communication.

EXPERIMENTAL

Ethyl β-keto-δ,δ-dimethylhexanoate. Methylneopentyl ketone[4] (17) was condensed with diethyl carbonate in the presence of sodium ethoxide by the method of Wallingford, Homeyer, and Jones (10). The product, b.p. 103° at 15 mm., was obtained in 53.5% yield.

Ethyl β-keto-α,δ,δ-trimethylhexanoate. This was prepared in 89% yield, by alkylation of the above ester. To an absolute ethanol solution containing 10.4 g. (0.45 mole) of sodium was added 84 g. (0.45 mole) of ethyl β-keto-δ,δ-dimethylhexanoate. A copious white precipitate developed, which seriously hindered stirring. Sufficient alcohol was added to render the mixture pliable, and then 64 g. (0.45 mole) of methyl iodide was introduced rapidly. Gentle spontaneous refluxing occurred, and a clear solution resulted in the course of ten minutes. After 1½ hours the reaction was complete. The product had b.p. 68–70° at 2 mm; n_D^{31} 1.4241. Treatment with phenylhydrazine formed the phenylhydrazone, m.p. 167–168°, after recrystallization from aqueous alcohol.

Anal.[5] Calc'd for $C_{17}H_{26}N_2O_2$: N, 9.65. Found: N, 9.50.

Hydrolysis of ethyl β-keto-α,δ,δ-trimethylhexanoate. The ester (17 g., 0.085 mole) was refluxed with 100 ml. of 1:1 hydrochloric acid during four working days. The product was removed by steam-distillation, taken up in ether, and dried over sodium sulfate. After evaporation of the ether, the residue was distilled at 750 mm. pressure. About 8 g. (73% yield) of a colorless oil was obtained, b.p. 145–148°. The *2,4-dinitrophenylhydrazone* was prepared, and after recrystallization from methanol, had m.p. 135° (19).

Anal.[5] Calc'd for $C_{14}H_{20}N_4O_4$: N, 18.17. Found: N, 18.16.

The *semicarbazone* was prepared, m.p. 163–164°, after recrystallization from alcohol.

Anal.[5] Calc'd for $C_9H_{19}N_3O$: N, 22.68. Found: N, 22.82.

---

[4] We wish to thank the Enjay Co., New York, N. Y., for a gift of diisobutylene used in the preparation of this compound.

[5] Microanalysis by Mrs. J. E. Buck of these laboratories.

Bromination of ethyl β-keto-α,δ,δ-trimethylhexanoate. To 80 g. (0.40 mole) of ester in three volumes of chloroform at 0° was added, dropwise and with rapid stirring, 64 g. (0.40 mole) of bromine. Immediately after the addition of bromine was complete, a small sample was withdrawn from the flask, washed with water, and evaporated. The residual oil showed a very weak enol test when treated with ferric chloride solution. The reaction mixture was allowed to stand for 24 hours in the cold room to complete the rearrangement of the bromine to the γ-carbon atom (11). The product was then washed with ice-water and the chloroform was removed under a vacuum. Ethyl β-keto-γ-bromo-α,δ,δ-trimethylhexanoate was obtained in 94% yield, as a colorless oil, b.p. 105° at 3–4 mm. It gave a deep purple color with ferric chloride solution.

Anal. Calc'd for $C_{11}H_{19}BrO_3$: Br, 28.64. Found: Br, 28.46.

Reduction of ethyl β-keto-γ-bromo-α,δ,δ-trimethylhexanoate. A sample of bromoester, 10.0 g. (0.0387 mole), was dissolved in ethanol and 0.10 g. of Adams' catalyst was added. The uptake of hydrogen, at 40 p.s.i., was 90% after one hour, and no further reduction occurred. The product was acidic, and was washed with sodium bicarbonate solution and dried over sodium sulfate. On distillation at 4 mm., the colorless halogen-free ester, was obtained, b.p. 80°; n_D^{31} 1.4249. The ester was proved to be ethyl β-keto-α,δ,δ-trimethylhexanoate by formation of a phenylhydrazone, m.p. 167–168°, which gave a mixture m.p. 167–168°, with the phenylhydrazone of this ester.

3-Methyl-5-tert-butyltetronic acid. Attempts to form the tetronic acid by barium hydroxide hydrolysis of the above bromester were fruitless since a degraded product was obtained.[6] The standard pyrolysis method (18) therefore was used. A 10-g. sample (0.036 mole) of the bromoester was heated to 175–185° under a gentle nitrogen sweep, in a flask whose side-arm was attached to a trap cooled in Dry Ice. The bromoester boiled gently, and liquid slowly distilled into the trap. Traces of acidic fumes escaped from the trap exit. When no more distillate formed, the reaction mixture was cooled, and became semisolid. The brown solid was dissolved in sodium bicarbonate solution and filtered. Acidification with cold dilute hydrochloric acid formed a flocculent white solid, in 35% yield. After recrystallization from aqueous alcohol, or chloroform, the crystals had m.p. 184°. The substance was insoluble in cold water.

Anal. Calc'd for $C_9H_{14}O_3$: C, 63.50; H, 8.29.
Found: C, 63.70; H, 8.43.

With ferric chloride solution an orange color was produced. The molecular weight, from the neutralization equivalent determined in 25% ethyl alcohol, was 170 ± 4, compared with the calculated value 170 for 3-methyl-5-*tert*-butyltetronic acid.[7] The *p*Ka (average of the values determined at one-third, one-half, and two-thirds neutralization) was 4.84.[7] For comparison the *p*Ka of 3-ethyltetronic acid was determined under the same conditions, and found to be 4.294.[8] Treatment with aqueous sodium nitrite failed to give the color typical of tetronic acids free of substitution on the 3-position [compare Wolff (18)].

Wolff (18) reported that 3-methyltetronic acid required protracted boiling with strong barium hydroxide solution to effect "acid" cleavage of the molecule. When 3-methyl-5-*tert*-butyltetronic acid was similarly treated very little reaction occurred. After refluxing for 30 hours, the solution was distilled to a small volume, and the distillate was extracted with ether. After drying over sodium sulfate, the ether was evaporated, leaving two or three drops of an oil possessing an odor faintly reminiscent of ethyl neopentyl ketone. This oil was soluble in about ten parts of water, and it slowly reduced Fehling's solution in the cold. It is presumed that this oil is the unknown ketol, 4-hydroxy-5,5-dimethyl-3-hexanone, resulting from hydrolysis and decarboxylation of the tetronic acid. If a neopentyl rearrangement had occurred during the pyrolysis of ethyl β-keto-γ-bromo-α,δ,δ-trimethylhexanoate, the product would be the δ-lactone (XXVI), and hydrolysis of this

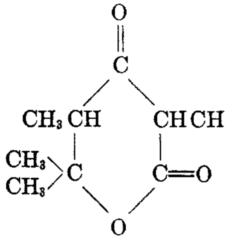
---

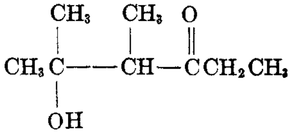
[6] The nature of this product is under investigation in these laboratories.

[7] We wish to thank Mr. T. E. Gompf for these determinations.

[8] We wish to thank Mr. H. W. Sause for this determination.

would lead to 5-hydroxy-4,5-dimethyl-3-hexanone (XXVII), or its dehydration product. The latter compounds would be stable to Fehling's solution.


XXVI



$$\mathrm{CH_3\underset{OH}{\overset{CH_3}{C}}{-}{-}\overset{CH_3}{CH}{-}\overset{O}{\overset{\|}{C}}CH_2CH_3}$$

XXVII

Acidification of the residue from basic hydrolysis regenerated unreacted tetronic acid, together with a trace of lower-melting acid. This material could not be obtained pure. Evaporation of the ether extracts of the acidified solution left a few drops of a liquid with the typical odor of propionic acid. The tetronic acid gave a positive test when treated with Baeyer's reagent, and, when tested with bromine in carbon tetrachloride, readily liberated hydrogen bromide.

The product obtained from the Dry-Ice trap was washed with water and dried over sodium sulfate. It was shown to be ethyl bromide, since it contained bromine, and had b.p. 38–39°.

Oxidation of 3-methyl-5-tert-butyltetronic acid. A ten-gram sample (0.062 mole) was oxidized with an excess of chromium trioxide and dilute sulfuric acid in the standard manner (1). A yellow oil was obtained in the distillate. This oil was relatively insoluble in water, and possessed the characteristic sharp odor of α-diketones. It was taken up in chloroform, and dried over sodium sulfate. Some difficulty was encountered in removing the last traces of solvent by distillation, the green-yellow product beginning to distil at about 150°, and becoming constant at 163°; n_D^{28} 1.4062. The yield was 2 g. (0.014 mole) or 23%. It formed a *dioxime*, m.p. 170°, after recrystallization from aqueous alcohol.

Anal. Calc'd for $C_8H_{16}N_2O_2$: C, 55.70; H, 9.31.

Found: C, 55.91; H, 9.41.

The green-yellow oil was oxidized as follows (24). A sample, 2 g., was treated with basic hydrogen peroxide, and sufficient methyl alcohol was added to effect solution of the oil. Heat was developed, and the green-yellow color faded. The solution was acidified after 15 minutes, and extracted with ether. After drying over sodium sulfate, the ether was removed and the residue distilled.

The first fraction had b.p. 95–105°, n_D^{20} 1.3715, and reduced basic potassium permanganate. This material was formic acid, (20), formed by oxidation of the methyl alcohol.

The second fraction had b.p. 105–120°. This was fused with excess calcium carbonate, and the vapors from the fusion were passed over basic *o*-nitrobenzaldehyde. The blue color of indigo showed the 105–120° fraction to contain acetic acid (21).

The third fraction had b.p. 180–185°. It was acidic, and possessed the odor of *tert*-butylacetic acid, and had n_D^{20} 1.4091. This was shown to be *tert*-butylacetic acid by direct comparison with authentic material (17).

Only a few drops of liquid were obtained between 120° and 180°, and no trimethylacetic acid could be obtained from them.

3-tert-Butyltetronic acid. Ethyl acetoacetate was alkylated with *tert*-butyl alcohol using boron trifluoride (22, 23). The product, *tert*-butyl α-*tert*-butylacetoacetate, was brominated in chloroform according to the previously described procedure. After standing overnight in the cold room, (to form the γ-bromo-ester), the reaction product was washed free of hydrogen bromide, and the solvent was evaporated under reduced pressure.

The enolic residue, obtained from brominating 56 g. (0.262 mole) of *tert*-butyl α-*tert*-butylacetoacetate, was added to 82 g. (0.262 mole) of barium hydroxide dissolved in 2.5 l.

of water. The mixture was shaken to effect solution, and allowed to stand at room temperature for one week.

At the end of this time a small amount of precipitate had formed. This was shown to be a mixture of barium hydroxide and barium carbonate. The solution was concentrated to 600 ml. under a vacuum, with the internal temperature maintained below 50°. The concentrated solution was then cooled in an ice-bath, and acidified to *p*H 1 with hydrochloric acid. This gave 21 g. (0.0135 mole) of crystalline 3-*tert*-butyltetronic acid; yield 50%, based on the *tert*-butyl α-*tert*-butylacetoacetate. After recrystallization from aqueous alcohol, or from chloroform, the compound had m.p. 182–183°. The substance was insoluble in dilute acid. It slowly reduced Fehling's solution, and gave a positive enol (ferric chloride) test. The sodium nitrite test was negative.

Anal. Calc'd for $C_8H_{12}O_3$: C, 61.52; H, 7.75.
Found: C, 61.40; H, 7.75.

Oxidation of 3-tert-butyltetronic acid. Nine grams (0.058 mole) of the acid, when treated with excess chromium trioxide in dilute sulfuric acid, showed no reaction when kept cold. Upon heating, carbon dioxide was evolved vigorously, and a green-yellow distillate was obtained. A small amount of the tetronic acid was seen to steam-distill. The green-yellow oil was extracted with chloroform and washed with sodium bicarbonate solution to remove all traces of tetronic acid, and also a small amount of trimethylacetic acid which had formed during the oxidation. After drying, the chloroform solution was distilled; as with the previous oxidation product, it was difficult to prevent some co-distillation of the α-diketone with the chloroform. The use of diethyl ether instead of chloroform effected no improvement. The pure 4,4-dimethyl-2,3-pentanedione had b.p. 125°. Yield, 3 g. (0.023 mole) or 40%.

Treatment with excess 2,4-dinitrophenylhydrazine formed the orange *2,4-dinitrophenylosazone*, m.p. 214–215°, after recrystallization from ethanol.

Anal. Calc'd for $C_{19}H_{20}N_8O_8$: C, 46.72; H, 4.13.
Found: C, 46.93; H, 4.27.

With excess hydroxylamine the *dioxime* formed, m.p. 182.5°, after recrystallization from aqueous ethanol.

Anal. Calc'd for $C_7H_{14}N_2O_2$: C, 53.14; H, 8.92.
Found: C, 53.38; H, 8.89.

When the green-yellow diketone was treated with basic hydrogen peroxide (24) an immediate reaction ensued. Heat was developed, and the color rapidly disappeared. After 15 minutes the reaction mixture was acidified, liberating an acidic oil. On standing this oil solidified, and had m.p. 35°. The mixture m.p. with authentic trimethylacetic acid was 35°.

SUMMARY

The synthesis of 3-methyl-5-*tert*-butyltetronic acid and 3-*tert*-butyltetronic acid is reported. These acids have been oxidized in acidic solution, and the α-diketones thus obtained show no evidence of rearrangement, despite the presence of the neopentyl system in the parent acids. Appropriate oxidation mechanisms have been discussed, and a decision has been reached against ionic mechanisms which involve carbonium ions. Evidence has been advanced in favor of a radical mechanism for the α-γ shift of α-bromoacetoacetic esters.

BALTIMORE 18, MARYLAND

REFERENCES

(1) REID, FORTENBAUGH, AND PATTERSON, *J. Org. Chem.*, **15**, 572 (1950).
(2) HUGHES, *Trans. Faraday Soc.*, **34**, 185 (1938); HUGHES AND INGOLD, *J. Chem. Soc.*, 244 (1935).

(3) Schenkel and Schenkel-Rudin, *Helv. Chim. Acta*, **31**, 514 (1948).
(4) Whitmore, *J. Am. Chem. Soc.*, **54**, 3274 (1932).
(5) Whitmore and Rothrock, *J. Am. Chem. Soc.*, **54**, 3431 (1932).
(6) Whitmore and Langlois, *J. Am. Chem. Soc.*, **54**, 3441 (1932).
(7) Whitmore and Homeyer, *J. Am. Chem. Soc.*, **54**, 3435 (1932).
(8) Whitmore and Fleming, *J. Am. Chem. Soc.*, **55**, 4161 (1933).
(9) Whitmore, Popkin, Bernstein, and Wilkins, *J. Am. Chem. Soc.*, **63**, 124 (1941).
(10) Wallingford, Homeyer, and Jones, *J. Am. Chem. Soc.*, **63**, 2252 (1941).
(11) Hantzsch, *Ber.*, **27**, 3168 (1894).
(12) Kharasch, Sternfeld, and Mayo, *J. Am. Chem. Soc.*, **59**, 1655 (1937).
(13) Rasmussen, Tunnicliff, and Brattain, *J. Am. Chem. Soc.*, **71**, 1068 (1949).
(14) Pinkus, *Ber.*, **31**, 36 (1898).
(15) Bernier and Evans, *J. Am. Chem. Soc.*, **60**, 1381 (1938).
(16) Clutterbuck and Raper, *Biochem. J.*, **20**, 59 (1926).
(17) Whitmore, Homeyer, and Trent, U. S. Patent 2,004,066 (1935).
(18) Wolff, *Ann.*, **288**, 1 (1895).
(19) Whitmore, Whitaker, Mattil, and Popkin, *J. Am. Chem. Soc.*, **60**, 2790 (1938).
(20) Heilbron, *Dictionary of Organic Compounds*, Eyre and Spotteswoode, London, 1943, Vol. II, p. 83.
(21) Feigl, *Spot Tests*, Nordemann Co., Inc., New York, N. Y., 2nd Edition, 1939, p. 331.
(22) Hauser and Breslau, *J. Am. Chem. Soc.*, **62**, 2386 (1940).
(23) Hauser and Adams, *J. Am. Chem. Soc.*, **64**, 728 (1942).
(24) Weitz and Scheffer, *Ber.*, **54**, 2327 (1921).