# THE CONDENSATION PRODUCT OF TETRAHYDRO-2,2,3,5,5-PENTAMETHYL-3-FURANOL WITH PYRUVIC ACID

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Abstract—The lactone formed in the reaction of tetrahydro-2,2,3,5,5-pentamethyl-3-furanol with pyruvic acid has been shown to be 2,3,4,5-tetrahydro-3-hydroxy- $\alpha$ ,2,2,3,5,5-hexamethylfuranacrylic acid lactone (IV).

IT HAS been shown that, contrary to earlier suggestions,<sup>3.4</sup> the structure of the product obtained by dehydration of tetrahydro-2,2,3,5,5-pentamethyl-3-furanol (I) with sulfuric acid or potassium hydrogen sulfate is 2,2,3,5,5-pentamethyl-2,5-dihydrofuran (II).<sup>5,6</sup> In the course of their original investigation, Bouveault and Locquin<sup>3</sup> found that when the dehydration of I is carried out with pyruvic acid, there is formed in addition to the dehydration product now known to be II a crystalline lactone,  $C_{12}H_{18}O_3$ . We discuss here the structure of this product.

A strong band at 5.65  $\mu$  in the I.R. spectrum of the compound corroborates the presence of a lactone ring and suggests that this is five-membered. A weak I.R. band at 5.98  $\mu$  and high intensity U.V. end absorption further indicates that the lactone is  $\alpha,\beta$ -unsaturated. These conclusions are confirmed by the formation on hydrogenation of the lactone over platinum of a dihydro compound,  $C_{12}H_{20}O_3$ , which shows a strong band in its I.R. spectrum at 5.61  $\mu$ , but lacks any band in the 6.0  $\mu$  region.

Ozonolysis of the lactone followed by decomposition of the ozonide with boiling water gives a neutral product,  $C_8H_{14}O_2$ , and an acid,  $C_9H_{16}O_4$ . The neutral product was shown to be identical with the ketone III, the precursor of I. The isolation of

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<sup>&</sup>lt;sup>a</sup> L. Bouveault and R. Locquin, Ann. Chim. [8] 21, 425 (1910).

<sup>&</sup>lt;sup>4</sup> M. Sulzbacher and E. D. Bergmann, J: Amer. Chem. Soc. 75, 3859 (1953).

<sup>&</sup>lt;sup>5</sup> C. Sandris, G. Ourisson and G. Dupont, Bull. Soc. Chim. Fr. 1079 (1954).

<sup>&</sup>lt;sup>6</sup> P. Yates and N. Yoda, *Chem. Ind.* 1480 (1955); we thank Professor Ourisson for drawing our attention to his earlier results.<sup>5</sup> Professor A. W. Burgstahler, University of Kansas, has also informed us that he and Professor Hennion, University of Notre Dame, had independently arrived at an identical conclusion regarding the structure of this dehydration product.



this product, and the above conclusions regarding the nature of the lactone ring permit the assignment to the lactone of the spiro structure IV. This assignment is corroborated by the properties of the acidic product obtained from the ozonolysis of the lactone, which is formulated as the hydroxy acid V. It forms a monomethyl ester (VI) which has a hydroxyl-stretching band at  $2.90 \mu$  in its I.R. spectrum, and is converted by warm dilute sulfuric acid to the ketone III.<sup>7</sup>



Oxidation of the lactone with potassium permanganate gives a compound,  $C_{12}H_{20}O_5$ , assigned structure VII. This on further oxidation with sodium periodatepotassium permanganate<sup>8</sup> gives the  $\alpha$ -hydroxy acid V. The latter is also obtained when the hydroxy acid (VIII), obtained by hydrolysis of the lactone, is oxidized with chromic acid. The dihydro compound obtained on hydrogenation of the lactone can now be formulated as IX.<sup>9</sup>



The assignment of structure IV to the lactone is fully confirmed by its N.M.R. spectrum (Table 1).<sup>10</sup> The signal at low field is assigned to the vinyl hydrogen atom (a) (see X), split into a quartet by coupling with the hydrogen atoms of the methyl group (b); the doublet with  $\tau = 8.10$  p.p.m. is assigned to the latter. The AB system in the region  $\tau = 8.0$  p.p.m. is considered to be associated with the hydrogen atoms (c) attached to the tetrahydrofuran ring; the observed value of J is in accordance

- <sup>8</sup> R. U. Lemieux and E. von Rudloff, Canad. J. Chem. 33, 1701 (1955).
- The stereochemistry of IX and VII has not been investigated; it is probable in each case that addition to the double bond occurs on the side of the lactone ring remote from the *gem*-dimethyl group at C.2 of the tetrahydrofuran ring.
- <sup>10</sup> We thank Dr. Mamoru Ohashi, Tokyo University of Education, for these measurements.

<sup>&</sup>lt;sup>7</sup> Cf., for example, the loss of the elements of formic acid from desoxonorquassinic acid on treatment with sulfuric acid: Z. Valenta, A. H. Gray, S. Paradopoulas and C. Podesva, *Tetrahedron* 15, 100 (1961).

Chemical shift $(\tau)$	Multiplicity	Relative intensity
3·44 p.p.m.	quartet, $J = 1.3$ c.p.s.	1
7·95	AB system, $J = 12$ c.p.s.	2
8.10	doublet, $J = 1.3$ c.p.s.	3
8·62 8·67	singlet singlet	6
8.82	singlet	3
9.06	singlet	3

TABLE I. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF LACTONE IV

with expectation for hydrogen atoms attached to a common sp<sup>3</sup> carbon atom.<sup>11</sup> The remaining four signals are assigned to the four methyl groups attached to the tetrahydrofuran ring. It seems probable that the two of these signals at highest field are associated with the two methyl groups at C.2 of the tetrahydrofuran ring, since their spatial relationship to the ethylenic and carbonyl double bonds of the lactone ring would be expected to lead to increased shielding.<sup>12</sup>



The pathway for the formation of IV from I is of interest. For, although the reaction formally involves condensation of pyruvic acid with a methyl group of I which is unactivated, clearly it cannot proceed in this fashion. A plausible type of route could involve equilibration of the dehydration product II with the isomer XI followed by addition of protonated pyruvic acid:<sup>13</sup>



- <sup>11</sup> L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry" Pergamon Press, London, p. 85 (1959).
- <sup>12</sup> Cf. reference 11, pp. 124, 129.
- <sup>13</sup> More fully concerted reaction paths can be envisaged of which the following is an extreme example:



Such formulations are distinctive in implying a specific function of both the ketone and carboxylic acid moieties of the  $\alpha$ -keto acid group in the process of carbon–carbon bond formation.

A similar scheme<sup>14</sup> has been suggested to account for the formation of the lactone XII on treatment of 2-methyl-2,4-pentanediol (XIII) with pyruvic acid. In these terms the reactions find analogy, in part, in the Prins reaction.<sup>15,16</sup>



There appears to have been no report of a similar reaction with pyruvic acid in the case of a simple alkene. It remains to be determined whether the oxygen atoms in XI and XIV play any role in facilitating the reaction of these compounds with pyruvic acid, although there is considerable evidence contraindicating the stabilization of carbonium ions by the oxygen atom of a hydroxyl or ether group which involves a four-membered ring.<sup>17</sup>

# EXPERIMENTAL<sup>18</sup>

# Condensation of tetrahydro-2,2,3,5,5-pentamethyl-3-furanol (I) with pyruvic acid

Formation of II and IV. A mixture of I (23.7 g, 0.15 mole) and pyruvic acid (35.2 g, 0.40 mole) was boiled under reflux for 5 hr. The mixture, whose color had changed from yellow to dark brown, was separated by fractional distillation into 3 fractions: (i) b.p. 127–128° (760 mm): the dehydration product II (4.0 g, 20%) (ii) b.p. 40–45° (5 mm): pyruvic acid (2.0 g) (iii) b.p. 130–135° (10 mm): the condensation product IV (6.6 g, 34%). The third fraction crystallized upon cooling. It was recrystallized several times from hexane to give needles, m.p. 121.5–122°,  $\lambda_{max}^{CS_2}$  5.65, 5.98 (w)  $\mu$ ,  $\lambda_{max}^{CSC_1}$  5.68, 5.99  $\mu$  (Found: C, 68.73; H, 8.73. Calc. for C<sub>1x</sub>H<sub>18</sub>O<sub>3</sub>: C, 68.54; H, 8.63%).

# Hydrogenation of IV

Formation of IX. On hydrogenation of IV in ethyl acetate over platinum at atm. press. one molar equivalent of hydrogen was taken up. Chromatography of the crude product on alumina followed by crystallization from pet ether gave the dihydro lactone IX as needles, m.p. 76.5-77°,  $\lambda_{mgx}^{CS}$  5.61  $\mu$ . (Found: C, 67.86; H, 9.35. Calc. for C<sub>12</sub>H<sub>20</sub>O<sub>3</sub>: C, 67.89; H, 9.50%).

#### Ozonolysis of IV

Formation of III and V. A solution of IV (2.0 g) in ethyl acetate (50 ml) was treated with ozonized oxygen at  $0-2^{\circ}$  for 1 hr. Water was added and the mixture was boiled under reflux for 1 hr. It was then cooled to room temp and the organic layer was separated. The aqueous layer was extracted with ether, the extract was combined with the ethyl acetate solution, and the resulting solution was extracted with dil. aqueous sodium carbonate. The organic layer was separated and dried (MgSO<sub>4</sub>). Remov..l of the solvent and distillation at atm. press. gave III, b.p. 148–149°, identified by comparison of its 1.R. spectrum with that of an authentic sample. (Found: C, 67·25; H, 9·98. Calc. for C<sub>8</sub>H<sub>14</sub>O<sub>8</sub>: C, 67·57; H, 9·93%).

The aqueous layer from the extraction with aqueous sodium carbonate was acidified with dil. hydrochloric acid. The solution was extracted with ether and the ethereal extract was dried (MgSO<sub>4</sub>) and freed of solvent. The residue crystallized on cooling and was recrystallized several times from ether-petroleum ether to give V as prisms, m.p. 107-108°,  $\lambda_{max}^{\text{HCl}_3} 2.90$ , 3-4, 5.80  $\mu$ . (Found: C, 57.95; H, 8.23. Calc. for C<sub>9</sub>H<sub>18</sub>O<sub>4</sub>: C, 57.43; H, 8.57%).

<sup>14</sup> P. Dietrich, E. Lederer and D. Mercier, Ann. 603, 8 (1957).

<sup>15</sup> A. T. Blomquist and J. Wolinsky, J. Amer. Chem. Soc. 79, 6025 (1957).

<sup>16</sup> L. J. Dolby, J. Org. Chem. 27, 2971 (1962).

<sup>17</sup> This evidence has recently been summarized by Dolby.<sup>16</sup>

<sup>18</sup> M.p.'s are uncorrected.

The condensation product of tetrahydro-2,2,3,5,5-pentamethyl-3-furanol with pyruvic acid 853

Esterification of this acid with ethereal diazomethane followed by chromatography of the crude product on alumina gave the methyl ester VI as prisms, m.p. 40-41°,  $\lambda_{\max}^{\text{CRCl}}$  2.90, 5.75  $\mu$ . (Found: C, 59.12; H, 9.06. Calc. for C<sub>10</sub>H<sub>18</sub>O<sub>4</sub>: C, 59.38; H, 8.97%).

### Acid treatment of V

Formation of III. A mixture of V (0.10 g) and and 6 N sulfuric acid (15 ml) was heated at 65–70° for 2.5 hr. The solution was neutralized with dil. aqueous sodium carbonate and extracted with ether. The extract was dried (MgSO<sub>4</sub>) and distilled. The distillate, b.p. 148–149°, (0.50 g, 67%) was identified as III by I.R. spectral comparison (Found: C, 67.31; H, 9.82. Calc. for C<sub>8</sub>H<sub>14</sub>O<sub>2</sub>: C, 67.57; H, 9.93%).

#### Permanganate oxidation of IV

Formation of VII. The lactone IV (0.50 g, 0.0024 mole) was added to a solution of potassium permanganate (0.75 g, 0.0047 mole) in water (16 ml) and acetone (20 ml). The mixture was allowed to stand overnight at room temp. The manganese dioxide which had precipitated was filtered off and acetone was removed from the filtrate under red. press. The remaining aqueous solution was extracted with ether. The extract was dried (MgSO<sub>4</sub>) and freed of solvent to give a crystalline product which was twice recrystallized from hexane to give VII (0.12 g, 20%) as needles, m.p. 143.5–144°,  $\lambda_{max}^{CBG1} 2.84$ , 5.68  $\mu$  (Found: C, 58.65; H, 8.19. Calc. for C<sub>12</sub>H<sub>20</sub>O<sub>5</sub>: C, 59.00; H, 8.25%).

#### Permanganate-periodate oxidation of VII

Formation of V. A solution of VII (0.34 g) in methanol (7.5 ml) was treated with a solution of potassium permanganate (0.80 g), sodium metaperiodate (1.6 g) and potassium carbonate (0.50 g) in water (100 ml). The mixture was allowed to stand at room temp overnight. The methanol was removed under red. press. and the remaining solution was acidified with dil. hydrochloric acid and extracted with ether. The extract was dried (MgSO<sub>4</sub>) and freed of solvent. The crystalline residue was recrystallized from ether-petroleum ether to give prisms, m.p. 107-108°, shown to be V by I.R. spectral comparison with the acid product from the ozonolysis of IV. (Found: C, 57.85; H, 8.19. Calc. for  $C_pH_{16}O_4$ : C, 57.43; H, 8.57%).

### Hydrolysis of IV

Formation of VIII. The lactone IV (4.5 g) was heated on a steam bath with aqueous 10% sodium hydroxide (35 ml) for 5 hr. After cooling the solution was extracted several times with ether; this ethereal extract yielded a small amount of the lactone IV. The aqueous solution was acidified with dil. hydrochloric acid and was then extracted with ether (3  $\times$  100 ml). This ethereal extract was dried (MgSO<sub>4</sub>) and freed of solvent to afford a colorless crystalline product. This was recrystallized twice from ethyl acetate to give VIII (1.35 g, 27.5%) as needles, m.p. 225–226°,  $\lambda_{max}^{\text{CHEO}} = 5.86 \,\mu$  (Found: C, 62.54; H, 8.79. Calc. for C<sub>12</sub>H<sub>28</sub>O<sub>4</sub>: C, 63.13; H, 8.83%).

#### Oxidation of VIII

Formation of V. To a solution of VIII (0.29 g) in acetic acid (15 ml) was added dropwise with shaking a solution of chromium trioxide (0.40 g) in acetic acid (10 ml) and water (0.5 ml). After standing overnight at room temp the mixture was diluted with water (20 ml) and extracted several times with ether. The combined ethereal extracts were washed with cold dil. aqueous sodium hydroxide and dried (MgSO<sub>4</sub>). The residue obtained upon removal of the solvent was chromatographed on alumina (15 g). Elution with benzene-petroleum ether (1:1) afforded a crystalline solid which after 2 recrystallizations from ether-petroleum ether yielded prisms (0.11 g, 46%), m.p. 107-108°, shown to be V by I.R. spectral comparison and mixed m.p.