758. *Experiments on the Synthesis of Carbonyl Compounds. Part VI.* A New General Synthesis of Ketones and β-Keto-esters.*

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Esters of tetrahydropyran-2-ol (such as the acetate) undergo thermal decomposition to 2 : 3-dihydropyran and the carboxylic acid under mild conditions. This led to a new and apparently general synthesis of ketones starting from malonic acids and acid chlorides (cf. *Chem. and Ind.*, 1951, 742).

The main object of the work recorded in this series of papers has been to evolve new methods of synthesis of ketones starting from acid chlorides and substituted malonic esters. The problem is to convert acylmalonic esters (II) into their acids (III), preferably without recourse to aqueous hydrolysis; thermal degradation of the latter then yields the ketones (IV). We described in Part I (*J.*, 1950, 322) the use of acidolysis for the case where $R = H$ and $R' = Et$, and in Part II (*J.*, 1950, 325) and in subsequent papers a more general method whereby the benzyl esters (II; $R' = CH_2Ph$) are catalytically hydrogenated to the free acids (III) which, on being heated, furnish the ketones (IV). The last method is

$$\begin{array}{ccccccc} R{\cdot}CH(CO_2R')_2 & \xrightarrow{R''{\cdot}COCl} & R''{\cdot}CO{\cdot}CR(CO_2R')_2 & \longrightarrow & R''{\cdot}CO{\cdot}CR(CO_2H)_2 & \longrightarrow & R''{\cdot}CO{\cdot}CH_2R \\ \text{(I)} & & \text{(II)} & & \text{(III)} & & \text{(IV)} \end{array}$$

satisfactory in many cases, but applies only to the preparation of ketones containing functional groups resistant to hydrogenation, and is also limited by rather difficult and exacting techniques. We therefore attempted to extend the synthesis in a more general manner; when these experiments were almost completed Fonker and W. S. Johnson

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* Part V, *J.*, 1951, 2758.

(*J. Amer. Chem. Soc.*, 1952, **74**, 831) reported an elegant new method employing di-*tert.*-butyl malonate.

Malonic esters of tetrahydropyran-2-ol appeared attractive on account of the mild conditions under which it was expected that they would undergo hydrolysis (cf. Jones and Taylor, *Quart. Reviews*, 1950, 207) although, as will be seen, the investigation developed in another direction and we have not examined this last possibility.

Reaction of 2 : 3-dihydropyran and carboxylic acids appears to have been restricted hitherto to the preparation of the *p*-nitrobenzoate (Woods and Kramer, *J. Amer. Chem. Soc.*, 1947, **69**, 2246) and the acetate, the latter formed in 60% yield by refluxing a mixture of dihydropyran and acetic acid for a short time (Bremner and Jones, B.P. 606,764). We have confirmed the yield in the latter preparation by analytical methods and by direct isolation of the product by distillation at low temperatures. On distillation at atmospheric pressure, however, the acetate suffered partial decomposition, giving a mixture of the ester, dihydropyran, and acetic acid in approximately the same proportions as were obtained by interaction of dihydropyran and acetic acid at the boiling point.

We next examined the influence of acid catalysts, since these have been shown to be effective in the preparation of ethers of tetrahydropyran-2-ol (Woods and Kramer, *loc. cit.*) and, indeed, at room temperature in the presence of a trace of *m*-xylenesulphonic acid, the addition proceeded rapidly with evolution of heat to completion. The reaction is therefore catalysed by hydrogen ions and the position of equilibrium is markedly temperature-dependent, being almost completely in favour of ester at room temperature. The ease of preparation and pyrolytic decomposition of these esters under such mild conditions offers a new method for the protection of carboxylic acid groupings and with its aid a new ketone synthesis has been evolved. The malonic acid is suspended in benzene and brought into reaction with an excess of dihydropyran in the presence of a trace of sulphuric acid, a rapid exothermic reaction occurring with dissolution of the acid. After a short time, solvent and excess of dihydropyran are removed under reduced pressure to give (I; R′ = tetrahydro-2-pyranyl). The latter is then converted into its sodio-derivative with metallic sodium and the acid chloride added, all operations being conducted below 40°. Refluxing the resultant mixture, preferably in the presence of a small amount of acetic acid, then brings about irreversible degradation of the keto-ester to ketone, carbon dioxide and, presumably, dihydropyran.

In this manner we prepared the simple ketones 1-phenyltetradecan-3-one (*n*-dodecanoyl chloride and benzylmalonic acid; 60%), 1-phenyldecan-1-one (benzoyl chloride and *n*-octylmalonic acid; 50%), tetracos-1-en-11-one (undec-10-enoyl chloride and *n*-dodecylmalonic acid; 76%), 13-ketotricos-22-enoic acid * (undec-10-enoyl chloride and undecane-1 : 1 : 11-tricarboxylic acid; 75%), and ethyl 2-ketoundecanoate (ethoxalyl chloride and *n*-octylmalonic acid; 65%); the last ester was hydrolysed in good yield to the known parent α-keto-acid.

In extending the method to ketones which are more difficult of access by other reactions we obtained 2-chlorodecan-3-one (α-chloropropionyl chloride and *n*-hexylmalonic acid; 92%), 1-phenyldec-1-yn-3-one (phenylpropiolyl chloride and *n*-hexylmalonic acid; 85%), trideca-2 : 4-dien-6-one (sorboyl chloride and *n*-hexylmalonic acid; 90%), and ethyl *trans*-4-ketoheptadec-2-enoate (ethyl fumaryl chloride and *n*-dodecylmalonic acid; 45%).

Acid anhydrides may also be used, as shown by the use of glutaric anhydride and *n*-amylmalonic acid to give 5-ketoundecanoic acid in 45% yield. Finally, we extended the method to β-keto-esters and prepared, by slightly modified procedures, ethyl 3-ketononoate (*n*-heptanoyl chloride and ethyl hydrogen malonate; 77%) and ethyl 3-keto-2-methyltetradecanoate (*n*-dodecanoyl chloride and ethyl hydrogen methylmalonate; 50%).

It will be noted that the yields described above were somewhat variable and except when anhydrides were used it is probably not fortuitous that they increased as our experience of the method grew. This is not clear on inspection since the experiments are not set out in chronological order, and in no case was any preparation repeated.

In the Experimental section many derivatives, as well as some further reactions of the ketones prepared in this manner, are described.

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* Geneva numbering, CO_2H = 1, throughout.

EXPERIMENTAL

Light petroleum refers throughout to the fraction of b. p. 60—80°. Benzene was " AnalaR " material stored over sodium wire.

Dihydropyran was supplied by Imperial Chemical Industries Limited and was purified by distillation through a column, material of b. p. 85—86° being collected.

Reaction of Dihydropyran and Acetic Acid.—(1) *In absence of catalyst.* A mixture of dihydropyran (84 g., 1 mol.) and redistilled glacial acetic acid (30 g., 0·5 mole) was refluxed for 4 hours; determinations of free acidity of the reaction mixture showed that after 1 hour the amount of free acid had dropped to one-third of the initial amount and was unaffected by further refluxing. The products of reaction were worked up as described in B.P. 606,764.

(2) *In presence of* m-*xylenesulphonic acid.* To dihydropyran (84 g., 1 mole) and *m*-xylenesulphonic acid (5 mg.), stirred in absence of moisture, acetic acid (30 g., 0·5 mole) was added dropwise with stirring during 0·5 hour, the temperature of the reaction mixture rising to 40°. After 0·5 hour at room temperature, at least 99% of the acetic acid had reacted, and the product was neutralised by stirring it with a slurry of potassium carbonate (2 g.) in water (4 ml.) and, after decantation, was distilled. The yield of tetrahydropyranyl acetate, b. p. 42—43°/1 mm., n_{D}^{20} 1·4378, was 62 g. (90%).

General Method for Ketone Synthesis.—The requisite malonic acid (0·05 mole) was added in portions to a solution of dihydropyran (0·075 mole per carboxyl grouping in the malonic acid) in benzene (50 ml.) containing concentrated sulphuric acid (1 drop), with cooling to $<30°$. Heat was evolved during the addition and for some time afterwards. In all cases, the reaction was substantially complete when a clear solution was obtained, but in practice the mixture was left at room temperature for a further 0·5 hour. At this stage we frequently determined free acidity to confirm the almost complete conversion into ester. Traces of free acid were then removed by shaking or stirring the solution with solid potassium hydroxide (4 g.) for 0·5 hour and the solution was decanted from inorganic material. Solvent and excess of dihydropyran were removed by distillation *in vacuo* (bath-temp. $<30°$) and the residual ester in benzene was (50 ml.) added to sodium powder (0·05 g.-atom) in benzene (100 ml.), with cooling to $<35°$. When dissolution of the metal was complete, a solution of the acid chloride (0·05 mole) in benzene (50 ml.) was added and, after 0·5 hour at room temperature, acetic acid (5 ml.) was added and the solution boiled under reflux until evolution of carbon dioxide ceased (*ca.* 1·5 hours). The cooled mixture was washed with water or, if the final product was neutral, with dilute alkali. After removal of solvent, the resulting material was purified by distillation or crystallisation.

The addition of acetic acid is optional but, since it reduces the time necessary for decarboxylation and rarely attacks the ketonic compound, is advantageous.

The following were obtained from the materials and in the yields stated on p. 3946 :

1-*Phenyltetradecan*-3-*one*, an oil, b. p. 170—172°/0·8 mm., which solidified and then crystallised from methanol in thin plates, m. p. 31° (Found : C, 83·9; H, 11·0. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%).

1-*Phenyldecan*-1-*one*, an oil, b. p. 142—146°/2 mm., which solidified and then separated from methanol in slender needles, m. p. 33—33·5° (Found : C, 82·7; H, 10·0. $C_{16}H_{24}O$ requires C, 82·7; H, 10·3%). Its *phenylsemicarbazone* crystallised from methanol–ethyl acetate in small needles, m. p. 110° (Found : N, 11·5. $C_{23}H_{31}ON_3$ requires N, 11·5%).

Tetracos-1-*en*-11-*one* was obtained as a solid mass (m. p. 57°) which separated from ethyl acetate in plates, m. p. 57° (Found : C, 82·1; H, 13·0. $C_{24}H_{46}O$ requires C, 82·2; H, 13·2%). Catalytic hydrogenation with palladium oxide in ethyl methyl ketone furnished *tetracosan*-11-*one* as lustrous plates (from methanol), m. p. 64—64·5° (Found : C, 81·6; H, 13·4. $C_{42}H_{48}O$ requires C, 81·7; H, 13·7%) which formed an *oxime*, prisms (from methanol), m. p. 38° (Found : N, 3·7. $C_{24}H_{49}ON$ requires N, 3·8%). On Wolff–Kishner reduction using Huang-Minlon's modified conditions (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) the unsaturated ketone furnished *tetracos*-1-*ene* (90%) as leaflets, m. p. 46—46·5°, from ethyl acetate (Found : C, 85·7; H, 14·1. $C_{24}H_{48}$ requires C, 85·7; H, 14·3%).

2-*Chlorodecan*-3-*one* was prepared by the general procedure except that reaction with the acid chloride, which was added in one portion, was carried out at 0°, after which the mixture was allowed to rise to room temperature overnight. The product was a colourless oil (92%), b. p. 70—71°/1 mm., n_{D}^{20} 1·4512 (Found : C, 63·2; H, 10·0. $C_{10}H_{19}OCl$ requires C, 63·0; H, 10·0%).

1-*Phenyldec*-1-*yn*-3-*one*, a pale yellow oil, b. p. 127—128°/0·5 mm., n_{D}^{20} 1·5275 (Found : C, 83·4; H, 9·1. $C_{16}H_{20}O$ requires C, 84·2; H, 8·8%). On hydrogenation in ethyl methyl ketone over palladium oxide, the product absorbed 2 mols. of hydrogen and gave 1-*phenyldecan*-3-*one*, b. p. 128—129°/0·5 mm., n_D^{20} 1·4920 (Found : C, 82·6; H, 10·4. $C_{16}H_{24}O$ requires C, 82·7; H, 10·4%), which formed a 2 : 4-*dinitrophenylhydrazone*, orange plates (from ethanol), m. p. 73° (Found : C, 64·1; H, 6·9; N, 14·1. $C_{22}H_{28}O_4N_4$ requires C, 64·1; H, 6·8; N, 13·6%).

Trideca-2 : 4-dien-6-one, a pale yellow oil, b. p. 105—106°/1 mm., n_D^{20} 1·4860 ($\lambda_{max.}$ 273 mμ, $\varepsilon_{max.}$ 19,300 in ethanol). In spite of repeated efforts we were unable to obtain reproducible or the required analytical figures (Found : C, 76·0—78·5; H, 10·9—11·6%. Calc. for $C_{13}H_{22}O$: C, 80·4; H, 11·4%), although by oxime titration the material was at least 98% pure. It formed a 4-*phenylsemicarbazone*, pale yellow needles (from methanol), m. p. 123—124° (Found : C, 73·5; H, 9·1; N, 13·3. $C_{20}H_{29}ON_3$ requires C, 73·4; H, 8·9; N, 12·9%).

Ethyl 2-*ketoundecanoate*, a colourless oil, b. p. 110—111°/1·3 mm., n_D^{20} 1·4374 (Found : C, 68·2; H, 10·3. $C_{13}H_{24}O_3$ requires C, 68·4; H, 10·5%), formed an *oxime*, needles (from light petroleum), m. p. 66—67° (Found : N, 5·85. $C_{13}H_{25}O_3N$ requires N, 5·8%). The ester (4 g.) was refluxed with constant-boiling hydrochloric acid (50 ml.) and acetic acid (20 ml.) for 6 hours. When the cooled solution was poured into water the product crystallised (3 g.). 2-Ketoundecanoic acid crystallised from light petroleum in glistening plates, m. p. 54·0—54·5° (Found : C, 66·2; H, 9·8. Calc. for $C_{11}H_{20}O_3$: C, 66·0; H, 10·0%), and formed a *phenylhydrazone*, almost colourless nacreous plates (from light petroleum), m. p. 93·5—94·0° (Found : N, 9·7. $C_{17}H_{26}O_2N_2$ requires N, 9·7%) ; on reduction in ethyl methyl ketone over palladium oxide, it gave 2-hydroxyundecanoic acid, needles (from light petroleum), m. p. 68·5—69° (lit., 69°).

13-*Ketotricos*-22-*enoic acid* was obtained a solid (m. p. 75—80°) after washing of the final reaction product with 70% ethanol. The pure acid was obtained by crystallisation from light petroleum, from which it separated in rectangular plates, m. p. 85—86° (Found : C, 75·4; H, 11·3. Calc. for $C_{23}H_{42}O_3$: C, 75·4; H. 11·5%). It formed a p-*bromophenacyl* ester, colourless plates (from ethyl acetate), m. p. 85° (Found : C, 66·0; H, 8·4. $C_{31}H_{47}O_4Br$ requires C, 66·1; H, 8·3%). On catalytic reduction, as previously, it gave 13-*ketotricosanoic acid*, plates (from methanol), m. p. 93—93·5° (Found : C, 74·9; H, 11·7. $C_{23}H_{44}O_3$ requires C, 74·9; H, 11·9%), and on Wolff–Kishner reduction (Huang-Minlon, *loc. cit.*) it furnished tricos-22-enoic acid, rectangular plates (from light petroleum), m. p. 73·5—74·0° (Found : C, 78·7; H, 12·6. Calc. for $C_{23}H_{44}O_2$: C, 78·4; H, 12·5%). E. Stenhagen (*Arkiv Kemi*, 1949, **13**, 99) reports m. p.s of 86·5—86·7° and 74·3—74·5° for the keto-enoic and the enoic acid respectively. A sample of the latter was catalytically reduced in the usual manner to *n*-tricosanoic acid, m. p. 79°, undepressed on admixture with an authentic specimen (Ames, Bowman, and Mason, *J.*, 1950, 174).

Ethyl trans-4-*ketoheptadec*-2-*enoate* [from ethyl fumaryl chloride (Eisner, Elvidge, and Linstead, *J.*, 1951, 1508) and *n*-dodecylmalonic acid] distilled as a colourless liquid, b. p. 170—180°/1 mm., which rapidly solidified and then crystallised from methanol in clusters of needles, m. p. 38—38·5°, $\lambda_{max.}$ 222 mμ, $\varepsilon_{max.}$ 11,900 in ethanol (Found : C, 73·4; H, 10·7. $C_{19}H_{34}O_3$ requires C, 73·5; H, 11·0%). Attempts to obtain the free acid by alkaline or acid hydrolysis led to coloured gums.

5-*Ketoundecanoic Acid*.—*n*-Amylmalonic acid (0·05 mole) was converted into the sodiobistetrahydropyranyl ester in benzene according to the general method, and glutaric anhydride (5·7 g., 0·05 mole) in benzene (20 ml.) added. After 1 hour at room temperature the reaction mass solidified to a colourless gel. Acetic acid (20 ml.) was then added and the mixture boiled under reflux until evolution of carbon dioxide ceased (0·5 hour). Water was added and the organic extract evaporated to dryness under reduced pressure, to give an oil which solidified (10 g.). Crystallisation from ethyl acetate and then ethyl acetate–light petroleum furnished the keto-acid (4 g., 45%) as colourless plates, m. p. 59—60° (Found : C, 66·2; H, 10·0. Calc. for $C_{11}H_{20}O_3$: C, 66·0; H, 10·1%). It formed p-*bromophenacyl* ester, laminæ (from moist ethanol), m. p. 78—79° (Found : C, 57·5; H, 6·2. $C_{19}H_{45}O_4Br$ requires C, 57·4; H, 6·3%).

Ethyl 3-*Ketononoate*.—Ethyl hydrogen malonate (b. p. 101—102°/2 mm., n_D^{20} 1·4295; 26 g., 0·2 mole) was added slowly to a solution of dihydropyran (25 g.) in benzene (30 ml.) containing 3 drops of a 10% solution of *m*-xylenesulphonic acid in methanol, during 0·5 hour; the initial and the final temperature of the mixture were 16° and 34° respectively. Excess of solvent and dihydropyran were removed *in vacuo* and the colourless residual ester con verted into its sodioderivative and treated with *n*-heptanoyl chloride (0·2 mole), as previously . After decarboxylation and isolation in the usual manner, the product was distilled, the fraction of b. p. 88—90°/1·5 mm. (14 g., 77%) being collected. This material, which was the almost pure keto-ester, was purified with very little loss by washing its solution in light petroleum with sodium hydrogen carbonate solution; it then distilled at 96—97°/3 mm. and had n_D^{20} 1·4415 (Found: C, 66·4; H, 10·1. Calc. for $C_{11}H_{20}O_3$: C, 66·0; H, 10·1%). It formed a phenylpyrazolone, m. p. 83°; Wahl and Doll (*Bull. Soc. chim.*, 1913, **13**, 275) reported m. p. 83—84°.

Ethyl 3-*Keto*-2-*methyltetradecanoate*.—This *ester* was prepared from *n*-dodecanoyl chloride and ethyl hydrogen methylmalonate (cf. Breslow, Baumgarten, and Hauser, *J. Amer. Chem. Soc.*, 1944, **66**, 1287) in the usual manner, the crude product in light petroleum being washed with aqueous sodium hydrogen carbonate before distillation; it was obtained as a colourless oil, b. p. 144—145°/1·5 mm., n_D^{20} 1·4450 (Found: C, 72·6; H, 11·1. $C_{17}H_{32}O_3$ requires C, 71·8; H, 11·3%). It furnished a p-*nitrophenylpyrazolone*, yellow prisms (from light petroleum–ethyl acetate), m. p. 85—86° (Found: C, 67·6; H, 8·5. $C_{21}H_{31}O_3N_3$ requires C, 67·5; H, 8·4%). The keto-ester (2·5 g.) was hydrolysed by refluxing it with acetic acid (15 ml.) and sulphuric acid (5 ml. of 80%) for 1 hour. The cooled mixture was poured into water and the material isolated in the usual manner as a solid (1·5 g.; m. p. 32°) which crystallised from methanol in glistening plates, m. p. 33—33·5°. Blaise and Guerick (*Bull. Soc. chim.*, 1903, **29**, 1208) give the m. p. of tetradecan-3-one as 34°.

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