The Structure of Glutaconic Anhydride and the Synthetic Utility of its Diels–Alder Adduct with Cyclopentadiene

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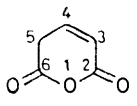
In non-polar solvents glutaconic anhydride exists predominantly as its dioxo-tautomer (1). Diels–Alder reaction with cyclopentadiene affords 3-*endo*-carboxynorborn-5-en-2-*endo*-ylacetic acid anhydride (5) having considerable synthetic potential, and which on hydrolysis gives the corresponding bis-*endo*-dicarboxylic acid (6a). The dimethyl ester of (6a) may be epimerised and hydrolysed to the *trans*-dicarboxylic acid, 3-*exo*-carboxynorborn-5-en-2-*endo*-ylacetic acid (9a). The acids (6a) and (9a) have been characterised as a γ-iodolactone (7a) and a δ-iodolactone (13), respectively.

ALTHOUGH glutaconic anhydride was first prepared in 1890 [1] its Diels–Alder reaction with dienes has not been described. This is probably because the accepted [2] structure is that of the 6-hydroxy-2-pyrone (2). This structure was assigned [3] because the compound forms a monosodium salt and gives a positive iron(III) chloride test. We have now examined the ^{1}H n.m.r. spectrum of



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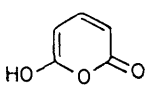

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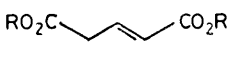

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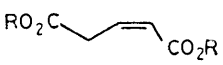
b; R = Me



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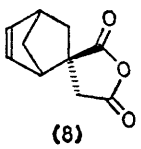

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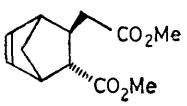

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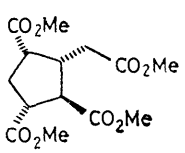

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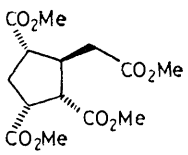

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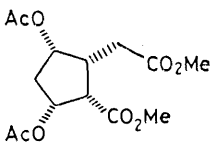


(14)

glutaconic anhydride in $CDCl_3$ and find three signals at δ 3.56 (2 H, dd, *J* 3.5 and 2 Hz), 6.31 (1 H, dt, *J* 10 and 2 Hz), and 6.96 (1 H, dt, *J* 10 and 3.5 Hz) which are consistent only with the dioxo-tautomer (1). Addition of CD_3OD causes proton-deuteron interchange at ring positions 3 and 5 as shown by the disappearance of the signals at δ 3.56 (H-5) and 6.31 (H-3), and collapse of the multiplet at 6.96 (H-4) to a singlet. Thus the keto-form (1) must under these conditions be in equilibrium with a trace amount of the enol tautomer (2). I.r. spectra (mull and CH_2Cl_2) also support the anhydride structure (1) and show no hydroxy-absorptions. In acetonitrile the u.v. spectrum exhibits a relatively weak band at $\lambda_{max.}$ 352 nm (ε 1 050) attributable to the highly conjugated hydroxy-pyrone (2), but the major absorption, due to the αβ-unsaturated anhydride (1), has $\lambda_{max.}$ 210 nm (ε 7 120).

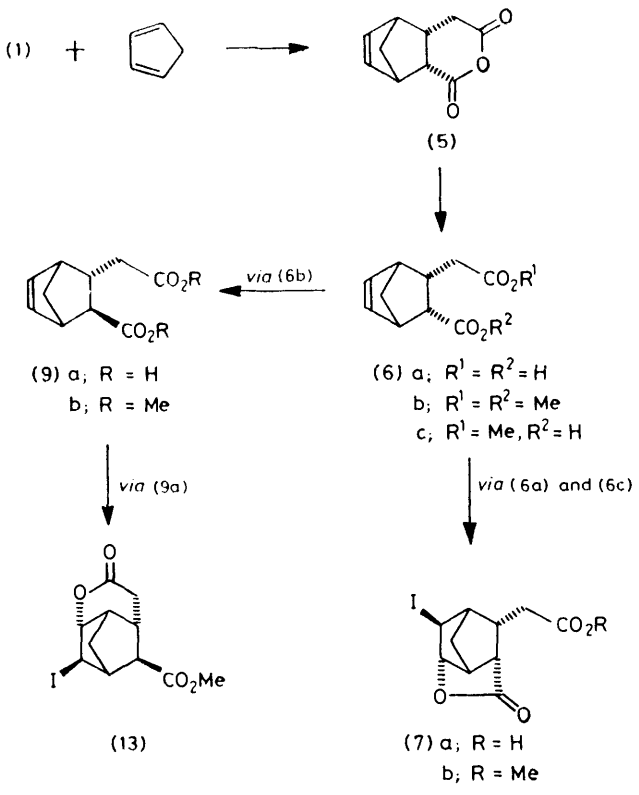
Glutaconic anhydride may be conveniently prepared from *trans*-glutaconic acid (3a).[1,3-6] The best dehydrating agent is acetic anhydride but the highest reported yield is only 47%.[4] We have now improved the isolation procedure, and by vacuum sublimation can obtain pure glutaconic anhydride in 69% yield. Moreover, the crude product is sufficiently pure for direct use in subsequent reactions.

The Diels–Alder reaction between glutaconic anhydride and cyclopentadiene occurred smoothly in toluene under reflux to give, after 2 h, the expected *endo*-adduct (5) (70%). The stereochemistry was established by hydrolysis to the diacid (6a) followed by iodolactonisation. The product was the γ-lactone (7a) [$\nu_{max.}$ ($CHCl_3$) 1 785 cm^{-1}] which afforded the monomethyl ester (7b) after treatment with diazomethane. It is interesting that in this presumably kinetically controlled reaction, formation of the γ-iodolactone (7a) is preferred over the alternative δ-iodolactone.

cis-Glutaconates (4) undergo ready thermal isomerisation into the thermodynamically more stable *trans*-glutaconates (3).[4] Thus the stereostable glutaconic anhydride is a superior and stereoselective dienophile. For example, the *cis*-diester (6b) was prepared in only 28% yield by the direct reaction of cyclopentadiene and dimethyl *cis*-glutaconate (4b) at 130 °C.[7] On the other hand treatment of the crude anhydride adduct (5) with methanol, and then with diazomethane, affords the same diester (6b) in 75% overall yield from *trans*-glutaconic acid (3a). Interestingly, methanol reacts regioselectively with the less hindered carbonyl group of the anhydride adduct (5) to give the half-ester (6c). The position of methylation was established by iodolactonisation to

the γ-lactone (7b). The adduct (8) of itaconic anhydride and cyclopentadiene has similarly been shown to react with methanol at the less hindered carbonyl group.[8]

Although *trans*-glutaconates (3) are stereostable, their Diels–Alder reactions with 1,4-substituted-1,3-dienes give mixtures of isomers. For example, cycloaddition of dimethyl *trans*-glutaconate (3) and cyclopentadiene afforded two isomeric bis-esters (9b) and (10),[9] which required preparative g.l.c. for complete separation. This



is a disadvantage since (9b) and (10) are intermediates in the synthesis of two potential degradation products, (11) and (12), of ikarugamycin.[9] We now describe an unambiguous stereocontrolled route to the bis-ester (9b) which confirms the original structural assignment. Epimerisation of the *endo-cis*-bis-ester (6b) by sodium methoxide and hydrolysis *in situ* afforded the *trans*-diacid (9a). Methylation gave the bis-ester (9b), with properties identical to those reported.[9] For further characterisation the diacid (9a) was iodolactonised and methylated to give the δ-iodolactone (13) [$\nu_{max.}$ ($CHCl_3$) 1 735 cm^{-1}].

The products obtained from the adduct (5) of glutaconic anhydride and cyclopentadiene have considerable value in synthesis. The *endo-cis*-bis-ester (6b) should be readily convertible by standard methods[10] into the important prostaglandin synthon (14).[11] We are currently engaged in the conversion of the δ-iodolactone (13) into novel analogues of the prostaglandin endoperoxide PGH, which is reported in the following paper.

EXPERIMENTAL

Glutaconic Anhydride (1) (cf. *ref.* 3).—*trans*-Glutaconic acid (3a) (0.6 g, 4.8 mmol) and acetic anhydride (2.0 g, 19.6 mmol) were refluxed for 25 min. The excess of acetic anhydride was removed by vacuum distillation to afford a dark brown residue, which was sublimed at 85—100 °C and 0.01 mmHg to give glutaconic anhydride (1) as a white solid (0.36 g, 3.5 mmol, 69%), m.p. 77—82 °C (lit.,[3] m.p. 87 °C); δ(90 MHz, $CDCl_3$) 6.96 (dt, H-4), 6.31 (dt, H-3), and 3.56 (q, H-5); *J* (Hz) (3, 4) 10, (3, 5) 2, and (4, 5) 3.6; $\nu_{max.}$ (cm^{-1}, CH_2Cl_2) 1 805 and 1 750 (C=O), 1 610 (C=C), and 1 070 and 1 050 (C–O); $\nu_{max.}$ (cm^{-1}, Nujol) 1 802, 1 782, 1 738 (C=O), 1 640 (C=C), and 1 080 and 1 060 (C–O) [lit.,[12] $\nu_{max.}$ (cm^{-1}, $CHCl_3$) 1 800 and 1 700 (C=O), and 1 600 (C=C)]; *m/e* 112 ($M^{+\cdot}$), 84 ($M^{+\cdot}$ − CO), and 72 ($M^{+\cdot}$ − CO_2); $\lambda_{max.}$ (acetonitrile) 352 (ε 1.05 × 10^3) and 210 nm (ε 7.12 × 10^3) [lit.,[12] $\lambda_{max.}$ (water) 340 (ε 2.17 × 10^3) and 220 nm (1.26 × 10^4)].

3-endo-*Carboxynorborn*-5-*en*-2-endo-*ylacetic Acid Anhydride* (5).—A mixture of glutaconic anhydride (1) (0.42 g, 3.5 mmol), cyclopentadiene (0.46 g, 7.0 mmol), and toluene (10 ml) was refluxed for 2 h under nitrogen. The toluene and unreacted cyclopentadiene were removed by reduced-pressure evaporation and the residue sublimed at 105 °C and 0.015 mmHg to afford the *anhydride* (5) (0.46 g, 2.45 mmol, 70%) as a white crystalline solid, m.p. 124—128 °C (decomp.) (Found: C, 67.8; H, 5.9. $C_{10}H_{10}O_3$ requires C, 67.40; H, 5.66%); δ(90 MHz, C_6D_6) 5.99 (q, H-5), 5.73 (q, H-6), 2.96 (m, H-4), 2.59 (m, H-3-*exo*), 2.27 (m, H-1), 1.52—2.05 (m, H-2 and H-8), 1.15 (dt, H-7-*syn*), and 0.80 (d, H-7-*anti*); *J* (Hz) (1, 6) 3.1, (1, 7-*syn*) 1.8, (4, 5) 2.9, (4, 7-*syn*) 1.8, and (5, 6) 5.6; $\nu_{max.}$ (cm^{-1} CH_2Cl_2) 1 805 and 1 755 (C=O), and 1 060 (C–O); *m/e* 178 ($M^{+\cdot}$), 150 ($M^{+\cdot}$ − CO), 134 ($M^{+\cdot}$ − CO_2), and 133 ($M^{+\cdot}$ − CO_2H).

3-endo-*Carboxynorborn*-5-*en*-2-endo-*ylacetic Acid* (6a).—*trans*-Glutaconic acid (3a) (5 g, 38.5 mmol) and acetic anhydride (12.5 g, 123 mmol) were refluxed for 25 min. The excess of acetic anhydride was removed by azeotropic distillation under reduced pressure with toluene (2 × 25 ml) to afford a red tarry residue of glutaconic anhydride (1). This residue was mixed with cyclopentadiene (12.7 g, 193 mmol) and toluene (50 ml) and refluxed for 1.5 h. The toluene and unreacted cyclopentadiene were removed by distillation at reduced pressure and the residue treated with a solution of sodium hydrogencarbonate (13.4 g, 160 mmol) in water (100 ml). The resultant solution was stirred for 1 h, extracted with diethyl ether (2 × 30 ml), acidified to pH 2 with hydrochloric acid, and extracted with diethyl ether (4 × 30 ml). The ethereal extracts from the acidified solution were combined, dried over magnesium sulphate, filtered, and the solvent evaporated under reduced pressure to afford the crude endo-cis *dicarboxylic acid* (6a) (4.61 g, 24.5 mmol, 61%) as an off-white solid, which was characterised by conversion to the γ-iodolactone (7a) without purification; δ(60 MHz, $CDCl_3$) 11.55 (s, CO_2H), 6.24 (m, H-5 and H-6), 2.55—3.3 (m, H-1, -2, -3, and -4), 2.1—2.55 (m, H-8), and 1.43 (m, H-7).

3-endo-*Carboxy*-5-endo-*hydroxy*-6-exo-*iodonorborn*-2-endo-*ylacetic Acid* γ-*Lactone* (7a).—The dicarboxylic acid (6a) (1.96 g, 10 mmol) was dissolved in a solution of sodium hydrogencarbonate (3.36 g, 40 mmol) in water (15 ml) and the resultant solution treated with iodine (2.54 g, 10 mmol) and potassium iodide (6.64 g, 40 mmol) in water, using the procedure for iodolactonisation of van Tamelen and Shamma.[13] The crude product was recrystallised from

ethyl acetate–light petroleum (b.p. 60—80 °C) to afford the *γ-iodolactone* (7a) (1.71 g, 5.3 mmol, 53%) as white crystals, m.p. 156—160 °C (Found: C, 37.6; H, 3.35. $C_{10}H_{11}IO_4$ requires C, 37.29; H, 3.44%); δ(60 MHz, $CDCl_3$) 9.36 (s, CO_2H), 5.17 (d, H-5-*exo*), 4.13 (d, H-6-*endo*), 3.26 (m, H-4), 2.45—2.9 (m, H-1, -2, -3, -8), 2.46 (d, H-7-*syn*), and 1.93 (br d, H-7-*anti*); *J* (Hz) (4, 5-*exo*) 5.0, (6-*endo*, 7-*anti*) 2.5, and (7-*syn*, 7-*anti*) 12.0; $\nu_{max.}$ (cm^{-1}, $CHCl_3$) 1 785 and 1 705 (C=O); *m/e* 322 ($M^{+\cdot}$), 305 ($M^{+\cdot}$ − OH), 247 ($M^{+\cdot}$ − CH_2CO_2H), and 195 ($M^{+\cdot}$ − I).

Methyl 3-endo-*Carboxy*-5-endo-*hydroxy*-6-exo-*iodonorborn*-2-endo-*ylacetate γ-Lactone* (7b).—(A) *From* (7a). The iodolactone (7a) (161 mg, 0.5 mmol) was methylated with diazomethane in ether solution. Concentration of the resultant ethereal solution by evaporation followed by recrystallisation of the solid residue from ethyl acetate–light petroleum (b.p. 60—80 °C) afforded the *methyl ester γ-lactone* (7b) (160 mg, 0.45 mmol, 95%) as a white crystalline solid, m.p. 116—117 °C; δ(90 MHz, $CDCl_3$) 5.14 (d, H-5-*exo*), 4.08 (d, H-6-*endo*), 3.72 (s, OMe), 3.24 (m, H-4), 2.4—2.8 (m, H-1, -2, -3, -8), 2.43 (d, H-7-*syn*), and 1.94 (d, H-7-*anti*); *J* (Hz) (4,5-*exo*) 5, (6-*endo*, 7-*anti*) 2.6, and (7-*syn*, 7-*anti*) 12.0; $\nu_{max.}$ (cm^{-1}, $CHCl_3$) 1 785 and 1 735 (C=O); *m/e* 336 ($M^{+\cdot}$), 305 ($M^{+\cdot}$ − OMe), 277 (M^{+} − CO_2Me), 209 ($M^{+\cdot}$ − I), and 193 ($M^{+\cdot}$ − I − O).

(B) *From* (5). The anhydride (5) (104 mg, 0.58 mmol) was dissolved in dry methanol (25 ml), the solution heated under reflux for 2 h, and the methanol then removed by evaporation. The resultant residue of half-ester (6b) was dissolved in a solution of sodium hydrogencarbonate (96 mg, 1.16 mmol) in water and the solution obtained treated with iodine (179 mg, 0.7 mmol) and potassium iodide (664 mg, 4.0 mmol) in water, employing the iodolactonisation procedure of van Tamelen and Shamma.[13] The crude product on recrystallisation as above gave the methyl ester γ-lactone (7b) (162 mg, 0.47 mmol, 81%) as a white crystalline solid with properties as previously reported.

Methyl 3-endo-*Methoxycarbonylnorborn*-5-*en*-2-endo-*ylacetate* (6b).—A mixture of *trans*-glutaconic acid (3a) (10 g, 77 mmol) and acetic anhydride (22 g, 212 mmol) was refluxed for 25 min under nitrogen. The acetic anhydride was removed by azeotropic distillation with toluene (2 × 50 ml) and the red tarry residue of glutaconic anhydride (1) was treated with cyclopentadiene (10.2 g, 154 mmol) and toluene (20 ml); this mixture was then refluxed for a further 1.5 h. The toluene was removed by distillation, dry methanol (50 ml) was distilled into the reaction vessel, and the methanolic solution refluxed for 2 h and then concentrated by distillation at reduced pressure. The resultant residue was then treated with diazomethane in ether solution. Concentration of the resultant ethereal solution afforded the *endo-cis*-bis-ester (6b) (12.96 g, 57.7 mmol, 75%) as a yellow oil, b.p. 95—100 °C at 0.1 mmHg (lit.,[7] b.p. 100—120 °C at 2 mmHg) (Found: C, 63.7; H, 7.25. Calc. for $C_{12}H_{16}O$: C, 64.27; H, 7.19%); δ(90 MHz, $CDCl_3$) 6.26 (q, H-5), 6.08 (q, H-6), 3.64 (s, Me), 3.56 (s, Me), 3.07 (m, H-4), 2.85 (m, H-1), 2.7—3.2 (m, H-3-*exo* and H-2-*exo*), 2.20 (octet, H-8), and 1.41 (overlapping d, H-7); *J* (Hz) (1, 6) 2.6, (2-*exo*, 8a) 7.5, (2-*exo*, 8b) 6.6, (4, 5) 2.4, (5, 6) 5.6, and (8a, 8b) 16; $\nu_{max.}$ (cm^{-1}, liquid film) 1 735 (C=O) and 739 (*cis*-olefinic H); *m/e* 224 ($M^{+\cdot}$), 193 ($M^{+\cdot}$ − OMe), 164 ($M^{+\cdot}$ − HCO_2Me), and 151 (M − CH_2CO_2Me).

3-exo-*Carboxynorborn*-5-*en*-2-endo-*ylacetic Acid* (9a).—Dry methanol (25 ml) was distilled into a flask containing sodium (460 mg, 20 mmol) under nitrogen. When the sodium had dissolved and the solution cooled to room temperature, the ester (6b) (1.0 g, 4.1 mmol) was added and the solution refluxed for 3 h. After cooling to room temperature, water (40 ml) was added and the solution refluxed for a further 1 h. The cooled aqueous solution was acidified to pH 2 with hydrochloric acid and extracted with ethyl acetate (4 × 30 ml). The combined extracts were dried over magnesium sulphate, filtered, and concentrated at reduced pressure. The resultant residue was recrystallised from ethyl acetate–light petroleum (b.p. 60—80 °C) to afford the *trans*-dicarboxylic acid (9a) (875 mg, 3.6 mmol, 89%) as white crystals, m.p. 119—120 °C (lit.,[9] m.p. 115—117 °C); δ(60 MHz, $CDCl_3$) 10.9 (s, CO_2H), 6.19 (m, H-5, -6), 2.99 and 2.92 (m, H-1, -4), 2.67 (m, H-3-*endo*), 2.27 (d, H-8), 1.85 (m, H-2-*exo*), 1.74 (br d, H-7-*syn*), and 1.44 (br d, H-7-*anti*); *J* (Hz) (2-*exo*, 8) 7 and (7-*syn*, 7-*anti*) 10; $\nu_{max.}$ (cm^{-1}, CH_2Cl_2) 3 000 (OH) and 1 710 (C=O); *m/e* 196 ($M^{+\cdot}$), 178 ($M^{+\cdot}$ − H_2O), and 159 ($M^{+\cdot}$ − H_2O − H_3O).

Methyl 3-exo-*Methoxycarbonylnorborn*-5-*en*-2-endo-*ylacetate* (9b).—The dicarboxylic acid (9a) (225 mg, 1.1 mmol) was methylated with diazomethane in ether solution. Concentration of the resultant ethereal solution by evaporation, followed by distillation of the residue, afforded the *trans*-bis-ester (9b) (175 mg, 0.8 mmol, 71%) as a clear oil, b.p. 90—95° at 0.1 mmHg [lit.,[9] b.p. 143—152 °C at 18 mmHg when mixed with (10)]; δ(90 MHz, $CDCl_3$) 6.13 (octet, H-5, -6), 3.70 and 3.65 (s, OMe), 2.97 and 2.88 (m, H-1, -4), 2.69 (pentuplet, H-3-*endo*), 2.20 (d, H-8), 1.83 (m, H-2-*exo*), 1.73 (d, H-7-*syn*), and 1.47 (d, H-7-*anti*); *J* (Hz) (1, 6) *ca.* 3.0, (2-*exo*, 8) 7.3, (4, 6) *ca.* 3.0, (5, 6) 5.6, and (7-*syn*, 7-*anti*) 9.1 [lit.,[9] δ(60 MHz, CCl_4) 3.55 (3 H, s), 3.59 (3 H, s), 5.96 (1 H, dd, *J* 5.6 and 3.0 Hz), and 6.19 (1 H, dd, *J* 5.6 and 3.0 Hz)]; $\nu_{max.}$ (cm^{-1}, CCl_4) 1 735 (C=O); *m/e* 224 ($M^{+\cdot}$), 193 ($M^{+\cdot}$ − OMe), 164 ($M^{+\cdot}$ − HCO_2Me), 159 ($M^{+\cdot}$ − C_5H_5), and 151 ($M^{+\cdot}$ − CH_2CO_2Me) [lit.,[9] 224 ($M^{+\cdot}$), 159, 151, and 66].

3-exo-*Methoxycarbonyl*-6-endo-*hydroxy*-5-exo-*iodonorborn*-2-endo-*ylacetic Acid δ-Lactone* (13).—The *trans*-dicarboxylic acid (9a) (1.16 g, 5.9 mmol) was dissolved in a solution of sodium hydrogencarbonate (2.02 g, 24 mmol) in water (40 ml) and the resultant solution treated with iodine (3.03 g, 12 mmol) and potassium iodide (6.0 g, 36 mmol) in water (20 ml), using the iodolactonisation procedure of van Tamelen and Shamma.[13] The crude product was methylated with diazomethane in ether solution, and the resultant methyl ester purified by column chromatography (60 g, SiO_2) using ethyl acetate–light petroleum (b.p. 60—80 °C) (15 : 85) as eluant to afford the *methyl ester δ-iodolactone* (13) (1.1 g, 3.4 mmol, 58%) as a white crystalline solid, m.p. 118—121 °C on recrystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C) (Found: C, 39.3; H, 4.0; I, 37.15. $C_{11}H_{13}IO_4$ requires C, 39.30; H, 3.90; I, 37.76%); δ(90 MHz, $CDCl_3$) 5.27 (dd, H-6-*exo*), 3.88 (dd, H-5-*endo*), 3.72 (s, OMe), 2.85 (m, H-4), 2.72 (m, H-3-*endo* and H-8), 2.50 (m, H-1), 2.18—2.31 (m, H-2-*exo* and H-7-*syn*), and 2.01 (m, H-7-*anti*); *J* (Hz) (1, 6-*exo*) 5.0, (5-*endo*, 6-*exo*) 1.8, (5-*endo*, 7-*anti*) 2.9, and (7-*syn*, 7-*anti*) 12.0; $\nu_{max.}$ (cm^{-1}, $CHCl_3$) 1 735 (C=O); *m/e* 336 ($M^{+\cdot}$), 306 ($M^{+\cdot}$ − CH_2O), 277 ($M^{+\cdot}$ − CO_2Me), and 209 ($M^{+\cdot}$ − I).

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