[Chem. Pharm. Bull. 29(10)2762—2768(1981)]

Use of β-Ketocarboxylic Acids for Syntheses of 6-Substituted 4-Hydroxy-2-pyrones and Acyclic β-Diketones

Shunsaku Ohta,* Atsuhiko Tsujimura, and Masao Okamoto*

Kyoto College of Pharmacy, Misasagi, Yamashina-ku, Kyoto 607, Japan

(Received January 30, 1981)

β-Ketocarboxylic acids including β-ketoglutaric acid half-esters were cyclized by treating them with 1,1′-carbonyl-diimidazole to give 6-substituted 3-acyl-4-hydroxy-2-pyrones in good yields. 5-Aryl-3,5-dioxo-1-pentanoic acid and monomethyl malonate gave 6-aryl-4-hydroxy-2-pyrone and dimethyl β-ketoglutarate, respectively, on similar treatment. Anibin, one of the Aniba alkaloids, was synthesized from 5-(3-pyridyl)-4-hydroxy-2-pyrone. In addition, it was confirmed that reaction of magnesium β-ketocarboxylate with acylimidazolide gave the corresponding acyclic β-diketone in excellent yield.

Keywords——β-ketocarboxylic acid; biogenetic-type synthesis; 4-hydroxy-2-pyrone; β-polyketide; β-ketoglutaric acid; dehydroacetic acid; anibin; Aniba alkaloid; 3-acyl-4-hydroxy-2-pyrone; β-diketone

Biogenetic-type synthesis of organic compounds is of considerable interest in the field of organic chemistry, and it is well known that malonyl S-coenzyme A and polyacetyl S-coenzyme A play very important roles in the biogenesis of fatty acids and many other naturally occurring compounds.[1] Many reports on the conversion of protected and unprotected β-polyketones and also β-polyketocarboxylic acids to phenolic compounds have been presented and the protection of β-polyketides by formation of the 4-hydroxy-2-pyrone system is one of the strategies used in such investigations.[2] This paper deals with several interesting reactions of β-ketocarboxylic acids with 1,1′-carbonyldiimidazole (Im_2CO) to afford 4-hydroxy-2-pyrone derivatives.

Generally, β-ketocarboxylic acids (**4**) can be prepared by hydrolysis of the corresponding β-ketocarboxylic esters (**3**) or by carboxylation of methylketones using lithium diisopropylamide (LDA) and carbon dioxide.[3] Banerji and Masamune, in their recent papers,[4] reported a convenient method for the biogenetic-type synthesis of the β-ketocarboxylic esters (**3**) using an elegant reaction of 1-acylimidazole (**2**) with the monomagnesium salt of malonic half-ester. This method was applied to the preparation of the β-ketocarboxylic esters **3a** (R^1=*n*-C_4H_9) and **3c** (R^1=cyclohexyl), which were hydrolyzed with aqueous 1 N NaOH at room temperature followed by acidification with hydrochloric acid to afford the corresponding β-ketocarboxylic acids **4a** (R^1=C_6H_5),[5] **4b** (R^1=*n*-C_4H_9) and **4c** (R^1=cyclohexyl). Acetoacetic acid (**4d**, R^1=CH_3) was prepared by treatment of *tert*-butyl acetoacetate (**14**)[6] with trifluoroacetic acid (TFA).

It was found that benzoylacetic acid (**4a**) was smoothly converted to 3-benzoyl-4-hydroxy-6-phenyl-2-pyrone (**5a**) by treating **4a** with Im_2CO in tetrahydrofuran (THF), and **4b**, **4c** and **4d** were also converted to the corresponding 3-acyl-4-hydroxy-2-pyrones (**5b**, **5c** and **5d**, respectively), which were identified by inspection of their melting points, spectral data and analytical data (Chart 1, Table I).

Although dehydroacetic acid (**5d**), which is a useful compound convertible to orcinol, 2,6-dimethyl-4-pyrone and other aromatic compounds,[2] has been prepared in 53% yield at best by pyrolysis of ethyl acetoacetate[7] and **5a** has also been obtained in the same manner,[8] a more convenient method for the preparation of these compounds and their homologs would be desirable. The reaction of the present method proceeds smoothly under milder conditions

and the yields are excellent; this method is therefore considered to be superior to previously known methods.[7]

Furthermore, it was found that the present method can also be applied to monoalkyl β-ketoglutarate **13a** (prepared by methanolysis of β-ketoglutaric anhydride (**12**)) and **13b** (prepared by carboxylation of *tert*-butyl acetoacetate[6,9]) to give the novel 4-hydroxy-2-pyrone derivatives **15a** and **15b** in 15.5 and 92.2% yields, respectively; these products can be regarded as protected β-pentapolyketides. The di-*tert*-butyl ester (**15b**), obtained as a colorless viscous oil, is considered to be potentially useful for conversion to 3,5-dihydroxyhomophthalic acid and 2,6-dicarboxymethyl-4-pyrone derivatives. Table I shows the yields of 6-substituted 3-acyl-4-hydroxy-2-pyrones (**5a**, **5b**, **5c**, **5d**, **15a**, and **15b**) obtained by the new method and their physical and analytical data.

Further application of the new pyrone synthesis to the 3,5-dioxo-1-pentanoic acid system was attempted. Prior to preparation of the system, it was necessary to synthesize acylacetones (**7m** and **7n**) effectively, and it was considered that corresponding β-diketones in a similar manner to Masamune's method for biogenetic-type synthesis of β-ketocarboxylic esters, mentioned above. Thus, various magnesium β-ketocarboxylates **6a** ($R^1=C_6H_5$), **6b** ($R^1=n$-C_4H_9), **6c** ($R^1=tert$-C_4H_9) and **6d** ($R^1=CH_3$) were prepared as powdered solids by treating the corresponding β-ketocarboxylic acid (**4**) with commercial magnesium ethoxide in THF or methanol. Carboxylic acid was treated with 1.1 molar equivalent of Im_2CO in dimethylformamide (DMF) at room temperature to give the corresponding 1-acylimidazole (**2′**). The magnesium β-ketocarboxylate (**6**) was added to the reaction mixture, and the resulting mixture was stirred at room temperature for several hours to give the corresponding β-diketone (**7**) in good yield, as expected.

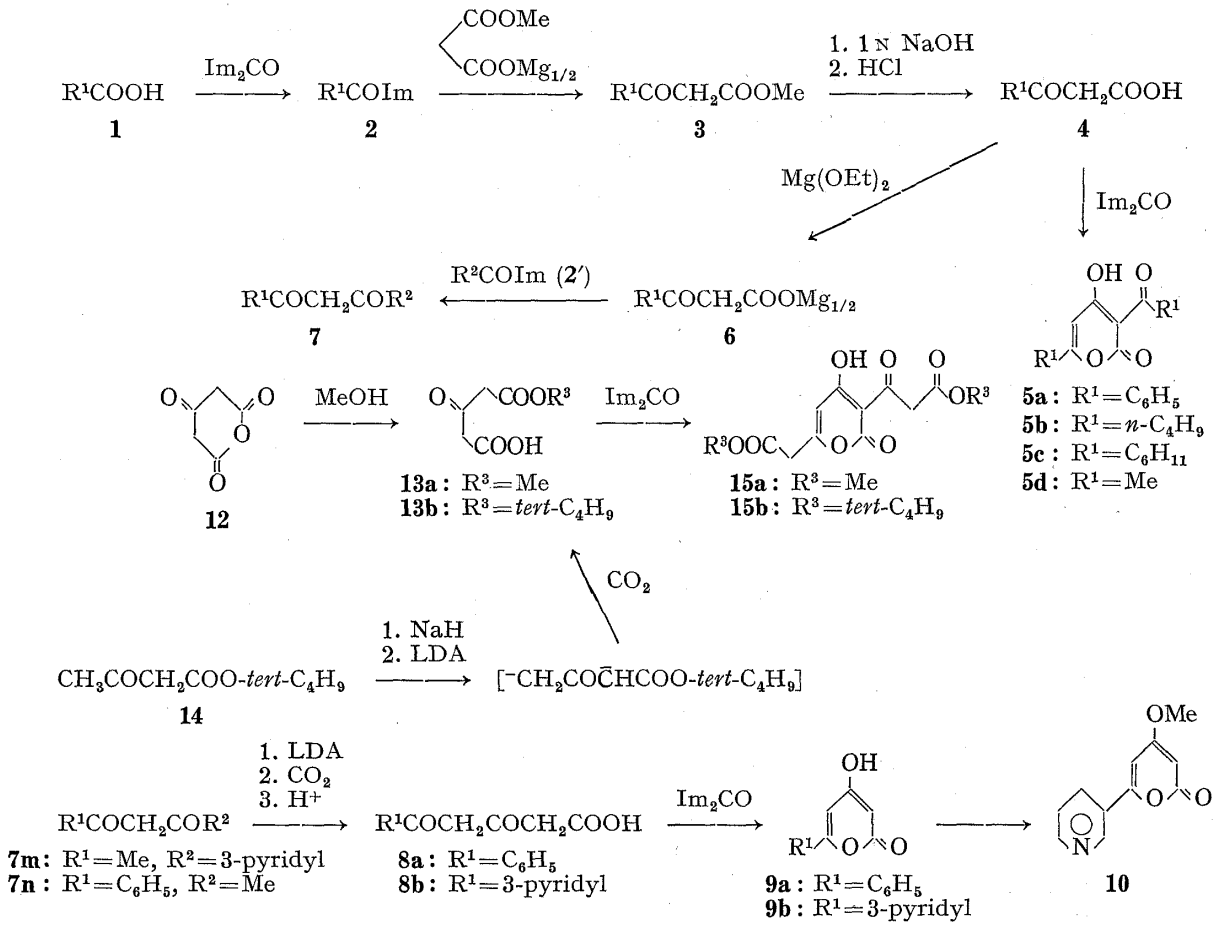

Chart 1

Table I. 6-Substituted 3-Acyl-4-hydroxy-2-pyrones

Compd.	mp (°C) (Recryst. solv.) [Formula]	Yield (%)	Analysis (%) Calcd (Found) C	H	IR ν_{CO} (cm^{-1}) (Phase)	^{1}H-NMR ($CDCl_3$, 60 MHz) δ ppm
5a	173 (lit. mp 172)[8] (MeOH) [$C_{18}H_{12}O_4$]	92.5	73.96 (74.24	4.14 3.94)	1740 1725 1625 (KBr)	15.93 (br, 1H, OH), 8.03—7.30 (m, 10H, arom. H), 6.64 (s, 1H, olefinic H)
5b	43 (Et_2O–*n*-hexane) [$C_{14}H_{20}O_4$]	95.2	66.64 (66.30	7.99 8.15)	1725 1637 (KBr)	16.80 (br, 1H, OH), 5.90 (s, 1H, olefinic H), 3.08 (t, 2H, $COCH_2$, J=7 Hz), 2.50 (t, 2H, $CH_2C=$, J=7 Hz), 1.95—0.75 (m, 14H, $CH_2CH_2CH_3\times2$)
5c	93 (MeOH) [$C_{18}H_{24}O_4$]	82.0	71.02 (71.22	7.95 8.02)	1730 1637 (KBr)	17.05 (br, 1H, OH), 5.88 (s, 1H, olefinic H), 3.72 (br, 1H, $COCH<$), 2.40 (br, 1H, $>CH-$), 2.20—1.00 (m, 20H, other protons)
5d	110 (lit. mp 108)[7] [$C_8H_8O_4$]	72.5			1710 1635 (KBr)	16.63 (s, 1H, OH), 5.94 (q, 1H, olefinic H), 2.65 (s, 3H, $COCH_3$), 2.23 (d, 3H, $CH_3C=$)
15a	78 (AcOEt–*n*-hexane) [$C_{12}H_{12}O_8$]	15.5	50.71 (50.82	4.26 4.43)	1740 1645 1617 ($CHCl_3$)	15.77 (br, 1H, OH), 6.21 (s, 1H, olefinic H), 4.05 (s, 2H, $COCH_2CO$), 3.77 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.56 (s, 2H, CH_2COOCH_3)
15b	Viscous oil [$C_{18}H_{24}O_8$]	92.2	Accurate MW by high resol. MS {Calcd: 368.14712 {Found: 368.14542		1732 1635 ($CHCl_3$)	15.80 (br, 1H, OH), 6.09 (s, 1H, olefinic H), 3.89 (s, 2H, $COCH_2CO$), 3.32 (s, 2H, CH_2COO-*tert*-Bu), 1.20 (s, 18H, $C_4H_9\times2$)

Table II shows the yields of various acyclic β-diketones (**7**) obtained by the new method, and Table III lists physical, analytical and spectral data for four new β-diketones. The structures of the β-diketones in Table II were supported by their IR, ^{1}H-NMR and high resolution mass spectra (MS) and/or elemental analyses and/or comparisons of melting point with reported values.

The new method for preparation of β-diketones is considered to be superior to previously known methods[10] in respect of mildness of reaction conditions, ease of manipulation, high yield, selective formation of the desired β-diketone and availability of the starting carboxylic

Table II. Yield of β-Diketone ($R^1COCH_2COOMg_{1/2}+R^2COIm \rightarrow R^1COCH_2COR^2$)

Compound	R^1	R^2	Yield (%)	Literature of known β-diketone
7a	C_6H_5	C_6H_5	81	ref. 22
7b	C_6H_5	*p*-Me-C_6H_4	74	ref. 23
7c	C_6H_5	*o*-Me-C_6H_4	45	ref. 24
7d	C_6H_5	*o*-OH-C_6H_4	77	ref. 11
7e	C_6H_5	3,5-$(NO_2)_2C_6H_3$	92	
7f	C_6H_5	2,4-$(NO_2)_2C_6H_3$	66	
7g	C_6H_5	Cyclohexyl	54	ref. 25
7h	C_6H_5	*n*-Butyl	82	ref. 26
7i	C_6H_5	*tert*-Butyl	62	
7j	Cyclohexyl	Cyclohexyl	60	ref. 27
7k	Cyclohexyl	*n*-Butyl	76	
7k	*n*-Butyl	Cyclohexyl	65	
7l	*n*-Butyl	*n*-Butyl	quant.	ref. 28
7m	Me	3-Pyridyl	87	ref. 17
7n	C_6H_5	Me	85	ref. 29

TABLE III. Spectral, Physical and Analytical Data for New β-Diketones

Compd.	bp or mp (°C) (Appearance and recryst. solv.) [Formula]	Analysis (%) Calcd (Found) C	H	N	Accurate MW by high resol. MS Calcd (Obsd.)	IR ν_{CO} (cm^{-1}) (Phase)	^{1}H-NMR (60 MHz) δ ppm (Solv.)
7e	mp 213 (Yellow needles, $CHCl_3$) $[C_{15}H_{10}NO_6]$	57.33 (57.08	3.21 2.99	8.92 8.81)		1625 (KBr)	9.26—8.90 (m, 3H, arom. H), 8.35—8.11 (m, 2H, arom. H), 7.76—7.36 (m, 3H, arom. H), 7.63 (1H, =CHCO) (d_6-DMSO)
7f	mp 170 (Yellow prisms, $CHCl_3$) $[C_{15}H_{10}NO_6]$	57.33 (57.03	3.21 3.14	8.92 8.68)		1600 (KBr)	8.85—8.53 (m, 2H, arom. H), 8.30—7.96 (m, 3H, arom. H), 7.77—7.50 (m, 3H, arom. H), 7.13 (s, 1H, =CHCO) (d_6-DMSO)
7i	bp 80 (2.0 mmHg) (Colorless oil) $[C_{13}H_{16}O_2]$				204.11508 (204.11503)	1600 ($CHCl_3$)	16.40 (br, 1H, enol OH), 8.12—7.75 (m, 2H, arom. H), 7.61—7.33 (m, 3H, arom. H), 6.31 (s, 1H, =CHCO), 1.25 (s, 9H, CH_3 ×3). ($CDCl_3$)
7k	bp 110 (1.0 mmHg) (Colorless oil) $[C_{13}H_{22}O_2]$				210.16206 (210.16181)	1610 ($CHCl_3$)	15.62 (br, 1H, enol OH), 5.48 (s, 1H, =CHCO), 2.68—0.70 (m, 20H, aliph. H) ($CDCl_3$)

acid. The β-diketone (**7d**) can be converted to a flavone,[11] and other flavonoids may be conveniently synthesized in the same manner. Although the diketone (**7m**) was obtained by the reaction of nicotinoyl-1-imidazole with magnesium acetoacetate, in this case only, an interesting symmetric β-diketone (dinicotinoylmethane, **7o**) was also produced in 3% yield.[12]

The acylacetones (**7n**[13] and **7m**) were converted to the corresponding 5-aryl-3,5-dioxo-1-pentanoic acids (**8a** and **8b**) by treatment with excess LDA followed by carboxylation and acidification.[14] The β,δ-diketocarboxylic acid (**8a**) did not dimerize on treatment with Im_2CO but gave an intramolecular cyclization product, 4-hydroxy-6-phenyl-2-pyrone (**9a**).[14] Such cyclization reactions have hitherto been achieved by treating 5-substituted 3,5-dioxo-1-pentanoic acid (**8**) with polyphosphoric acid,[15] with acetic anhydride[16] at elevated temperature or most efficiently with liquid hydrogen fluoride,[14] but these methods have some disadvantages compared with the new method, such as poor suitability for heat- and/or acid-sensitive compounds, troublesome manipulation (HF method) and low yield (except for the HF method).

6-(3-Pyridyl)-4-hydroxy-2-pyrone (**9b**), obtained in the same manner as **9a**, was treated with diazomethane to give the 4-methoxy derivative (**10**), which is one of the Aniba alkaloids, Anibin, isolated from *Aniba Duckei Kosterm*[17] and was firstly synthesized by condensation of 3-acetylpyridine with di-(2,4-dichlorophenyl)benzoylmalonate at 250 °C followed by treatment of the product 3-benzoyl-4-hydroxy-6-(3-pyridyl)-2-pyrone with $AlCl_3$ at 160 °C (gave **9a**) and then with diazomethane.[18] Identification of our synthetic anibin was based on its melting point (mp 178—180 °C, lit. mp 179—180 °C [17]), and infrared (IR), ultraviolet (UV) and ^{1}H-NMR spectra.

We are also interested in the reactivities of malonic half-esters toward Im_2CO in view of their close relation to β-ketocarboxylic acid derivatives. Thus, monomethyl malonate (**16**) was treated with Im_2CO in THF at room temperature to give dimethyl β-ketoglutarate (**18**) in quantitative yield as an interesting intermolecular condensation product. On the other hand, monoethyl methylmalonate (**19**) and 2-methylacetoacetic acid (**20**), which were prepared by alkaline hydrolysis of diethyl methylmalonate and ethyl methylacetoacetate,

respectively, did not dimerize under reaction conditions similar to those used for **17** in spite of the observation that vigorous evolution of carbon dioxide occurred after the addition of Im_2CO[19] (Chart 2).

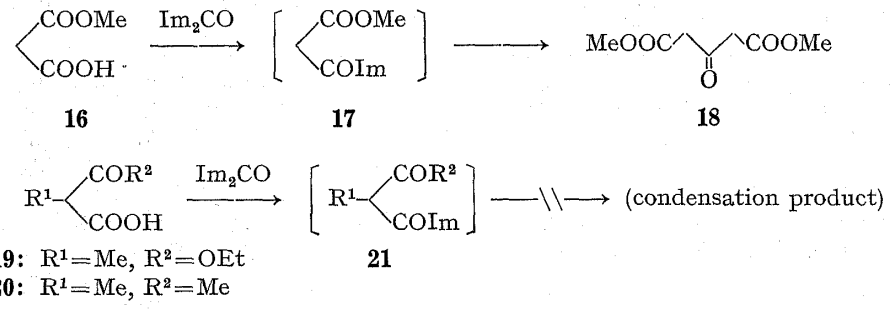

Chart 2

Experimental[20]

β-Ketocarboxylic Acids (4)——i) $R^1=C_6H_5$: Ethyl benzoylacetate (3.84 g) was stirred overnight in 20 ml of aqueous 1 N NaOH at room temperature, and after removal of the remaining ester by washing the mixture with ether, the aqueous layer was acidified with conc. HCl under ice-cooling to precipitate a white solid, which was collected by suction, washed with cold water and dried *in vacuo*. Yield, 2.72 g (83%). mp 102°C (dec.) (lit. mp 103°C (dec.)).[5]

ii) $R^1=n$-Butyl: The β-ketoester (**3b**, $R^1=n$-butyl) was prepared from valeric acid in quantitative yield by Masamune's method[4] as a colorless oil. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ ppm: 3.75 (s, 3H, OCH_3), 3.46 (s, 2H, $COCH_2CO$), 2.56 (t, 2H, $COCH_2CH_2$, J=6.5 Hz), 1.90—0.70 (m, 7H, other protons).

β-Ketoacid (**4**, $R^1=n$-butyl), colorless leaflets from *n*-hexane, mp 53.5—54°C, obtained in the same manner as in i) in 75% yield. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ ppm: 10.86 (s, 1H, COOH), 3.50 (s, 2H, $COCH_2CO$), 2.58 (t, 2H, $COCH_2CH_2$–), 1.90—0.70 (m, 7H, other protons).

iii) R^1=Cyclohexyl: The β-ketoester (**3**, R^1=cyclohexyl) was prepared from cyclohexanecarboxylic acid in quantitative yield by Masamune's method.[4] Colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1630. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ ppm: 10.55 (br, 1H, COOH), 3.55 (s, 2H, $COCH_2CO$), 2.71—0.94 (m, 11H, aliph. H). *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 62.99; H, 8.40.

iv) $R^1=CH_3$: Commercial *tert*-butyl acetoacetate (4.75 g) was dissolved in 15 ml of TFA. The solution was stirred overnight at room temperature, then TFA was removed azeotropically with benzene as a co-solvent under reduced pressure; the residual oil crystallized on cooling. The crude product was used in the next step because further purification was difficult.

Although the crystalline acetoacetic acid was very hygroscopic, it could be stored at −20°C under N_2 for several months.

Typical Procedure for Preparation of 6-Substituted 3-Acyl-4-hydroxy-2-pyrones (5a, 5b, 5c, 5d, 15a, and 15b)——Im_2CO (5.5 mmol) was added to a solution of benzoylacetic acid (5 mmol) in 10 ml of anhyd. THF, and the mixture was stirred overnight at room temperature, then acidified with dil. HCl and extracted with ethyl acetate. The organic phase was washed with brine and dried over Na_2SO_4. Removal of the solv. gave a pale yellow crystalline residue which was recrystallized from MeOH to give pale yellow prismatic **5a**. In the case of **15a**, the crude product was obtained as a red oil containing some impurities and it was purified by preparative thin-layer chromatography. Other data are given in Table I.

Monoester of β-Ketoglutaric Acid (13a and 13b)——i) **13a**: β-Ketoglutaric anhydride (**12**), which was prepared by treatment of β-ketoglutaric acid with acetic anhydride,[21] was stirred in an excess of methanol for 30 min, then the solvent was removed under reduced pressure to give a colorless oil, which was used for the preparation of **15a** without further purification because of its instability. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2550, 1730.

ii) **13b**: Commercial *tert*-butyl acetoacetate (**14**) (10 mmol) was dissolved in 20 ml of anhyd. THF under N_2, and an excess of NaH pellets (Alfa Products) was added to the solution at room temperature. The mixture was stirred for 30 min, then ice-cooled and *n*-butyllithium (10.5 mmol) in *n*-hexane (15% solution) was added. The whole was stirred for 10 min, then poured onto an excess of dry-ice (CO_2). Water and dil. HCl were added to the resulting mixture to acidify it.

Separated oily product was extracted with ethyl acetate and the organic layer was washed with water and dried over Na_2SO_4. Removal of the solvent gave a colorless oily product containing a trace of the starting material (**14**), which was used for the preparation of **13b** without further purification because of its instability; however, the product could be stored for several months at −20 °C in the crystalline state. Yield, 1.76 g (96.7%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2650, 1730.

General Procedure for Preparation of the Magnesium Salt of β-Ketocarboxylic Acid (6)——β-Ketocarboxylic acid (10 mmol) was dissolved in 20 ml of anhyd. THF (or methanol), and 5 mmol of magnesium ethoxide (Alfa Products) was added to the solution. After stirring for several hours, the solvent was removed under reduced pressure and ethanol formed was azeotropically removed by using benzene as a co-solvent to give the powdered magnesium salt. If necessary, the powder was washed with ether so as to remove ether-soluble impurities.

Typical Procedure for Preparation of β-Diketone (7)——Benzoic acid (2 mmol) was treated with Im_2CO (2.2 mmol) in 4 ml of DMF under N_2 and after stirring at room temperature for 1 h, magnesium benzoylacetate (**6**, $R^1=C_6H_5$) (2.2 mmol) was added to the mixture. The whole was stirred for 4 h, then acidified with dil. HCl and extracted with ethyl acetate. The organic layer was washed with water, 5% $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of the solv. under reduced pressure gave almost pure dibenzoylmethane (**7a**), which crystallized on standing as colorless needles. On recrystallization from petr. ether, the melting point was raised to 77°C. Yield, 365 mg (81%).

Reaction of 1-Nicotinoylimidazole (2′, R^2=3-Pyridyl) with Magnesium Acetoacetate (6, R^1=Me)——Nicotinic acid (10 mmol) was treated with Im_2CO (11 mmol) in 20 ml of DMF under N_2 and after stirring at room temperature for 1 h, magnesium acetoacetate (11 mmol) was added to the mixture. The whole was stirred for 4 h, then acidified with dil. acetic acid and extracted with ethyl acetate. The organic layer was washed with water, 5% $NaHCO_3$ and brine, then dried over Na_2SO_4. Removal of the solvent gave a partly crystallized yellow oil, to which ether was added. The insoluble portion was collected and washed with water. The collected crystals were recrystallized from ethyl acetate to give colorless needles, mp 204—205°C. Yield, 70 mg (3.1%) This product was identified as dinicotinoylmethane (**7o**) from the following data. IR ν_{max}^{KBr} cm^{-1}: 1590. ^{1}H-NMR ($CDCl_3$, 80 MHz) δ ppm: 16.4 (br, 1H, enol OH), 9.15 (q. 2H, C-2H and C-2′H), 8.75 (q. 2H, C-6 and C-6′H), 8.25 (m, 2H, C-5H and C-5′H), 7.35 (m, 2H, C-4H, and C-4′H), 6.84 (s, 1H, =CHCO). *Anal.* Calcd for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.92; H, 4.21; N, 12.25.

The ethereal filtrate, described above, was concentrated to give a yellow viscous oil, which crystallized on standing. It was recrystallized from Et_2O–*n*-hexane to give pale yellow needles, mp 81—83°C (lit. mp 84°C).[17] Yield, 1.42 g (87.0%). IR ν_{max}^{KBr} cm^{-1}: 1590. ^{1}H-NMR ($CDCl_3$, 80 MHz) δ ppm: 15.85 (br, 1H, enol OH), 9.05 (d, 1H, C-2H), 8.70 (q. 1H, C-6H), 8.13 (m, 1H, C-5H), 7.37 (q. C-4H), 6.17 (s, 1H, =CHCO), 2.23 (s, 3H, CH_3). *Anal.* Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.85. Found: C, 65.83; H, 5.47; N, 8.60. This was **7m** (R^1=Me, R^2=3-pyridyl).

4-Hydroxy-6-phenyl-2-pyrone (9a)——Im_2CO (200 mg) was added to a stirred solution of 5-phenyl-3,5-dioxo-1-pentanoic acid (**8a**)[14] (206 mg) (prepared by carboxylation of benzoylacetone[13] with LDA and dry-ice) in 5 ml of anhyd. THF, and the mixture was stirred overnight. The solvent was removed under reduced pressure, then 10% HCl was added to the residue to precipitate a colorless solid, which was collected by suction, washed with water and ether, dried and recrystallized from methanol to give pale yellow needles, mp 248—252°C (dec.) (lit. mp 254—256°C).[15] Yield, 162 mg (86.1%). ^{1}H-NMR (DMSO-d_6, 80 MHz) δ ppm: 8.80 (q.-like, 2H, arom. H), 7.50 (t-like, 3H, arom. H), 6.73 (d, 1H, C-5H, J=2 Hz), 5.38 (d, 1H, C-2H, J=2 Hz, disappeared on addition of D_2O).

Synthesis of Anibin (10)——A THF solution of nicotinoylacetone (**7m**, 2 mmol) was added dropwise to a stirred solution of LDA [prepared by treating diisopropylamine (5 mmol) in 10 ml of THF with 4.5 mmol of 15% *n*-butyllithium in *n*-hexane] at −78°C, then after 15 min stirring, the reaction mixture was poured onto an excess of dry-ice. The volatile portion of the reaction mixture was removed under reduced pressure and a solution of *p*-toluenesulfonic acid (5 mmol) in 10 ml of THF was added to the residue. The mixture was stirred for 2 h at room temperature. Im_2CO (10 mmol) was added to the mixture and after stirring overnight, acetic acid (2 ml), water (5 ml) and ethyl acetate were added under stirring, then the organic phase was evaporated to dryness under a vacuum to give a solid mass of **9b**, mp 220—222°C (dec.). Yield, 150 mg (39.7%).

This product (120 mg) was treated with an excess of diazomethane in ether–MeOH solution and the reaction mixture was evaporated to dryness under reduced pressure to give a crystalline residue, which was purified by preparative thin-layer chromatography to give pale yellow needles, mp 178—180°C (lit. mp 179—180°C).[17] Yield, 50 mg. IR ν_{max}^{KBr} cm^{-1}: 1720, 1645, 1567. ^{1}H-NMR ($CDCl_3$, 80 MHz) δ ppm: 8.98 (d-like, 1H, C-8H), 8.65 (q.-like, 1H, C-10H), 8.07 (m, 1H, C-11H), 7.37 (m, 1H, C-12H), 6.47 (d, 1H, C-5H, J=2 Hz), 5.56 (d, 1H, C-3H, J=2 Hz), 3.85 (s, 3H, OCH_3). UV λ_{max}^{EtOH} nm (log ε): 228 (4.62), 257 (3.62), 315 (4.11); λ_{min}^{EtOH} nm (log ε): 270 (3.60). Reported UV λ_{max}^{EtOH} nm (log ε): 228.5 (4.32), 254 (3.70), 315 (4.09). λ_{min}^{EtOH} nm (log ε): 269 (3.67).[17]

Dimethyl β-Ketoglutarate (18)——Monomethylmalonate (**17**) (590 mg) was dissolved in 3 ml of THF and Im_2CO (1.00 g) was added to the solution under stirring. The mixture was kept standing overnight and then ethyl acetate and dil. HCl were added under stirring. The organic layer was washed with water, 5% $NaHCO_3$ and brine, and dried over Na_2SO_4. Removal of the solvent gave the oily product (**18**). The IR spectrum was identical with that of commercial dimethyl β-ketoglutarate. Yield, 410 mg (94.3%).

Acknowledgement The authors are grateful to Mr. Yasuhiro Fujiwara, Dr. Keiji Hashimoto and

Dr. Yoshio Sumida of this College for their measurements of ^{1}H-NMR and high resolution MS, and also to the staff of the Elemental Microanalysis Room of Nippon-Shinyaku Co. Ltd.

References and Notes

1) J.D. Bu'Lock, "The Biosynthesis of Natural Products," McGraw-Hill, London, 1965; R. Robinson, "Structural Relation of Natural Products," Clarendon, Oxford, 1955; J.H. Richards and J.B. Hendrickson, "The Biosynthesis of Steroids, Terpenes and Acetogenins," W.A. Benjamin, New York, N.Y., 1964; A.J. Birch, Fortschr, *Chem. Org. Naturst.*, **14**, 186 (1957); *idem*, *Proc. Chem. Soc.*, **1962**, 3; *idem*, *Science*, **156**, 202 (1967).
2) T. Money, *Chem. Rev.*, **70**, 553 (1970); and lit. therein.
3) S. Reifers, H. Wynberg, and J. Straiting, *Tetrahedron Lett.*, **1971**, 3001.
4) A. Banerji, R.B. Jones, G. Mellows, L. Phillips, and K.Y. Sim, *J. Chem. Soc. Perkin I*, **1976**, 2221; D.W. Brooks, L.-D. Lu, and S. Masamune, *Angew. Chem. Int. Ed. Engl.*, **18**, 72 (1979); *c.f.* R.E. Ireland and J.A. Marshall, *J. Am. Chem. Soc.*, **81**, 2907 (1959); *c.f.* G. Bram and M. Vilkas, *Bull. Soc. Chim. Fr.*, **1964**, 945.
5) R. Levine and C.R. Hauser, *J. Am. Chem. Soc.*, **66**, 1768 (1944).
6) Commercially available from Aldrich Chemicals Co.
7) F. Arndt, "Organic Syntheses", Coll. Vol. III, 231 (1955), and lit. therein.
8) A. Baeyer and W.H. Perkin, *Chem. Ber.*, **17**, 64 (1884).
9) *c.f.* N.S. Huckin and L. Weiler, *J. Am. Chem. Soc.*, **96**, 1082 (1974).
10) Recent methods are described in the following references: E.R. Rotman and G.G. Moore, *Tetrahedron Lett.*, **1969**, 2553; A.K. Beck, M.S. Hoekstraand, and D. Seebach, *ibid.*, **1977**, 1187; H. Ishihara and Y. Hirabayashi, *Chem. Lett.*, **1978**, 1007; D. Enders and P. Weuster, *Tetrahedron Lett.*, **1978**, 2853; A.S. Howard, C.A. Meerholz, and J.P. Michael, *ibid.*, **1979**, 1339; I. Kuwajima and K. Matsumoto, *ibid.*, **1979**, 4095.
11) T.S. Wheeler, "Organic Syntheses", Coll. Vol. IV, 478 (1963).
12) The reason for the formation of the symmetric diketone (**7o**) is unclear.
13) The diketone (**7n**, $R^1=C_6H_5$, $R^2=CH_3$) is commercially available, though it could be prepared from magnesium benzoylacetate (**6**, $R^1=C_6H_5$) and acetyl-1-imidazole (**2'**, $R^2=CH_3$).
14) T.M. Harris and C.M. Harris, *J. Org. Chem.*, **31**, 1032 (1966).
15) C.R. Hauser and T.M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958); W.I. O'Sullivan and C.R. Hauser, *J. Org. Chem.*, **25**, 1110 (1960).
16) W. Borsche and C.K. Bodenstein, *Chem. Ber.*, **62**, 2521 (1929).
17) W.B. Mors, O.G. Gottlieb, and C. Djerassi, *J. Am. Chem. Soc.*, **79**, 4507 (1957).
18) E. Ziegier and E. Nölken, *Monatsch.*, **89**, 391, 716 (1958).
19) The result suggests that it might be possible to condense substituted malonic half-ester imidazolides or substituted β-ketoacylimidazolides with various magnesium salts of halfmalonic esters or magnesium β-ketocarboxylates.
20) All melting points are uncorrected. Spectral data were obtained as follows: IR with a Shimadzu 420 spectrometer, ^{1}H-NMR with Varian A-60A (60 MHz) and Varian CFT-20 spectrometer. Abbreviations for NMR signal patterns are as follows: s (singlet), d (doublet), t (triplet), quar. (quartet), m (multiplet) and br (broad).
21) R. Willstätter and A. Pfannenstiehl, *Ann.*, **422**, 7 (1921).
22) C. Waygand, *Chem. Ber.*, **59**, 2249 (1926).
23) C. Waygand, E. Bauer, H. Günther, and W. Heynemann, *Ann.*, **459**, 99 (1972).
24) R.L.N. Harris and J.L. Huppatz, *Aust. J. Chem.*, **30**, 2225 (1977).
25) G. Rainer, U.S. Patent 4146721 [*C.A.*, **91**, P 20496*y* (1979)].
26) R Levine, J.A. Conroy, J.T. Adams, and C. Hauser, *J. Am. Chem. Soc.*, **67**, 1510 (1945).
27) T. Sekiguchi and K. Nakazawa, Jpn. Patent 7916555 [*C.A.*, **91**, P 58124*p* (1979)].
28) O. Diels and H. Schrum, *Ann.*, **530**, 68 (1937).
29) L. Claisen, *Chem. Ber.*, **38**, 695 (1905).