Notes

[Chem. Pharm. Bull. 13(11)1359~1361(1965)]

UDC 547.514.4.07

Kentaro Hiraga: Syntheses of 1,3-Cyclopentanediones.

(*Chemical Research Laboratories, Research & Development Division, Takeda Chemical Industries, Ltd.*[*1])

It has been shown[1] that 1,3-cyclopentanediones are the important starting materials for the syntheses in gonane series.

Thus, several 2-substituted 1,3-cyclopentanediones were prepared by the method[2] used for the synthesis of 2-methyl-1,3-cyclopentanedione (Ⅳ, R=CH_3) (see Chart 1). The yield of each step was almost the same as that of the corresponding step in the literature.[2] The melting points of the intermediates and the products were listed in Table I. The physicochemical nature of these compounds will be discussed in the following paper.

Instead of the Wolff-Kishner process in the above synthesis, Clemmensen's method was applied for the reduction of 3-substituted 1,2,4-cyclopentanetrione (Ⅱ), and this was found to give the objective diones in fairly good yields. It was interesting that only the oxo-group at carbon 1 in substituted 1,2,4-cyclopentanetrione (Ⅱ) has ketonic nature as indicated by the above reactions.

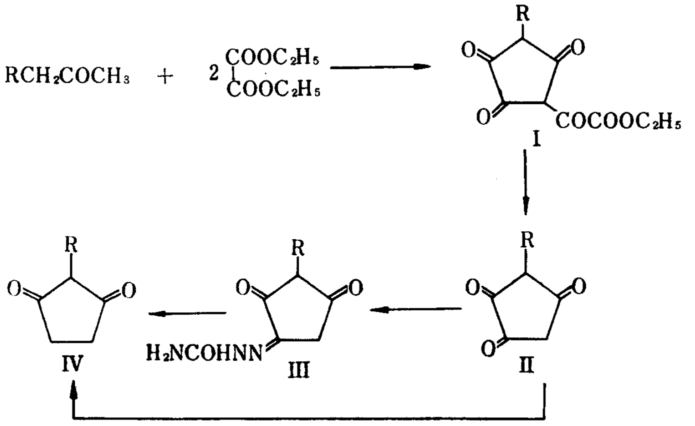


Chart 1.

Table I. Melting Points of Cyclopentanepolyones (°C)

R	C_2H_5	iso-C_3H_7	CH_2-C_6H_5
I	195~197	200	141~142
Ⅱ	79	99~100	82~85
Ⅲ	>300	>300	278
Ⅳ	177~178[4]	208[4]	196

Only a few methods to synthesize 1,3-cyclopentanediones have been described previously.[2,3]

While 1,3-cyclohexanediones are easily obtained by internal condensation from δ-ketoesters, the corresponding five-membered diketones can be prepared from γ-ketoesters similarly only in the event that the β-position of the γ-ketoester is fully substituted with methyl groups[5] or the δ-position is activated with phenyl group[6]:

[*1] Juso-nishino-cho, Higashiyodogawa-ku, Osaka (平賀謙太郎).

1) T. Miki, K. Hiraga, T. Asako: This Bulletin, **13**, 1285, 1289, 1294 (1965).

2) *a*) J. J. Panouse, C. Sannie: Bull. soc. chim. France, **1955**, 1036. *b*) C. B. C. Boyce, J. S. Whitehurst: J. Chem. Soc., **1959**, 2022.

3) *a*) R. B. Woodward, E. R. Blout: J. Am. Chem. Soc., **65**, 562 (1943). *b*) F. Merényi, M. Nilsson: Acta Chem. Scand., **17**, 1801 (1963). *c*) M. Vandewalle: Bull. Soc. Chim. Belg., **73**, 628 (1964).

4) H. Smith, *et al.*: J. Chem. Soc., **1964**, 4472.

5) *a*) E. Rothstein, J. F. Thorpe: J. Chem. Soc., **1926**, 2011. *b*) A. Kandiah: *Ibid.*, **1931**, 952.

6) B. E. Betts, W. Davey: *Ibid.*, **1961**, 3333.

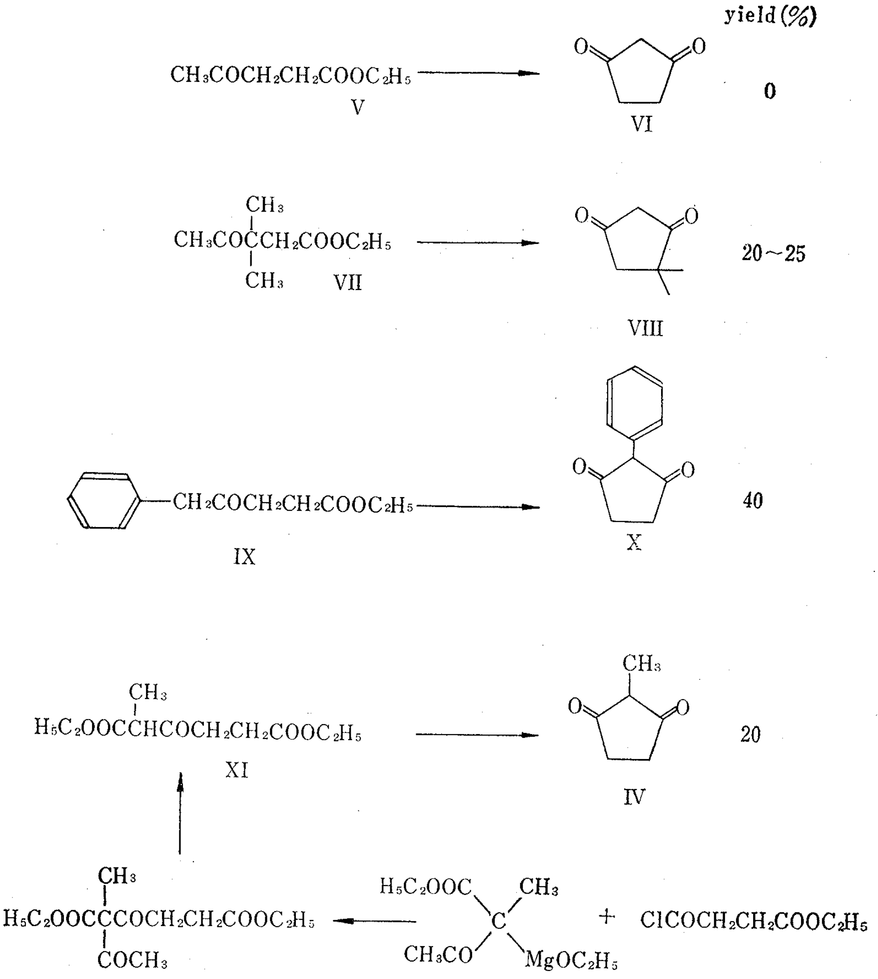


Chart 2.

for example, 1,3-cyclopentanedione was not obtained by internal cyclization of ethyl levulinate.[7]

The author took diethyl 2-methyl-3-oxoadipate (XI), a derivative of ethyl levulinate activated at δ-position with an ethoxycarbonyl group, and its cyclization reaction was investigated. The adipate (XI) was prepared easily by the successive reactions shown in Chart 2. On heating at a rather high temperature (180°) in the presence of potassium *tert*-butoxide, XI was cyclized directly to 2-methyl-1,3-cyclopentanedione (IV, $R=CH_3$) albeit the yield was rather low.

Experimental*2

Ethyl 4-Ethyl-2,3,5-trioxocyclopentylglyoxylate (I, $R=C_2H_5$)——A mixture of 43 g. of 2-pentanone and 146 g. of diethyl oxalate was added to a stirred solution of 23 g. of Na in 250 ml. of EtOH during 30 min. under ice-cooling.

The reaction mixture was heated at the refluxing temperature for 45 min. to give a black viscous solution. After cooling, 120 g. of 50% H_2SO_4 was added gradually, and the resulting precipitate of Na_2SO_4 was filtered. Evaporation of the solvent afforded a yellow crystalline material, which was recrystallized from AcOEt to give yellow needles (100 g.), m.p. 195~196°.

3-Ethyl-1,2,4-cyclopentanetrione (II, $R=C_2H_5$)——The solution of 60 g. of I ($R=C_2H_5$) in 70 ml. of 6*N* HCl was heated at the refluxing temperature for 45 min.

---

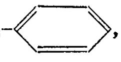
*2 All melting points are uncorrected.

[7] *a*) P. de Rosanbo: Ann. Chim., 9, **19**, 327 (1923). *b*) P. Duden, R. Freydag: Ber., **36**, 947 (1903).

After 2/3 volume of the solvent was distilled off, the residual solution was extracted with ether 8 times and the combined extracts were washed with H_2O, dried over Na_2SO_4 and concentrated to give a crystalline material, which was recrystallized from H_2O to give colorless needles (35 g.), m.p. 79°.

1-Semicarbazone of 3-Ethyl-1,2,4-cyclopentanetrione (III, R=C_2H_5)——To a solution of 60 g. of Ⅱ (R=C_2H_5) in 430 ml. of EtOH and 430 ml. of H_2O was added a solution of 48 g. of semicarbazide hydrochloride and 65 g. of AcONa in 430 ml. of H_2O at room temperature and the mixture was allowed to stand at room temperature for 30 min. The resulting precipitate was collected on a filter and washed with EtOH and dried to afford 65 g. of pale yellow crystals, m.p. $>$300°.

2-Ethyl-1,3-cyclopentanedione (IV, R=C_2H_5)——A suspension of 65 g. of Ⅲ (R=C_2H_5) and 65 g. of NaOH in 650 ml. of ethylene glycol was heated at the refluxing temperature for 14 hr. The solvent was evaporated under reduced pressure, and the residue was diluted with a small amount of H_2O and acidified with conc. HCl, giving a crystalline material, which was collected on a filter and recrystallized from H_2O to give colorless needles (30 g.), m.p. 177~178°. *Anal.* Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found : C, 66.79; H, 7.90.

2-Isopropyl-1,3-cyclopentanedione (Ⅳ, R=iso-C_3H_7, m.p. 218°, *Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found : C, 68.46; H, 8.58) and 2-benzyl-1,3-cyclopentanedione (Ⅳ, R=CH_2-, m.p. 196°, *Anal.* Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found : C, 76.11; H, 6.40) were prepared starting from the corresponding ketones and ethyl oxalate by the same procedure.

Cyclization of Diethyl 2-Methyl-3-oxoadipate (XI)——A mixture of 10 g. of X, 1.7 g. of *t*-BuOK and 50 ml. of toluene was heated at 200° for 10 hr. in a sealed tube.

After cooling, the reaction mixture was shaken with H_2O, and the H_2O layer was separated, acidified with HCl, and evaporated under reduced pressure. The residue afforded 1 g. of Ⅳ (R=CH_3), m.p. 205~208°, by trituration with a small amount of H_2O.

Clemmensen Reduction of 3-Methyl-1,2,4-cyclopentanetrione (II, R=CH_3)——A mixture of 1.5 g. of Ⅱ (R=CH_3), 25 ml. of conc. HCl, 15 ml. of H_2O and 5 g. of amalgamated Zn was heated at the refluxing temperature for 3 hr. After separating the Zn by decantation, the H_2O solution was concentrated under reduced pressure. The residue was extracted with AcOEt and the AcOEt solution was washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated to yield 0.7 g. of Ⅳ (R=CH_3), m.p. 205~207°.

The author wishes to express to Takeda Chemical Industries, Ltd. for permission to publish this report, to Dr. Y. Abe and Dr. T. Miki for their guidance and encouragement throughout this work.

He is also indebted to Mr. T. Asako and Mr. H. Masuya for their technical assistance, to Mr. M. Kan and his associates for elemental analysis.

Summary

2-Ethyl, 2-isopropyl and 2-benzyl-1,3-cyclopentanediones were synthesized by the known method.

Diethyl 2-methyl-3-oxoadipate was cyclized to 2-methyl-1,3-cyclopentanedione by heating with potassium *tert*-butoxide.

3-Methyl-1,2,4-cyclopentanetrione was reduced to 2-methyl-1,3-cyclopentanedione by Clemmensen method.

(Received April 19, 1965)