152. *Experiments Relating to the Synthesis of Patulin. Part II. Derivatives of 2 : 3-Diketo-4-acetyltetrahydrofuran.*

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Ethyl acetopyruvate has been condensed with formaldehyde in presence of aqueous potassium carbonate, yielding 2 : 3-*diketo*-4-*acetyltetrahydrofuran* (I), from which the corresponding enolic acetate, 2-*keto*-3-*acetoxy*-4-*acetyldihydrofuran*, was prepared. The enolic ethyl ether, 2-*keto*-3-*ethoxy*-4-*acetyldihydrofuran*, was prepared from both these compounds. Attempts to introduce an additional carbon atom into these compounds to give, for example, 2 : 3-diketo-4-β-hydroxypropionyltetrahydrofuran, were unsuccessful.

In Part I (preceding paper), attempts to synthesise patulin from compounds containing a γ-tetrahydropyrone ring were described. In the present paper, attempts have been made to synthesise patulin from compounds containing a tetrahydrofuran ring, namely, 2 : 3-*diketo*-4-*acetyltetrahydrofuran* and its derivatives.

For the condensation of formaldehyde with ethyl acetopyruvate, piperidine and potassium carbonate were selected as catalysts (cf. Claisen, *Ber.*, 1891, **24**, 116; Ruhemann, J., 1906, **89**, 1236). Preliminary experiments showed that with two equivalents of potassium carbonate, condensation took place readily at room temperature over a wide pH range, but that the best results were obtained by controlling the pH within narrow limits. By this method one hydroxymethyl group was introduced, and on acidification and extraction with ether, 2 : 3-diketo-4-acetyltetrahydrofuran (I) was obtained.

(I.) $CH_3 \cdot CO \cdot CH(CO{-}CO)O{-}CH_2$

(II.) $C_6H_5 \cdot CH{=}CH \cdot CO \cdot CH(CO{-}CO)O{-}CH_2$

Hydrolysis of the ester group presumably occurred during the acidification of the potassium derivative of ethyl β-methylolacetopyruvate; acetopyruvic acid is obtained in the same way by acidifying an alkaline solution of the sodium derivative of the ester (Lehninger and Wetzman, *J. Amer. Chem. Soc.*, 1942, **64**, 875).

In ethyl alcohol, 2 : 3-diketo-4-acetyltetrahydrofuran has a similar absorption spectrum ($\lambda_{max.}$ 2670 A., $\varepsilon = 13{,}700$) to that of the phenyl analogue ($\lambda_{max.}$ 2680 A., $\varepsilon = 11{,}900$) prepared by the method of Ruhemann (*loc. cit.*). In water, however, the spectrum exhibits a second maximum ($\lambda_{max.}$ 2700 A., $\varepsilon = 7000$ and $\lambda_{max.}$ 3180 A., $\varepsilon = 7800$), which is attributed to partial enolisation of the compound in aqueous solution.

The *anil* and the *phenylhydrazone* of 2 : 3-diketo-4-acetyltetrahydrofuran were prepared. The former was soluble and the latter insoluble in cold aqueous sodium carbonate solution. Ruhemann (*loc. cit.*) recorded similar properties for the corresponding derivatives of 2 : 3-diketo-4-acetyl-5-phenyltetrahydrofuran. 2 : 3-Diketo-4-acetyltetrahydrofuran itself was stable to hot concentrated mineral acid, but could not be recovered after treatment with 0·1N-alkali at room temperature for some hours.

Attempts to introduce a second hydroxymethyl group into 2 : 3-diketo-4-acetyltetrahydrofuran in the hope of preparing 2 : 3-diketo-4-β-hydroxypropionyltetrahydrofuran were unsuccessful, a *compound*, m. p. 241° (decomp.), being obtained. A small quantity of the same compound was isolated from a condensation between ethyl acetopyruvate and formaldehyde when catalysed by piperidine.

Benzaldehyde, on the other hand, condensed readily with 2 : 3-diketo-4-acetyltetrahydrofuran in dry ethyl acetate saturated with hydrogen chloride, giving 2 : 3-*diketo*-4-*cinnamoyltetrahydrofuran* (II). Chloral, however, was unreactive, and would not condense with 2 : 3-diketo-4-acetyltetrahydrofuran under conditions similar to or even more drastic than those successfully used with benzaldehyde.

Reaction with diphenylformamidine also failed to introduce an additional carbon atom, and only the anil of 2 : 3-diketo-4-acetyltetrahydrofuran could be isolated from such a reaction.

2 : 3-Diketo-4-acetyltetrahydrofuran, on treatment with acetic anhydride, yields the enolic acetate, 2-*keto*-3-*acetoxy*-4-*acetyldihydrofuran*, of which the acetyl group appears to be extremely labile, for, although it did not give a red colour with cold aqueous ferric chloride solution, it readily did so after warming with water. Treatment of 2 : 3-diketo-4-acetyltetrahydrofuran with ethyl orthoformate yielded the enolic ether, 2-*keto*-3-*ethoxy*-4-*acetyldihydrofuran*; the same compound was obtained when the enolic acetate of 2 : 3-diketo-4-acetyltetrahydrofuran was treated with excess (5 mols.) of ethyl orthoformate in acetic anhydride (10 mols.).

The enolic ethyl ether was stable to mineral acids, and therefore an attempt was made to condense it with formaldehyde, with a trace of mineral acid as catalyst; the reaction was also carried out in buffer solutions, but in neither instance did any condensation occur. No reaction appeared to take place with piperidine and dimethylamine hydrochlorides and formaldehyde.

Attempts to condense 2 : 3-diketo-4-acetyltetrahydrofuran, the enolic acetate, or enolic ethyl ether with

ethyl oxalate or ethyl formate in presence of sodium ethoxide, molecular sodium or sodium triphenylmethyl under various conditions were uniformly unsuccessful.

Owing to pressure of other work this investigation cannot be continued, but as some of the components herein described have interesting pharmacological properties, which will be described elsewhere, it is considered desirable to place these results on record.

Experimental.

2 : 3-*Diketo*-4-*acetyltetrahydrofuran* (I).—Freshly prepared ethyl acetopyruvate (25 g.) was dissolved in an aqueous solution (150 ml.) containing 13·2 ml. of 37% formalin and 21·8 g. of potassium carbonate. The pH was adjusted to 8·8—9·0 by addition of more potassium carbonate, and the solution left at room temperature. A voluminous precipitate soon separated, which was redissolved by addition of water. For the next few hours the pH of the solution gradually fell until it reached 8·3; the solution was then acidified with 2N-hydrochloric acid and extracted continuously with ether for 4—5 hours. The extract was dried over sodium sulphate and evaporated, leaving an oily solid. This was recrystallised from benzene, yielding a white crystalline solid (11·9 g.), m. p. 126—126·5°, which could be sublimed readily at 30°/0·004 mm. (Found : C, 50·6; H, 4·35; *C*-CH_3, 12·4. $C_6H_6O_4$ requires C, 50·7; H, 4·2; 1 *C*-CH_3, 10·5%).

The quantity of potassium carbonate required to bring the pH of the aqueous solution to 8·8—9·0, and the period of time necessary for the pH to fall to 8, varied with different batches of ester. In order to obtain good yields it was essential to maintain the pH of the reaction mixture between 8·3 and 9·0 for 5—7 hrs. by addition of potassium carbonate.

2 : 3-*Diketo*-4-*acetyltetrahydrofuranphenylhydrazone* was prepared in the usual way and recrystallised from alcohol, yielding pale yellow needles, m. p. 167° (decomp.) (Found : C, 61·7; H, 5·0; N, 12·2. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2; N, 12·1%).

The *anil*, prepared in a similar manner, was obtained in yellow prisms, m. p. 211·5° (decomp.) (Found : C, 66·4; H, 5·1; N, 6·3. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1; N, 6·45%).

Reaction of 2 : 3-*Diketo*-4-*acetyltetrahydrofuran with Formaldehyde.*—2 : 3-Diketo-4-acetyltetrahydrofuran (1 g.) was treated with an aqueous solution (35 ml.) of 0·56 ml. of formalin (37·4%) and 0·2 ml. of 2N-hydrochloric acid at room temperature for 3 days. The solution, which still smelled strongly of formaldehyde, was evaporated under reduced pressure, leaving a solid residue. This was extracted with boiling benzene and precipitated with water first from alcohol and then from acetic acid as a pale pink, amorphous solid, m. p. 241° (decomp.). Yield 480 mg. The substance gave a red colour with alcoholic ferric chloride, but was insoluble in camphor and its molecular weight was therefore determined ebullioscopically in acetic acid. The result, although only approximate, indicated a molecular weight of 250—270 (Found : C, 50·8, 50·8; H. 3·9, 4·0; *C*-CH_3, 1·3; active H, 0·56. $C_{15}H_{16}O_{10}$ requires C, 50·5; H, 4·5; 2 active H, 0·56%).

2 : 3-*Diketo*-4-*cinnamoyltetrahydrofuran* (II).—A solution of 2 : 3-diketo-4-acetyltetrahydrofuran (4 g.) in dry ethyl acetate (50 ml.) was saturated at 0° with hydrogen chloride, treated with benzaldehyde (4 g.), and left at room temperature for 24 hrs. The thick crystalline mass deposited was collected, washed with a little ethyl acetate, and recrystallised from alcohol–benzene and then from dilute alcohol. It formed pale yellow platelets (3·1 g.), m. p. 191°. The *compound* could be sublimed at 150°/0·005 mm. [Found : C, 67·7; H, 4·5; *M* (Rast), 240. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·35%; *M*, 230]. The absorption spectrum had a maximum at 3250 A, ϵ 20,000 in alcohol.

Reaction of Diphenylformamidine with 2 : 3-*Diketo*-4-*acetyltetrahydrofuran.*—2 : 3-Diketo-4-acetyltetrahydrofuran (1 g.) was heated at 135° with diphenylformamidine (1·4 g.) for 5 mins., and the mixture then cooled and triturated with alcohol. Crystallisation of the precipitated solid from alcohol gave the anil of 2 : 3-diketo-4-acetyltetrahydrofuran as pale yellow needles, m. p. 211·5° (decomp.), not depressed by an authentic specimen (Found : C, 66·0; H, 5·1; N, 6·3%).

2-*Keto*-3-*acetoxy*-4-*acetyldihydrofuran.*—A mixture of 2 : 3-diketo-4-acetyltetrahydrofuran (3 g.) and acetic anhydride (25 ml.) was heated on a steam-bath for 3 hrs. and then evaporated under reduced pressure. The residual crystalline solid was recrystallised from benzene, yielding 1·85 g. of white platelets, m. p. 78·5°, which sublimed readily at 70—80°/0·005 mm. (Found : C, 52·1; H, 4·3. $C_8H_8O_5$ requires C, 52·2; H, 4·3%). It gave a red colour with ferric chloride solution.

2-*Keto*-3-*ethoxy*-4-*acetyldihydrofuran.*—A mixture of 2 : 3-diketo-4-acetyltetrahydrofuran (10 g.) and ethyl orthoformate (25 g.) was heated under reflux for 24 hrs. The residual oil left after evaporation under reduced pressure was fractionated in a vacuum. The fraction (4·7 g.), b. p. 62—63°/0·02 mm., slowly crystallised in the refrigerator. It was sublimed at 30°/0·002 mm. on to a glass tube cooled with acetone–solid carbon dioxide; the substance formed white platelets, m. p. 31·5° (Found : C, 56·7; H, 5·9; EtO, 25·2. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9; EtO, 26·5%), and gave no coloration with cold aqueous or alcoholic ferric chloride solution.

A crystalline 3 : 5-*dinitrophenylhydrazone* was prepared in the normal manner. After recrystallisation from glacial acetic acid and then from ethyl acetate it formed yellow needles, m. p. 222—223°, which gave a positive Neuberg reaction with alcoholic caustic potash (Found : C, 48·1; H, 3·9; N, 15·8; EtO, 13·2; *C*-CH_3, 9·9. $C_{14}H_{14}O_7N_4$ requires C, 48·0; H, 4·0; N, 16·0; EtO, 12·9; 2*C*-CH_3, 8·6%).

The *phenylhydrazone*, m. p. 156°, was also prepared (Found : C, 64·2; H, 6·0; N, 10·4; EtO, 17·8; *C*-CH_3, 15·0. $C_{14}H_{16}O_3N_2$ requires C, 64·6; H, 6·15; N, 10·75; EtO, 17·3; 2*C*-CH_3, 11·5%). As will be noted, the Kuhn–Roth determinations of *C*-CH_3 were consistently high in this series of compounds.

An identical product was obtained when 2-keto-3-acetoxy-4-acetyldihydrofuran (6 g.) was heated under reflux for 24 hrs. with acetic anhydride (35 ml.) and ethyl orthoformate (51 ml.), and the resultant products fractionated in a vacuum. Yield, 2·6 g. of a fraction, b. p. 68—69°/0·06 mm., giving a 3 : 5-dinitrophenylhydrazone and a phenylhydrazone identical with those described above.

All melting points are uncorrected.

Microanalyses were carried out by Miss H. King.

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