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83. Takuichi Miki, Kentaro Hiraga, Tsunehiko Asako, and Hirotomo Masuya: New Synthesis of 2-Substituted Cyclopentane-1,3-dione.*1

(*Chemical Research Laboratories, Research and Development Division, Takeda Chemical Industries, Ltd.**2)

2-Methyl, 2-propyl and 2-phenethylcyclopentane-1,3-dione (Ⅲ) were prepared by the catalytic hydrogenation of the corresponding 2-(α-ethoxyalkylidene)cyclopent-4-ene-1,3-diones, (Ⅱ), which were obtained by the condensation of cyclopent-4-ene-1,3-dione (I) and ethyl ester of ortho acids.

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Recently, 2-substituted cyclopentane-1,3-diones are often used as the starting material for the syntheses of steroids.[1]

In the present paper we wish to report a new and economical method for preparing 2-substituted cyclopentane-1,3-diones by two steps from cyclopent-4-ene-1,3-dione (I).

Cyclopent-4-ene-1,3-dione (I) is stable in the neutral or acidic solution and exists in dikentonic form[2] but labile in basic circumstances readily polymerizing into a red substance.[3] Therefore the reaction in basic media is not conceivable and in fact a trial of methylation by methyliodide in the presence of a base did not proceed well. In acidic media Depuy obtained 2-benzalcyclopent-4-ene-1,3-dione by the condensation of I and benzaldehyde[3] and Kitahara reported the introduction of tropylium group into 2-position of I.[4] Thus we directed our effort to the condensation of I with an ortho ester.

When I and ethyl orthoformate were heated in acetic anhydride, a new substance melting at 81.5° was obtained. The NMR spectrum (Fig. 1) showed a triplet ($J=7.5$ c.p.s.) at 8.50τ, a quartet ($J=7.5$ c.p.s.) at 5.61τ for the ethoxy group and a singlet at 2.75τ for the methyne instead of two methylene protons of I at 7.08τ. The UV spectrum (Fig. 2) gave a curve with a tendency similar to that of the already reported 2-benzalcyclopent-4-ene-1,3-dione, which had the maxima at 224 mμ and 314 mμ.[3]

These data together with IR and elemental analysis suggested the structure of the product to be 2-(α-ethoxymethylidene)cyclopent-4-ene-1,3-dione (Ⅱa).

Addition of anhydrous zinc chloride increased the rate of the reaction and also improved the yield.

When Ⅱa was reduced catalytically in the presence of 5% palladium-charcoal, three moles of hydrogen per molecule of Ⅱa were absorbed rapidly and the product obtained in a good yield (90%) was identical in all respects with an authentic sample of 2-methylcyclopentane-1,3-dione (Ⅲa) prepared by the known method.[5]

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*2 Juso-Nishino-cho, Higashiyodogawa-ku, Osaka (三木卓一, 平賀謙太郎, 朝子典彦, 桝屋浩大).

[1] *a*) A review by T.B. Windholz and M. Windholz: Angew. Chem., **76**, 249 (1964). *b*) T.B. Windholz, *et al.*: Steroid, **6**, 410 (1965). *c*) C.H. Kuo, D. Taub, N.L. Wendler: Angew. Chem., **77**, 1142 (1965). *d*) A.V. Zakharychev, *et al.*: Izv. Akad. Nauk SSSR (Khim), **1965**, 760, 1413. *e*) T. Hiraoka, I. Iwai: This Bulletin, **14**, 262 (1966).

[2] K. Hiraga: This Bulletin, **13**, 1300 (1965).

[3] C.H. Depuy, P.R. Wells: J. Am. Chem. Soc., **82**, 2909 (1960).

[4] Y. Kitahara, I. Murata, T. Asano: Bull. Chem. Soc. Jap., **37**, 924 (1964).

[5] J.J. Panouse, C. Sannie: Bull. soc. chim. France, **1955**, 1036.

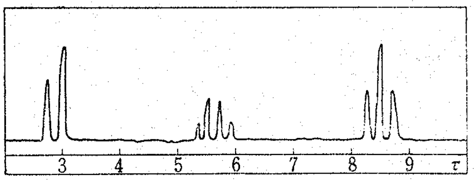


Fig. 1. The NMR Spectrum of 2-(α-Ethoxymethylidene)cyclopent-4-ene-1,3-dione (IIa) in CCl_4 Solution

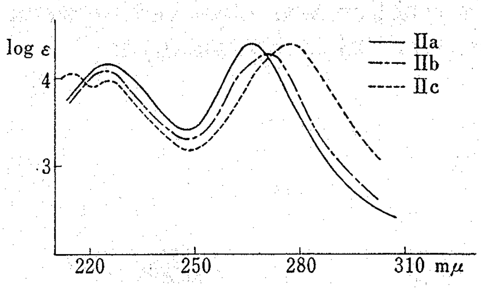


Fig. 2. UV Spectra of 2-(α-Ethoxyalkylidene)cyclopent-4-ene-1,3-diones (II) in EtOH

The reduction proceeded too fast to find which double bond, at endo or exo position in IIa, was attacked first. It should be noted that diethyl ethoxymethylenemalonate is not easily reduced under the same condition,[*3] whereas 2-hydroxymethylenecyclohexanone is easily reduced into 2-methylcyclohexanone.

Using the above method, several other derivatives of this kind were synthesized.

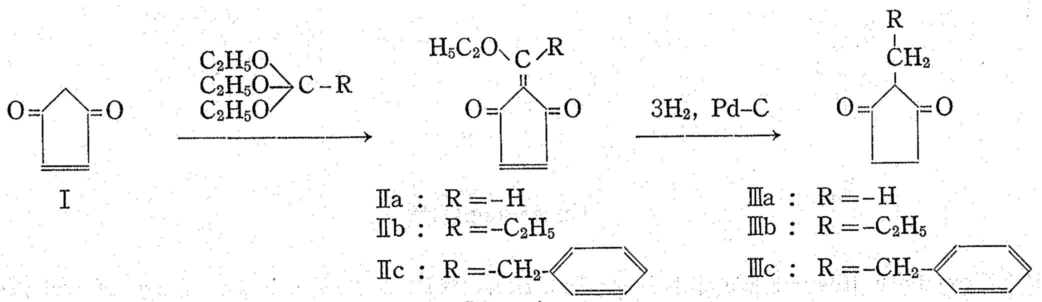


Chart 1.

Treatment of I with ethyl orthopropionate [C_2H_5-$C(OC_2H_5)_3$] or ethyl orthophenylacetate [$C_6H_5CH_2C(OC_2H_5)_3$] gave 2-(α-ethoxypropylidene)cyclopent-4-ene-1,3-dione (IIb) and 2-(α-ethoxyphenethylidene)cyclopent-4-ene-1,3-dione (IIc), which were then reduced to 2-propylcyclopentane-1,3-dione (IIIb)[1a)] and 2-phenethylcyclopentane-1,3-dione (IIIc) respectively in a rather good yield.

It was observed that the rate of the reduction of IIb to IIIb was a little slower than that of IIa to IIIa.

If the hydrogenation of IIb was stopped when 2.3 moles of hydrogen were absorbed, colorless needles melting at 76~78° were obtained along with the desired IIIb and the product could be readily reduced into IIIb by further catalytic hydrogenation.

The NMR spectrum (Fig. 3) showed a triplet (J=7.5 c.p.s.) at 8.86τ and a quartet (J=7.5 c.p.s) at 7.11τ for the ethyl group adjacent to an unsaturated bond and a symmetrical multiplet indicating A_2B_2 coupling patterns around at 7.42τ. Furthermore, one signal suggesting hydroxy proton forming a chelation with carbonyl oxygen was found at −4.1τ. The infrared absorption bands in the carbonyl region are almost the same as those of 2-acetylcyclopentane-1,3-dione, in which absorptions are observed at 1710, 1635 and 1595 cm^{-1}.[6)]

Thus the structure was found to be 2-propionylcyclopentane-1,3-dione (IV), probably existing in the form of IVa or IVb.

[*3] Diethyl ethoxymethylenemalonate is hydrogenated under a pressure as high as 1000~1500 lb to afford diethyl ethoxymethylmalonate. Org. Syn. Col. Vol., **4**, 298.

6) F. Merényi, M. Nilsson : Acta Chem. Scan., **18**, 1208 (1964).

No reaction was observed between cyclopentane-1,3-dione[7,8] and ethyl orthoformate or I and acetal of acetaldehyde.

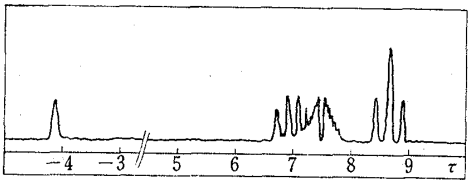


Fig. 3. The NMR Spectrum of 2-Propionylcyclopentane-1,3-dione (IV) in 10% CCl_4 Solution

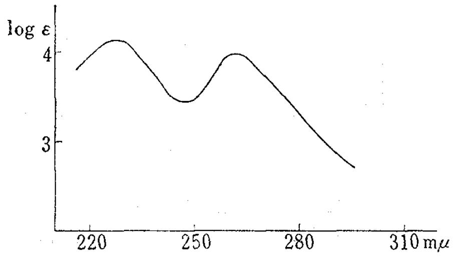
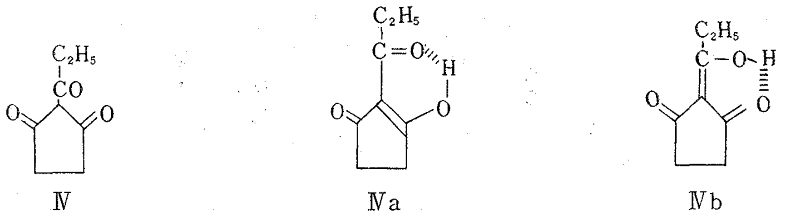


Fig. 4. UV Spectrum of 2-Propionylcyclopentane-1,3-dione (IV) in EtOH



IV IVa IVb

Chart 2.

Experimental*4

2-(α-Ethoxymethylidene)cyclopent-4-ene-1,3-dione (IIa)——To a solution of 3 g. of cyclopent-4-ene-1, 3-dione(I) in 7.2 g. of acetic anhydride were added 5.4 g. of ethyl orthoformate and 0.5 g. of anhydrous zinc chloride. The mixture was heated at 70∼80° for 6 hrs. while removing ethyl acetate from the reaction system and then filtered to remove zinc chloride. The filtrate was concentrated and cooled to give a solid, which was recrystallized from ether to obtain 2.5 g. of IIa as yellowish needles, m.p. 80∼81.5°. UV λ_{max}^{EtOH} mμ (ε): 263 (17000), 221.5 (15700). IR cm^{-1}: 1734, 1672, 1625. *Anal.* Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.77; H, 5.21.

2-Methylcyclopentane-1,3-dione (IIIa)——To a solution of 0.4 g. of IIb in 50 ml. of EtOH was added 0.3 g. of 5% palladium-charcoal as a catalyst. The mixture was shaken in a hydrogen stream. After 190 ml. of hydrogen (15°, 1 atm.) was absorbed, the mixture was filtered to remove the catalyst. The filtrate was concentrated to leave 0.28 g. of a residue, which was recrystallized from water to obtain IIIa as slightly yellow needles. m.p. 214°. UV λ_{max}^{EtOH} mμ (ε); 250 (16200). *Anal.* Calcd. for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.42; H, 7.14.

2-(α-Ethoxypropylidene)cyclopent-4-ene-1,3-dione (IIb)——To a solution of 2 g. of I in 9.5 g. of acetic anhydride were added 7.4 g. of ethyl orthopropionate and 0.8 g. of anhydrous zinc chloride. The mixture was stirred at 80∼90° for 4 hrs. and then filtered to remove zinc chloride. The filtrate was concentrated to give an oily residue, which was subjected to chromatography on silicagel. Elution with benzene gave 1.5 g. of IIb as a yellowish oily substance. UV λ_{max}^{EtOH} mμ (ε): 272 (16760), 222 (13720). IR (liquid) cm^{-1}: 1720, 1670, 1590, 1570. NMR τ^{CCl_4}: 8.83 (triplet. J=7.5 c.p.s.), 8.57 (triplet. J=7.1 c.p.s.), 7.60 (quartet. J=7.5 c.p.s.), 5.60 (quartet. J=7.5 c.p.s.), 3.20 (singlet. vinyl protons at 4- and 5-positions). *Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.43; H, 6.69.

2-Propylcyclopentane-1,3-dione (IIIb)——To a solution of 1 g. of IIb in 70 ml. of EtOH was added 0.1 g. of 5% palladium-charcoal as a catalyst, and the mixture was shaken in a hydrogen stream. After 390 ml. of hydrogen (20°, 1 atm.) was absorbed, the mixture was filtered to remove the catalyst. The filtrate was concentrated to leave a crude product, which was recrystallized from a mixture of water and EtOH (8:2) to obtain 0.7 g. of IIIb as colorless scaly crystals. m.p. 176∼177°. UV λ_{max}^{EtOH} mμ (ε): 250.5 (16240). *Anal.* Calcd. for $C_8H_{10}O_2$: C, 62.32; H, 6.54. Found: C, 62.71; H, 6.56.

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*4 All melting points were determined on a Yanagimoto micromelting point apparatus and they are uncorrected. Infrared spectra were measured on a Hitachi EPS-2 in Nujol mull.

7) C.H. Depuy, E.F. Zaweski: J. Am. Chem. Soc., **81**, 4920 (1959).

8) E. Grens, G. Vanags: Latvijas PSR Zinatnu Akad. Vestis, **1961**, 65.

2-Propionylcyclopentane-1,3-dione (IV) and IIIb——Hydrogenation was carried out with 1 g. of IIb and 0.1 g. of 5% palladium-charcoal as descrided above. When 300 ml. of hydrogen was absorbed, the reduction was stopped and the reaction mixture was filtered to remove the catalyst. The filtrate was concentrated to leave a crude product, which was separated into an ether extract and the residue. The extract was concentrated to give a solid material, which was recrystallized from acetone and water to obtain 0.25 g. of IV as colorless needles. m.p. 76~78°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (ε): 224 (12070), 259 (9560). IR cm^{-1}: 1702, 1632, 1590. *Anal.* Calcd. for $C_8H_{10}H_3$: C, 62.32; H, 6.54. Found: C, 62.71; H, 6.56. From the residue, 0.3 g. of IIIb was obtained.

2-(α-Ethoxyphenethylidene)cyclopent-4-ene-1,3-dione (IIc)——To a solution of 2 g. of I in 9.5 g. of acetic anhydride were added 12 g. of ethyl orphophenylacetate and 0.8 g. of anhydrous zinc chloride. The mixture was stirred at 80~85° for 4 hrs. The reaction mixture was poured into water and extracted with benzene. The extract was concentrated to leave a solid residue which was recrystallized from ether to obtain 0.8 g. of IIc as light yellowish plates. m.p. 115.5~116°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (ε): 211 (16700), 220 (14700), 276 (17700). IR cm^{-1}: 1715, 1685 (shoulder), 1670, 1605, 1590, 1580. NMR $\tau^{\mathrm{CCl_4}}$: 8.70 (triplet. J=7.5 c.p.s.), 5.72 (quartet. J=7.5 c.p.s.), 5.51 (singlet. $\mathrm{C}\text{-}\underline{\mathrm{CH}_2}\cdot\mathrm{C_6H_5}$), 3.07 (singlet, $-\underline{\mathrm{CH}}=\underline{\mathrm{CH}}-$), 2.23 (aromatic H). *Anal.* Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.26; H, 5.85.

2-Phenethylcyclopentane-1,3-dione (IIIc)——A mixture of 0.4 g. of IIc and 0.1 g. of 5% palladium-charcoal in 50 ml. of EtOH was shaken in a hydrogen stream. After 130 ml. of hydrogen was absorbed, the mixture was filtered to remove the catalyst. The filtrate was concentrated to leave crude crystals, which were recrystallized from water and EtOH (8:2) to obtain 0.1 g. of IIIc as colorless needles. m.p. 197.5~199°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (ε): 251.5 (15200). IR cm^{-1}: 2700~2300 (broad), 1565 (broad). *Anal.* Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.09; H, 6.68.

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