Reprinted from The JOURNAL OF ORGANIC CHEMISTRY Vol. 17, No. 3, March, 1952 Printed in U.S.A.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

2,2,6-TRIMETHYLPIMELIC ACID

S. KASMAN AND GEORGE F WRIGHT

Received December 10, 1951

Recently an acid was reported (1) which, on the basis of its preparation and reactions should be 2,2,6-trimethylpimelic acid. However its properties did not conform with those of an acid previously reported to have this structure (2). We have reinvestigated the chemistry involving the latter acid, and find it to be erroneous.

Colonge and Dumont obtained this acid by a series of reactions beginning with 2,2-dimethylbuten-3-oic acid of known structure (3). This was converted to the acid chloride (I), which was treated with 2-methylpropene and stannic chloride to yield two products. One of these was thought by them to be 2,2,5-trimethyl-hexadien-1,5-one-3 (III, Artemisia ketone) because the semicarbazone melted at the same temperature (96°) as that reported (4) for this ketone of known structure (4, 5). The second product was evidently a cyclized isomer of the first since it also could be formed from the first by the method of Marvel and Blomquist (6). Colonge and Dumont called this cyclic isomer 2,2,6-trimethyl-cyclohepten-3-one-1 (V).

This structure was assigned because oxidation of V yielded dimethylmalonic acid (7, no experimental work reported), while oxidation of hydrogenated V yielded an acid $C_{10}H_{18}O_4$. They designated this as 2,2,6-trimethylpimelic acid (VI) because they found that pyrolysis of its barium salt yielded 2,2,6-trimethylcyclohexanone (VII). They reported that the semicarbazone of this pyrolysate did not depress the melting point of an authentic sample.

It should be noted that Colonge and Dumont's identification of the reaction product with stannic chloride as Artemisia ketone rests entirely in the similarity of the melting point of the semicarbazone with that of Asahina and Takagi. Furthermore, the postulated cyclization $(III \rightarrow V)$ seems highly questionable since it involves the mutual addition of two carbon atoms which might be expected to possess similar polarity.

Upon repetition of the acid chloride-methylpropene synthesis of Colonge and Dumont we obtained from I and II with stannic chloride, principally the cyclic compound as its semicarbazone of expected melting point. This unsaturated ketone, which was our principal interest, was obtained by regeneration from the semicarbazone. Its physical properties agreed with those described by Colonge and Dumont. However its oxidation with potassium permanganate yielded 3,3dimethylglutaric acid (IX), rather than the dimethylmalonic acid reported by Colonge and Dumont. Furthermore, ozonization of the unsaturated ketone gave an appreciable yield of formaldehyde (as its dimedone derivative). Neither of these products could have been obtained from the cycloheptenone (V) postulated by Colonge and Dumont.



If the acyclic diunsaturated ketone obtained by Colonge and Dumont was indeed Artemisia ketone (III), then a profound transformation must have occurred during cyclization. The substance must necessarily have lost a methyl group from the carbon atom adjacent to the carbonyl group, since otherwise the permanganate oxidation product would have two methyl groups on the carbon atom α rather than β to a carboxyl group. This situation is best explained as a 1,2-rearrangement of methyl and hydrogen in the reaction involving III to IV. The resulting 2,5,6-trimethylheptadien-1,6-one-4 might cyclize in several ways, but only one of the rational cyclization products, 2,5,5-trimethyl-3-methylenecyclohexanone (VIII), would yield formaldehyde and 3,3-dimethylglutaric acid (IX) upon ozonization and oxidation respectively.

Reduction of the unsaturated ketone (VIII) ought to yield 2,3,5,5-tetramethylcyclohexanone (X) which upon oxidation would be converted to 2,2,4,5tetramethyladipic acid (XI). We believe this to be the structure of the acid of Colonge and Dumont, which we obtained by repetition of their successive reduction and oxidation. But this acid (XI) would not be expected to form 2,2,6trimethylcyclohexanone (VII) when it was pyrolyzed with barium hydroxide. Actually our repetition of this pyrolysis did not yield VII. We were unable to separate the mixture which we did obtain, but a semicarbazone and a 2,4dinitrophenylhydrazone prepared from it did not correspond either in melting points or in x-ray diffraction powder patterns with such derivatives of 2,2,6trimethylcyclohexanone. Presumably the derivatives which we obtained are those of 2,2,4,5-tetramethylcyclopentanone, but this has not been proven.

Our principal interest was identification of the acid which Colonge and Dumont called 2,2,6-trimethylpimelic acid but which we believe to be 2,2,4,5tetramethyladipic acid. Consequently we have not ascertained whether the acyclic dienone obtained by condensation of 2,2-dimethylbutene-3-oyl chloride and 2-methylpropene was actually Artemisia ketone (III) as Colonge and Dumont believed, or whether it was, instead, the 1,2-rearrangement product (IV).

EXPERIMENTAL

All melting points have been corrected against reliable standards. X-ray diffraction powder patterns were carried out with $\operatorname{CuK}_{\alpha}$ (Ni filtered) radiation. Spacings are in Å and relative intensities $[I/I_0]$ in scales of 10.

2,5,5-Trimethyl-3-methylenecyclohexanone. A 200-ml. Pyrex centrifuge bottle was equipped with a metal yoke for the purpose of retaining the rubber stopper when the pressure in the bottle was above atmospheric. Into this bottle was placed 41.4 g. (0.312 mole) of 2,2-dimethylbuten-3-oyl chloride and a sealed thin glass ampoule containing 6.36 g. (0.0244 mole) of stannic chloride. The whole was chilled to -78° and 35.0 g. (0.624 mole) of 2-methylpropene was distilled into it. The cold bottle was sealed, then shaken to break the ampoule, and maintained at -20° to -10° for 16 hours. The sealed bottle was then heated to 80° for one hour, cooled, and opened.

This scale of preparation was repeated exactly and the combined reaction mixtures were distilled at 755 mm. to yield two fractions, b.p. 80–185° and 185–225°. The second fraction was treated with 36.05 g. (0.325 mole) of semicarbazide hydrochloride and 45.8 g. (0.336 mole) of sodium acetate trihydrate in 186 ml. of water and 630 ml. of methanol. The semicarbazone which precipitated during 18 days weighed 35.1 g. (27% of theoretical), m.p. 210–220°.

The crude semicarbazone was boiled for one hour under reflux with 230 ml. of 10% aqueous sulfuric acid (0.421 mole). Both clear phases were steam-distilled together and the distillate extracted with ether. This ether solution was dried with magnesium sulfate and distilled, finally at 755 mm. The product boiled at 204-205°, $n_{\rm p}^{20}$ 1.4782 d_4^{20} 0.905. It weighed 20.5 g. (80% based on the semicarbazone; 21% based on the acid chloride).

Ozonolysis of 2,5,5-trimethyl-3-methylenecyclohexanone. A solution of 0.15 g. (0.001 mole) of 2,5,5-trimethyl-3-methylenecyclohexanone in 10 ml. of pre-ozonized and purified carbon tetrachloride was treated at 0° with 2% ozonized oxygen (3 l.) during three hours. The cloudy solution was then shaken during ten minutes with 5 ml. of 20% aqueous acetic acid and 1 g. of zinc dust, initially at 0° and finally at 20°. The aqueous layer was separated, partially neutralized with alkali, and treated with 40 ml. of a saturated aqueous solution of dimethyldihydroresorcinol. After one day 0.025 g. of the dimedone-formaldehyde condensation product was filtered off, m.p. 186-188°, and the constitution confirmed by mixture melting point. The yield is 9%. A control experiment utilizing carbon tetrachloride alone yielded none of this product.

3,3-Dimethylglutaric acid. A mixture of 1.00 g. (0.0066 mole) of 2,5,5-trimethyl-3-methylenecyclohexanone, 4.88 g. (0.0309 mole) of potassium permanganate, and 75 ml. of water was shaken vigorously until the initial reaction was complete, then heated under reflux for a day on the steam-bath. The filtered reaction mixture was acidified with hydrochloric acid and extracted with ether. Evaporation of the ether left an oil (0.38 g.) which crystallized slowly. It was twice crystallized from boiling water, yield 0.07 g., m.p. 98-100°. Since 60% was recovered during the second crystallization the extrapolated yield is 20%. A mixture melting point with the acid prepared by oxidation of dimethyldihydroresorcinol (8) was not depressed. The x-ray patterns showed identical d spacings with relative intensities as follows: [10] 4.79; [8] 2.31; [7] 3.45, 2.57; [6] 2.85; [5] 3.93, 3.08; [4] 5.06; [3] 5.24; [2] 5.60, 2.39; [1] 3.35.

Anal. Cale'd for C₇H₁₂O₄: C, 52.5; H, 7.56.

Found: C, 52.8; H, 7.53.

2,3,5,5.7-tetramethylcyclohexanone. After ten hours 187 ml. of hydrogen at 26° and 755 mm. (0.0076 mole) was absorbed by a mixture of 1.09 g. (0.0072 mole) of 2,5,5-trimethyl-3-methylenecyclohexanone and 0.15 g. of Raney nickel in 15 ml. of absolute ethanol. The filtrate was distilled; b.p. 190-193° (755 mm.), $n_{\rm p}^{20}$ 1.4411, wt. 1.00 g. (90.5%). The product was characterized as its semicarbazone, m.p. 143-145°. This melting point is higher than that previously reported, 141° (2).

2, 2, 4, 5-Tetramethyladipic acid. Repetition of Colonge and Dumont's oxidation with 53% nitric acid gave a 27% yield of crude product, m.p. 103-117°. Crystallization from water and sublimation (92° at 0.04 mm.) gave an analytically pure sample, m.p. 121° [previously reported as 126° (2)]. X-ray diffraction gave d spacings at relative intensities as follows: [10] 8.42, 4.17; [9] 4.55; [8] 6.46, 5.98; [7] 8.04; [6] 3.75; [5] 4.95; [4] 4.04, 3.97; [3] 4.77, 3.28; [2] 3.21, 2.63, 2.38, 2.31; [1] 2.74, 2.49, 2.43.

Anal. Calc'd for C₁₀H₁₈O₄: C, 59.4; H, 8.97.

Found: C, 59.1; H, 8.87.

A satisfactory potentiometric titration of this acid using glass and calomel electrodes could not be effected with standard alkali because of difficulty in obtaining equilibrium. The acid could be recovered from the solution. This behavior may be due to spontaneous anhydride formation.

2, 2, 4, 5-Tetramethyladipic anhydride. A finely powdered intimate mixture of 0.38 g. (0.0019 mole) of the acid and 0.02 g. (0.00012 mole) of anhydrous barium hydroxide was gradually heated. At about 250° a semisolid distillate was obtained, wt. 0.14 g. Crystallization of the waxy mass from ethanol-water followed by fractional sublimation gave a solid, m.p. 90°. This compound slowly gave an acid reaction toward wet litmus paper. On alkaline hydrolysis it yielded the parent acid, m.p. 121°. The x-ray diffraction pattern of the anhydride was [10] 6.32; [9] 6.42, 4.00; [8] 6.86; [6] 5.40, 3.45, 3.16; [5] 1.99; [4] 2.83; [3] 2.99; [2] 3.41, 2.33; [1] 4.15, 2.86, 2.19. Anal. Cale'd for C₁₀H₁₆O₃: C, 65.2; H, 8.76.

Found: C, 65.3; H, 8.77.

Pyrolysis of barium 2,2,4,5-tetramethyladipate. To a solution of 0.36 g. (0.00178 mole) of tetramethyladipic acid in 20 ml. of 3:7 ethanol-water was added 0.24 g. (0.0014 mole) of barium hydroxide. This solution was evaporated to dryness and the remaining 0.56 g. was finely powdered and heated slowly to 500°. The distillate of oil and water weighed 0.20 g. The oily phase was dried and distilled, b.p. 115° at 12 mm. Part of this was converted to a semicarbazone, m.p. 171-179°. Crystallization from ethanol-water raised this melting point to 177-179°. The x-ray powder diagram [entirely different from that of 2,2,6-trimethylcyclohexanone semicarbazone (1)] was found to be [10] 12.8, 4.57; [9] 2.01; [4] 8.26; [3] 6.75; [2] 7.37, 4.15, 2.43; [1] 8.93, 4.02.

The remainder of the oil was treated in acidic ethanol with dinitrophenylhydrazine. The impure derivative melted at $156-165^{\circ}$ after washing with petroleum ether (b.p. $40-60^{\circ}$). Admixture of a small amount of this crude dinitrophenylhydrazone with that of 2,2,6-trimethylcyclohexanone (m.p. $138-140^{\circ}$) depressed the mixture melting point to $103-137^{\circ}$. The powder diagram of the impure dinitrophenylhydrazone (which should be that of 2,2,4,5-tetramethylcyclopentanone) is [10] 2.00; [9] 14.7; [8] 7.82; [7] 4.15; [5] 5.27; [3] 10.0, 3.72; [2] 6.91, 5.79, 3.28; [1] 6.10, 4.62, 3.91, 2.97, 1.74. The high proportion of low-intensity arcs is probably due to impurity of the sample.

SUMMARY

1. The cyclic ketone produced by stannic chloride from 2,2-dimethylbuten-3-oyl chloride and 2-methylpropene according to Colonge and Dumont may be oxidized by permanganate to 3,3-dimethylglutaric acid and ozonized to formaldehyde.

2. These oxidation products would not be formed from 2,2,6-trimethylcyclohepten-3-one-1, which was reported to be the structure of the cyclic ketone. Oxidation and ozonization of 2,5,5-trimethyl-3-methylenecyclohexanone would yield these oxidation products.

3. Reduction of this latter ketone should yield 2,3,5,5-tetramethylcyclohexanone which on oxidation should yield 2,2,4,5-tetramethyladipic acid. We believe that this is the acid obtained by these reactions of Colonge and Dumont rather than 2,2,6-trimethylpimelic acid which they reported it to be.

4. Whereas 2,2,6-trimethylpimelic acid prepared by another method yields 2,2,6-trimethylcyclohexanone upon pyrolysis with barium hydroxide a repetition of Colonge and Dumont's pyrolysis of their acid failed to confirm their reported yield of this trimethylcyclohexanone.

TORONTO, CANADA

REFERENCES

- (1) BELL, STRICKLAND, AND WRIGHT, J. Org. Chem., 16, 1742 (1951).
- (2) COLONGE AND DUMONT, Bull. soc. chim., 14, 38 (1947).
- (3) COURTOT, Bull. soc. chim., 35, 118, 581 (1906).
- (4) ASAHINA AND TAKAGI, J. Pharm. Soc. Japan, 464, 837 (1920).
- (5) RUZICKA, et al., Helv. Chim. Acta, 19, 646 (1936).
- (6) MARVEL AND BLOMQUIST, J. Am. Chem. Soc., 55, 1655 (1933).
- (7) COLONGE AND DUMONT, Compt. rend., 220, 500 (1945).
- (8) WALKER AND WOOD, J. Chem. Soc., 89, 599 (1906).