Experiments Directed toward the Total Synthesis of Polycyclic Terpenes

Part II. The Synthesis and Some Reactions of 2-Methoxycarbonyl- methyl-3-Methoxycarbonyl-5-Methoxy Indanone¹⁾

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A synthetic sequence for conversion of *m*-methoxy benzaldehyde to 2-methoxycarbonyl-methyl-3-methoxycarbonyl-5-methoxy indanone and its reaction with methyl vinyl ketone are described.

After synthesizing ($\pm$)7-deoxyepiallogibberic acid methyl ester norketone (I)¹⁾ which has the same B,C,D ring stereochemical behavior as natural gibberellins, we were interested in the synthesis of the gibbane compound (III). The indanone (II) seemed to be a promising intermediate for the synthesis of the compound (III). In this paper the synthesis and the alkylation of the indanone diester (II) are described.

m-Methoxybenzaldehyde and diethylmalonate were treated with piperidine—acetic acid in benzene to give the diester (IV) in 95% yield. The diester (IV) was transformed to the cyanoester which was directly saponified to give the dibasic acid (V) in 80% yield. The dibasic acid (V) was cyclized in polyphosphoric acid to give in 90% yield the crude crystalline acid (VI) which was esterified to give the ester (VII) in 61% yield. The structure of VII was clearly determined by the NMR spectrum which showed three protons signals in the aromatic proton region as 1,2,4-substituted pattern; $J_{12}=8$ c.p.s., $J_{24}=2$ c.p.s., $J_{14}=0$ c.p.s.

For the purpose of the monoalkylation at C-2 the ester (VII) was acylated with dimethylcarbonate and sodium amide in benzene—ether to give an oily product which was alkylated with methyl bromoacetate and methanolic sodium methoxide in benzene. The resulting oily alkylated product was refluxed in conc. hydrochloric acid—dioxane to give the dibasic acid (VIII) m.p. 174~175°C in 45% yield from the diester (VII). The dibasic acid was converted into the corresponding dimethyl ester (II) m.p. 97~98°C in methanol containing sulfuric acid in 68% yield.

That the alkylation was occurred at C-2 of the ester (VII) was confirmed by the NMR spectrum of (II) which showed the signal of the C-3 proton at τ 5.83 as a doublet, $J=c.p.s.$ And the C-2 methoxycarbonylmethyl and the C-3 methoxycarbonyl groups were regarded as *trans* since the more stable *trans* isomer should be obtained under the reaction condition employed.

The reaction of the diester (II) with methyl vinyl ketone under basic condition was attempted with the hope to obtain the ketoacid (IX). But the unexpected product was isolated.

1) Part I, T. Ogawa and M. Matsui, This Journal, **31**, 1327 (1967).

FIG. 1.

in 36% yield after the chromatography on alumina of the oil obtained from the above reaction using sodium hydride as a base and anisole as a solvent. This compound (**Xa** or **Xb**) m.p. 164~165°C showed IR absorption bands at 1775, 1740, and 1710 cm^{-1} and UV absorption bands at 229 (ϵ 14,400), 275 (ϵ 16,200), 287 (ϵ 15,200), 296 (ϵ 14,400) $\text{m}\mu$. These data suggested that this compound had the γ -lacton function and had the same conjugated chromophore as the diester (**II**) which showed the UV absorption bands at 224 (ϵ 16,300), 270 (ϵ 17,400), 285 (ϵ 13,700) 293 (ϵ 12,300) $\text{m}\mu$. The NMR spectrum showed AB pattern signals at τ 6.37 and 7.51, $J=19$ c.p.s., two O-methyl singlets at τ 6.00, and 6.25, one methyl singlet at τ 8.70 and no signal corresponding to the C-3 proton. From these spectral data the structure of this compound was most probably regarded as **Xa** or **Xb**. Since the Dreiding model showed the lactonization seemed to occur more easily to give **Xa** than **Xb**; and the structure **Xa** was preferable but

the structure **Xb** could not be eliminated. The reaction seemed to proceed as shown in Fig. (1).

This reaction revealed that in the case of the indanone ester (**II**) the carbanion formation occurred at C-3 under the basic condition. As it is known¹⁾ that the diester (**XI**) gave the keto acid (**XII**) by the reaction with methyl vinyl ketone under the basic condition, it is reasonable to think that in the case of the diester (**XI**) the carbanion was developed at C-2. This difference in reactivity between **II** and **XI** seemed to be due to the bulkiness of the methyl group at C-4 in **XI** which prevented the maximum overlap between the p -electrons of the developing carbanion at C-3 and the π -electrons of the aromatic ring because of the steric repulsion between the methyl group at C-4 and the methoxy carbonyl group at C-3.²⁾

2) D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, 1965, pp. 52~65.

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In order to make clear the substituent effect on the alkylation of these indanone esters, the alkylation of the ester (VII) and (XIV) were further studied. The ester (VII) was directly alkylated with methyl bromoacetate using sodium methoxide as a base and transformed into the diester (XIII), different from the diester (II), in 45% yield. The structure of this isomeric diester (XIII) was confirmed by the NMR spectrum which showed two AB pattern

signals at τ 6.38, 7.35, $J=19$ c.p.s. and at τ 6.50, 7.33, $J=17$ c.p.s., partly overlapped with O-methyl singlet. This two AB pattern signals became clearly visible when the spectrum was taken in benzene, τ 6.26, 7.43, $J=19$ c.p.s.; τ 6.67, 7.73, $J=17$ c.p.s.

The indanone ester (XIV)³⁾ having no substituent on the aromatic ring was also directly alkylated with methyl bromoacetate using sodium methoxide as a base to give the keto-diester (XV), the structure of which was demonstrated by the NMR spectrum showing two AB pattern signals at τ 6.50, 7.45, $J=21$

3) K. Mori, M. Matsui and Y. Sumiki, This Journal, **27**, 27 (1963).

c.p.s. and τ 6.52, 7.40, $J=17$ c.p.s. These results showed that 3-methoxycarbonyl indanones without methyl group at C-4 were more easily alkylated at C-3 than at C-2 and that the specificity of these alkylation was reasonably due to the steric repulsion between the methyl group at C-4 and the methoxycarbonyl group at C-3.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were measured as Nujol mulls for solid samples and as films for liquid samples, unless otherwise stated. Ultraviolet spectra were determined for ethanol solutions. NMR spectra were determined at 60 Mc in deuteriochloroform using tetra-methylsilane as an internal reference.

Ethyl *m*-methoxybenzalmalonate (IV). *m*-Methoxy benzaldehyde (710 g) and diethyl malonate (1 kg) were refluxed in benzene (2 l) with piperidine (25 g) and acetic acid (25 ml) with continuous removal of water for ten hrs. The benzene layer was washed by aq. sodiumbicarbonate, dil. hydrochloric acid and saturated saline successively. Distillation of the product gave an oil, b.p. 170~195°C (4 mmHg), 1370 g, yield 95%. *Anal.* Found: C, 64.57; H, 6.50. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52%. $\nu_{\max}$ 1730, 1634, 1600, 1584 cm^{-1} .

***m*-Methoxyphenylsuccinic acid (V).** Malonate (IV, 690 g) in 99% ethanol (2 l) and potassium cyanide (165 g) in water (200 ml) was refluxed with stirring for 18 hrs. Ethanol and water were removed in vacuo. The residue was refluxed in 6N-aq. potassium hydroxide for 16 hrs. After cooling, the mixture was poured into ice—sulfuric acid. Crystalline product was corrected, 443 g, yield 80%. Recrystallization from aq. methanol, m.p. 178~180°C. *Anal.* Found: C, 58.60; H, 5.37. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40%. $\nu_{\max}$ 1710, 1607, 1500 cm^{-1} . $\nu_{\max}$ 224 (sh. ϵ 8,700), 270 (ϵ 2,500) $\mu\mu$.

3-Carboxy-5-methoxy indanone (VI). Dibasic acid (V, 250 g) was stirred in polyphosphoric acid (from phosphorus pentoxide 1.5 kg and 85% phosphoric acid 1 l) at 95~100°C for 50 min. The resulting slurry was poured into ice (4 kg) and the crystals were corrected, 207 g, yield 90%. Recrystallization from acetone, m.p. 187~188°C. *Anal.* Found: C, 64.03; H, 4.91. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89%. $\nu_{\max}$ 1700, 1600, 1490, 1290, 1260, 1230, 1087,

930 cm^{-1} . $\lambda_{\max}$ 223 (ϵ 14,500), 267 (ϵ 15,000), 283 (sh. ϵ 11,100), 294 (ϵ 9,900) $\mu\mu$.

3-Methoxycarbonyl-5-methoxy indanone (VII). Acid (VI, 83 g) was refluxed in methanol (500 ml) with sulfuric acid (1 ml) for 10 hrs. Evaporation of methanol to the half volume and on cooling crystals (54 g) was obtained in yield of 61%. Recrystallization from methanol, m.p. 117~118°C. *Anal.* Found: C, 65.02; H, 5.57. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49%. $\nu_{\max}$ 1740, 1710, 1690, 1605, 1580, 1109 cm^{-1} . τ 2.0~2.9 (3H; $J_{4H,6H}=2$ c.p.s., $J_{6H,7H}=8$ c.p.s., $J_{4H,7H}=0$), 5.63 (1H; quartet $J=4$, 7 c.p.s.) 5.97 (3H; singlet), 6.10 (3H; singlet), 6.5~7.35 (2H; AB part of ABX system, $J_{AB}=18$, $J_{AX}=4$, $J_{BX}=7$ c.p.s.).

2-Carboxymethyl-3-carboxy-5-methoxy indanone (VIII). To the suspension of sodium amide (from sodium 45 g) in ether (300 ml) was added dropwise the benzene solution (400 ml) of dimethylcarbonate (180 g) and the ester (VII, 130 g) under reflux during 8 hrs. After the mixture was left to stand overnight at room temperature, acetic acid (300 ml) and ice were added. The organic layer was washed with water and dried over magnesium sulfate. Evaporation of the solvent gave an oil (125 g). The oil was dissolved in dry benzene (600 ml) and mixed with methanolic sodium methoxide (sodium 11 g, methanol 150 ml). To the resulting mixture methyl bromoacetate (70 g) was added. Further stirring and refluxing were continued for 3 hrs. After the mixture was left to stand overnight at room temperature, water was added and benzene layer was concentrated to give an oil (144 g). This oil was refluxed in conc. hydrochloric acid (400 ml) and dioxane (200 ml) for 15 hrs. While hot, the solution was treated with active carbon and filtered. The filtrate was extracted with ethylacetate. The organic layer was washed with water and concentrated to give an oil which gave crystals (71 g) by trituration with ether. Yield 45%. Recrystallization from acetone—*n*-hexane, m.p. 174~157°C. *Anal.* Found: C, 59.24; H, 4.77. Calcd. for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58%. $\nu_{\max}$ 1720, 1710, 1600, 1500, 1295 cm^{-1} . $\lambda_{\max}$ 223 (ϵ 14,000), 268 (ϵ 15,900), 284 (sh. ϵ 11,900), 293 (sh. ϵ 10,500).

2-Methoxycarbonylmethyl-3-methoxycarbonyl-5-methoxy indanone (II). Ketoacid (VIII, 20 g) was refluxed in methanol (200 ml) with sulfuric acid (1 ml) for 6 hrs. After cooling, precipitated crystals were corrected (15 g), yield 68%. Recrystallization from methanol, m.p. 97~98°C. *Anal.* Found: C, 61.44;

H, 5.62. Calcd. for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52%. $\nu_{\max}$ 1748, 1703, 1608, 1500 cm^{-1} . $\lambda_{\max}$ 224 (ϵ 16,300), 270 (ϵ 17,400), 285 (sh. ϵ 13,700), 293 (sh. ϵ 12,300). τ 2.1~3.0 (3H; $J_{4H,6H}=2$, $J_{6H,7H}=8$, $J_{4H,7H}=0$ c.p.s.), 5.83 (1H; doublet, $J=4$ c.p.s.), 6.04 (3H; singlet), 6.10 (3H; singlet), 6.28 (3H; singlet), 6.4~7.2 (3H; multiplet).

($\pm$) **2 β -Carboxymethyl-3 β -methoxycarbonyl-5-methoxy-8 α -methyl-8 β -oxy-2,3-propano indanone 2 $\rightarrow$ 8 lactone (Xa).** The diester (II, 500 mg) and 50% sodium hydride (200 mg) were stirred in dry anisol (15 ml) at 15~20°C for 15 min. To this solution was added dropwise methyl vinyl ketone (200 mg) in anisol (5 ml) at 30~30°C during 30 min. The mixture was further stirred for 1 hr, neutralized with acetic acid, diluted with water and extracted with ethylacetate. Evaporation of the solvent gave an oil which was chromatographed over alumina (10 g). Elution with benzene-ethylacetate (10:1) gave crystals (200 mg). Yield 36%. Recrystallization from methanol or ethylacetate-*n*-hexane, m.p. 164~165°C. *Anal.* Found: C, 65.70; H, 5.79. Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49%. $\nu_{\max}$ 1775, 1740, 1710, 1610, 1590, 1495 cm^{-1} . $\lambda_{\max}$ 229 (ϵ 14,400), 275 (ϵ 16,200), 287 (ϵ 15,200), 296 (ϵ 14,400). τ 2.0~3.0 (3H; $J_{4H,6H}=2$, $J_{6H,7H}=8$, $J_{4H,7H}=0$ c.p.s.), 6.00 (3H; singlet), 6.25 (3H; singlet), 6.37 (1H; doublet, $J=19$ c.p.s.), 7.51 (1H; doublet, $J=19$ c.p.s.), 7.0~8.5 (4H; multiplet), 8.70 (3H; singlet).

3-Methoxycarbonyl-3-methoxycarbonylmethyl-5-methoxy indanone (XIII). Ester (VII, 1.1 g) was dissolved in methanolic sodium methoxide (sodium 130 mg and methanol, 20 ml) and the mixture was kept at 40°C for 30 min. Methyl bromoacetate (750 mg) in methanol (5 ml) was added dropwise at 15°C. The mixture was left to stand at room temperature

for 1 hr, and then refluxed for 10 min. After cooling, the mixture was diluted with water, extracted with ethylacetate and concentrated to give crystals by trituration with ether (650 mg). Yield 45%. Recrystallization from ethylacetate-*n*-hexane, m.p. 134~137°C. *Anal.* Found: C, 61.84; H, 5.48. Calcd. for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52%. $\nu_{\max}$ 1735, 1705, 1603, 1496 cm^{-1} . $\lambda_{\max}$ 225 (ϵ 17,400), 269 (ϵ 16,900), 284 (sh. ϵ 12,800), 293 (sh. ϵ 10,300). τ 2.3~3.2 (3H; multiplet), 6.10 (3H; singlet), 6.29 (3H; singlet), 6.31 (3H; singlet), 6.38 (1H; doublet, $J=19$ c.p.s.), 6.50 (1H; doublet, $J=17$ c.p.s.), 7.33 (1H; doublet, $J=17$ c.p.s.), 7.35 (1H; doublet, $J=19$ c.p.s.); τ (in benzene) 6.26 (1H; doublet, $J=19$ c.p.s.), 6.67 (1H; doublet, $J=17$ c.p.s.), 6.77 (3H; singlet), 6.85 (3H; singlet), 6.87 (3H; singlet), 7.43 (1H; doublet, $J=19$ c.p.s.), 7.73 (1H; doublet, $J=17$ c.p.s.).

3-Methoxycarbonyl-3-methoxycarbonylmethyl indanone (XV). Ester (XIV, 10 g) in benzene (150 ml) and methanolic sodium methoxide (sodium 1.2 g and methanol 20 ml) were mixed at room temperature. To the resulting mixture was added dropwise methyl bromoacetate (8 ml) with stirring. The mixture was refluxed for 1.5 hrs. Distillation of the product gave an oil, b.p. 137~150°C (0.05 mmHg), 2.3 g. By trituration with methanol crystals were obtained, 1.6 g, yield 12%. Recrystallization from methanol, m.p. 101~103°C. *Anal.* Found: C, 64.15; H, 5.56. Calcd. for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38%. $\nu_{\max}$ 1735, 1725, 1595, 1210, 1194, 1168 cm^{-1} . (in carbontetrachloride) 2.2~2.8 (4H; multiplet), 6.28 (3H; singlet), 6.30 (3H; singlet), 6.50 (1H; doublet, $J=21$ c.p.s.), 6.52 (1H; doublet, $J=17$ c.p.s.), 7.40 (1H; doublet, $J=17$ c.p.s.), 7.45 (1H; doublet, $J=21$ c.p.s.).