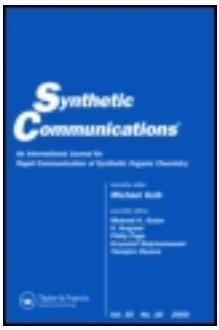

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Diels-Alder Reactions of 1,1-Disubstituted 3,4-Dimethylene-cyclopentanes. Preparation of Indanes and Diazaindanes

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DIELS-ALDER REACTIONS OF 1,1-DISUBSTITUTED 3,4-DIMETHYLENE-CYCLOPENTANES. PREPARATION OF INDANES AND DIAZAINDANES

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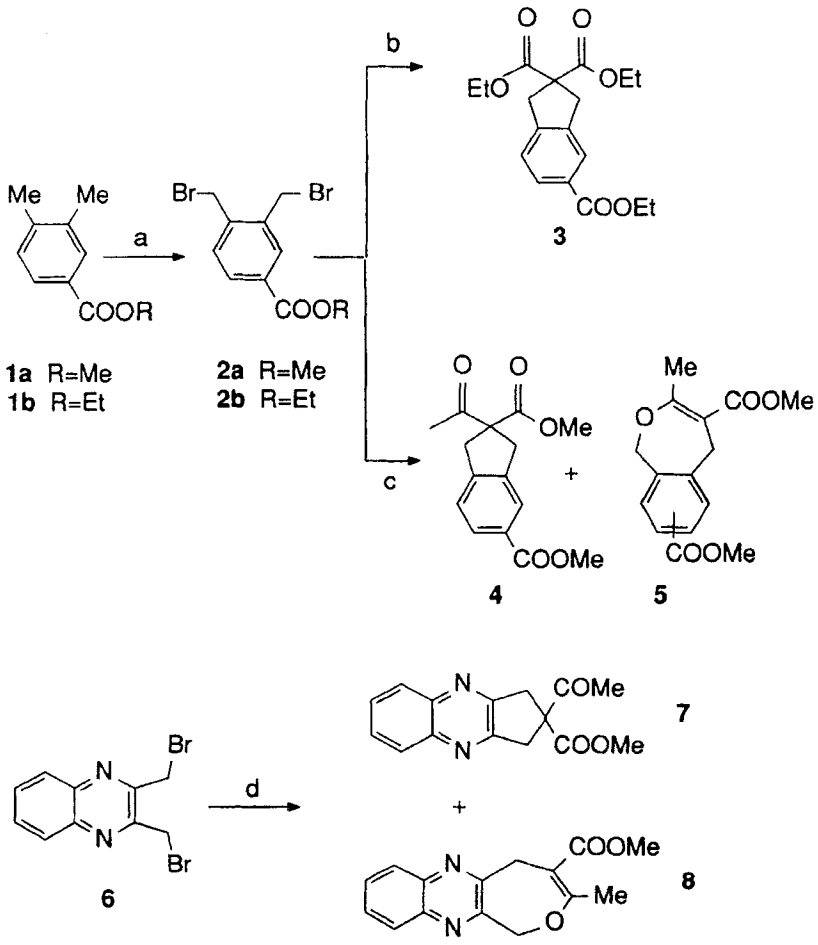
ABSTRACT.- Compounds possessing indane and diazaindane skeletons are prepared by two routes: i) reaction of 1,2-bis(bromomethyl)-benzenes with active methylene compounds and ii) Diels-Alder reaction of 1,1-disubstituted-3,4-dimethylenecyclopentanes.

INTRODUCTION

In the course of a synthetic project we required compounds possessing the bicyclo [4.3.0] nonane skeleton with the optional presence of nitrogen atoms on it. Recently Kotha and Kuki reported reactions of a methyl glycinate nucleophilic synthon with 1,2-bis(bromomethyl)benzenes.[1] This prompts us to report our own results since this approach is coincident with one of ours.



a) NBS, $(PhCOO)_2$, CCl_4, 2h, reflux. b) $(EtOCO)_2CH_2$, K_2CO_3, butanone, 18h, reflux. c) $MeCOCH_2COOMe$, K_2CO_3, butanone, 20h, reflux. d) $MeCOCH_2COOMe$, K_2CO_3, acetone, 6h, reflux.

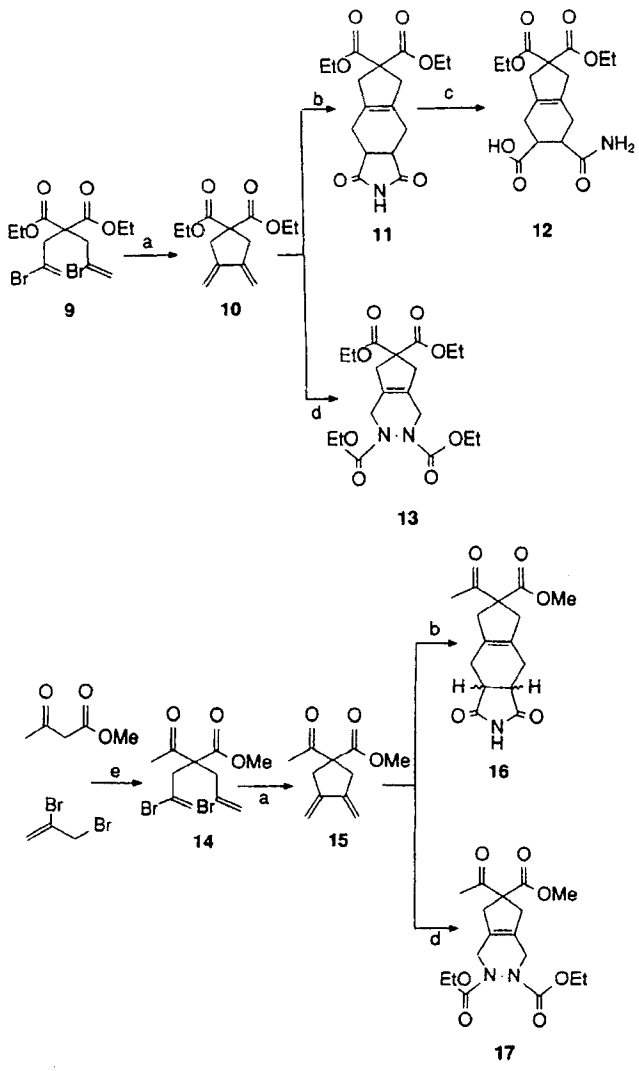
Scheme 1

RESULTS

Our results similar to those by Kotha and Kuki are summarized in Scheme 1. 3,4-Dimethylbenzoates **1** are brominated with NBS in carbon tetrachloride to afford 3,4-bis(bromomethyl)benzoates, **2.** Reaction of **2b** with diethyl malonate in refluxing butanone in the presence of potassium carbonate affords 2,2,5-tris(ethoxycarbonyl)indane, **3** (90%). Similarly, reaction of **2a** with methyl acetoacetate gives 2-acetyl-2,5-bis(methoxycarbonyl)indane, **4** (60%). A mixture (10%) of 4,7-bis(methoxycarbonyl)-3-methyl-1H,5H-2-benzoxepine and its 4,8-bis(methoxycarbonyl) isomer (compounds **5**) is also isolated. Oxepines **5** arise from intramolecular O-alkylation of the C-monoalkylated intermediate.

2,3-Bis(bromomethyl)quinoxaline, **6**,[2] reacts with methyl acetoacetate under similar conditions to afford 4'-acetyl-4'-methoxycarbonyl-2,3-cyclopentenoquinoxaline, **7** (73%). Traces of 4-methoxycarbonyl-3-methyl-1H,5H-oxepino [3,4-b] -quinoxaline, **8**, are also isolated.

Our second approach to the required structures is based on the Diels-Alder reactivity of diethyl 3,4-dimethylenecyclopentane-1,1-dicarboxylate, **10**, and the related methyl 1-acetyl-3,4-dimethylenecyclopentane-1-carboxylate, **15** (Scheme 2). Diene **10** or its dimethyl analogue has been described consecutively by Hegedus,[3] Grigg,[4] Trost,[5] and Guibé and Balavoine,[6] and their associates. We have used Grigg's method based on a reductive coupling of diethyl bis(2-bromoallyl)malonate, **9.** It can be successfully applied to methyl 2-bis(2-bromoallyl)acetoacetate,



a) PPh_3(1 eq), $Pd(OAc)_2$, K_2CO_3, CH_3CN, 5h, reflux, (Ref.4b). b) Maleimide, CH_2Cl_2, reflux, 5h for **11**, 1d for **16**. c) i: NaOH (1 eq), H_2O/EtOH; ii: H_3O^+, 5h, reflux. d) Diethyl azodicarboxylate CH_2Cl_2, reflux, 1d for **13**, 16h for **17**. e) K_2CO_3, butanone, 16h, reflux.

Scheme 2

14, to afford the so far unreported cyclopentane **15**. Although two Diels-Alder reactions of the dimethyl analogue of **10**[3b,5a] and a chelotropic reaction of **10**[4b] have been reported, this useful synthetic potential has not been emphasized.

Diene **10** reacts with maleimide to afford 4',4'-bis(ethoxycarbonyl)-5,6-cyclopenteno-1,3-dioxo-3a$\underline{H}$,4$\underline{H}$,7$\underline{H}$,7a$\underline{H}$-tetrahydroisoindoline, **11** (32%). Compound **11** is converted into 5-carboxy-2,2-bis(ethoxycarbonyl)-6-carbamoyl-2,3,4,5,6,7-hexahydroindene, **12** (58%), upon treatment with one equivalent of sodium hydroxide followed by acidic working up. An additional example of the usefulness of diene **10** is its reaction with diethyl azodicarboxylate to afford 1,2,4',4'-tetrakis(ethoxycarbonyl)-4,5-cyclopenteno-1,2,3,6-tetrahydropyridazine, **13** (90%).

Diene **15** behaves similarly. Thus, it affords both stereoisomers of constitution 4'-acetyl-4'-methoxycarbonyl-5,6-cyclopenteno-1,3-dioxo-3a$\underline{H}$,4$\underline{H}$,7$\underline{H}$,7a$\underline{H}$-tetrahydroisoindoline, **16** (69%), upon reaction with maleimide and 1,2-bis(ethoxycarbonyl)-4'-acetyl-4'-methoxycarbonyl-4,5-cyclopentene-1,2,3,6-tetrahydropyridazine, **17** (91%), by reaction with diethyl azodicarboxylate.

EXPERIMENTAL

^{1}H- and ^{13}-NMR spectra were recorded at 80 and 20MHz in $CDCl_3$. Compounds **1a**[7], **1b**[8], **2a**[9], **6**[2] and **10**[4b] were known.

Ethyl 3,4-bis(bromomethyl)benzoate, **2b**. Ester **1a** (4.00 g, 22.4 mmole), N-bromosuccinimide (7.97 g, 44.8 mmole) and a catalytic amount of benzoyl peroxide were refluxed in tetrachloromethane (50 ml) for 2h till all the solid came to the surface. The mixture was

ice-cooled and filtered. The filtrate was evaporated to afford an oil that crystallized upon treatment with hexane. Compound **2b** has mp 75-6ºC; IR(KBr): 1714 cm^{-1}; ^{1}H-NMR: 1.40 (t, J = 7.5 Hz, 3H), 4.35 (q, J = 7.5 Hz, 2H), 4.65 (s, 4H), 7.40 (d, J = 8.7 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 8.10 (s, 1H).

2,2,5-tris(Ethoxycarbonyl)indane, **3**. A mixture of diethyl malonate (1.48 g, 9.2 mmole), **2b** (3.10 g, 9.2 mmole), potassium carbonate (2.55 g, 18.5 mmole) and butanone (50 ml) was refluxed for 18h (glc monitoring). The mixture was filtered and the filtrate evaporated. The residue was crystallized from ethyl acetate to afford **3** (2.78 g, 90%), mp 234-6ºC; IR(KBr): 1732, 1721 cm^{-1}; ^{1}H-NMR: 1.25 (t, J = 7.0 Hz, 6H), 1.35 (t, J = 7.2 Hz, 3H), 3.60 (s, 4H), 4.15 (q, J = 7.0, 4H), 4.35 (q, J = 7.2 Hz, 2H), 7.20 (d, J = 7.7 Hz, 1H), 7.65-8.00 (m, 2H); ^{13}C-NMR: 13.8, 14.1, 40.0, 40.4, 60.3, 60.6, 61.6, 123.9, 125.2, 128.5, 129.5, 140.3, 145.3, 166.3, 171.0; MS (m/e): 334(M, 25), 289(19), 261(48), 260(100), 215(17), 187(29), 143(36), 115(28). Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.52; H, 6.65.

2-Acetyl-2,5-bis(methoxycarbonyl)indane, **4**. A mixture of methyl acetoacetate (5.41 g, 46.6 mmole), dibromoester **2a** (15.0 g, 46.6 mmole), potassium carbonate (12.88 g, 93.2 mmole) and butanone (250 ml) was refluxed for 20h (glc monitoring). The mixture was filtered and the filtrate was evaporated. The residue was chromatographed through a silica gel column using mixtures of hexane-ethyl acetate to afford in order of elution:

a) 4,7-bis(methoxycarbonyl)-3-methyl-1H,5H-2-benzoxepine and its

4,8-bis(methoxycarbonyl) isomer (compounds 5). This mixture had mp 103-4ºC; IR(KBr): 1728, 1721 cm^{-1}; ^{1}H-NMR: 2.15 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 3.95 (s, 2H), 5.20 (s, 2H), 7.35 (d, J = 7.5 Hz, 1H), 7.80-8.15 (m, 2H); a ^{1}H-NMR spectrum at 400 MHz showed the singlets at 2.15 and 5.20 to be duplicated, thus indicating that the sample contained two isomers (ratio about 1:1); ^{13}C-NMR: 22.4, 31.7, 51.3, 51.9, 70.1, 102.7, 128.3, 128.8, 129.0, 130.3, 135.5, 146.2, 166.0, 166.4, 169.6; MS(m/e): 276 (M, 12), 245(13), 217(38), 203(21), 175(61), 174(100), 145(28), 143(22), 131916), 129(14), 115(39), 59(14), 43(22). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.92; H, 6.06.

b) Indane **4** (5.80 g, 45%), mp 81-2ºC (ethyl acetate-hexane); IR(KBr): 1742, 1715 cm^{-1}; ^{1}H-NMR: 2.25 (s, 3H), 3.60 (s, 4H), 3.75 (s, 3H), 3.90 (s, 3H), 7.25 (d, J = 8.5 Hz, 1H), 7.75-8.00 (m, 2H); ^{13}C-NMR: 26.0, 38.7, 39.0, 51.9, 52.8, 66.8, 124.1, 125.5, 128.7, 129.3, 140.2, 145.3, 167.0, 172.5, 201.9; MS(m/e): 276(M, 2), 233(100), 201(29), 174(19), 143(15), 115(27), 43(51). Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.83; H, 6.08.

4'-Acetyl-4'-methoxycarbonyl-2,3-cyclopentenoquinoxaline, **7**. A mixture of methyl acetoacetate (2.68 g, 23.1 mmole), **6**[2] (7.30 g, 23.1 mmole), potassium carbonate (6.38 g, 46.2 mmole) and acetone (125 ml) was refluxed for 6h (glc monitoring). The mixture was filtered and the filtrate was evaporated. The residue crystallized from tetrachloromethane to give **7** (2.01 g, 32%), mp 136-7ºC; IR(KBr): 1736, 1706 cm^{-1}; ^{1}H-NMR: 2.30 (s, 3H), 3.80 (s, 4H), 3.85 (s, 3H), 7.50-8.20 m, 4H); ^{13}C-NMR: 25.9, 38.2, 53.2, 62.2, 128.7,

129.1, 141.8, 156.2, 171.8, 201.0; MS(m/e): 270(M, 3), 227(100), 195(26), 169(29), 43(35). Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.50; H, 5.18; N, 10.33.

Since the reaction crude presented a minor peak in glc, a sample was chromatographed through a silica gel column with hexane-ethyl acetate as eluent. Compound **7** was eluted first followed by 4-methoxycarbonyl-3-methyl-1H,5H-oxepino 3,4-b -quinoxaline, **8**, ^{1}H-NMR: 2.20 (long range coupled t, 3H), 3.80 (s, 3H), 4.35 (long range coupled q, 2H), 5.45 (s, 2H), 7.60-8.20 (m, 4H).

4',4'-bis(Ethoxycarbonyl)-5,6-cyclopenteno-1,3-dioxo-3aH,4H,7H,7aH-tetrahydroisoindoline, **11**. A mixture of diene **10** (0.75 g, 3.1 mmole), maleimide (0.30 g, 3.1 mmole) and dichloromethane (30 ml) was refluxed for 5h (glc monitoring). The solvent was evaporated and the residue was treated with diethyl ether to give **11** (0.34 g, 32%), mp 149-50ºC; IR(KBr): 3273, 1781, 1747, 1710; ^{1}H-NMR: 1.20 (t, J = 7.3 Hz, 6H), 2.40 (m, 4H), 2.80-3.30 (m, 6H), 4.20 (q, J = 7.3 Hz, 4H), 8.10 (broad s, 1H); ^{13}C-NMR: 13.9, 23.3, 39.5, 43.4, 57.6, 61.6, 130.5, 171.7, 172.0, 180.0; MS(m/e): 335(M, 18), 289(12), 262(35), 261(100), 243(24), 232(16), 216(69), 215(86). Anal. Calcd. for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.55; H, 6.48; N, 4.13.

5-Carboxy-2,2-bis(ethoxycarbonyl)-6-carbamoyl-2,3,4,5,6,7-hexahydroindene, **12**. A mixture of **11** (0.26 g, 0.79 mmole), 10% aqueous sodium hydroxide (0.32 ml, 0.79 mmole), water (2 ml) and ethanol (2 ml) was refluxed for 5h (IR monitoring). The solvent was partially evaporated and the residue was neutralized with 3N HCl.

The mixture was extracted with chloroform and the organic phase was dried and evaporated. The residue had mp 142-3ºC; IR(KBr): 3423, 3331, 3259, 3218, 1745, 1714, 1658 cm^{-1}; ^{1}H-NMR: 1.21 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.3 Hz, 3H), 2.15-2.55 (m, 4H), 2.75-3.15 (m, 2H), 2.90 (s, 4H), 4.14 (q, J = 7.1 Hz, 2H), 4.15 (q, J = 7.3 Hz, 2H), 4.90 (broad s, 1H), 6.20 (broad s, 1H), 6.70 (broad s, 1H); ^{13}C-NMR: 13.9, 26.2, 26.6, 40.7, 41.2, 43.2, 58.0, 61.5, 61.6, 129.4, 131.3, 172.1, 172.2, 176.7, 178.1; MS(m/e): 336(M-OH, 24), 291(12), 262(64), 234(100), 217(36), 189(46), 161(28), 143(16), 117(100), 91(24). Anal. Calcd. for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.77; H, 6.60; N, 3.80.

1,2,4',4'-Tetrakis(ethoxycarbonyl)-4,5-cyclopenteno-1,2,3,6-tetrahydropyridazine, **13**. A mixture of **10** (3.17 g, 13.3 mmole), diethyl azodicarboxylate (2.31 g, 13.3 mmole) and dichloromethane (80 ml) was refluxed for 24h (glc monitoring). The solvent was evaporated to give **13** (4.9 g, 90%), mp 94-6ºC; IR(KBr): 1737, 1705 cm^{-1}; ^{1}H-NMR: 1.20 (t, J = 7.0 Hz, 12H), 2.80-3.10 (m, 4H), 3.60-4.50 (m, 4H), 4.15 q, J = 7.0 Hz, 8H); ^{13}C-NMR: 13.4, 13.9, 40.5, 43.6, 57.5, 61.2, 61.9, 128.6, 155.0, 171.0; MS(m/e): 412(M, 29), 367(18), 339(40), 293(13), 265(15), 250(100), 249(88), 221(24), 193(24), 119(25), 91(45), 79(26). Anal. Calcd. for $C_{19}H_{28}N_2O_8$: C, 55.33; H, 6.84; N, 6.79. Found: C, 55.39; H, 6.90; N, 6.79.

Methyl 2,2-bis(2-bromoallyl)acetoacetate, **14**. A mixture of methyl acetoacetate ((6.17 g, 53.1 mmole), 2,3-dibromopropene (25.0 g, 106.3 mmole), potassium carbonate (14.68 g, 106.2 mmole) and butanone (80 ml) was refluxed for 16h (glc monitoring). The

mixture was filtered and the filtrate was evaporated. The residue was distilled to afford **14** (15.8 g, 84%), bp 115-7ºC/0.8 mmHg; IR(film): 1745, 1718 cm^{-1}; ^{1}H-NMR: 2.28 (s, 3H), 3.30 (internal peaks of the AB system, 4H), 3.78 (s, 3H), 5.60 (d, J = 2 Hz, 2H), 5.70 (broad s, 2H); ^{13}C-NMR: 26.8, 42.0, 52.5, 62.1, 121.7, 126.9, 170.1, 201.5; MS(m/e): 312(M-43, 1), 275(M-Br, 6), 243(11), 153(14), 91(15), 43(100). Anal. Calcd. for $C_{11}H_{14}Br_2O_3$: C, 37.32; H, 3.99. Found: C, 37.12; H, 3.91.

Methyl 1-acetyl-3,4-dimethylenecyclopentane-1-carboxylate, **15**. A mixture of dibromoester **14** (5.0 g, 14.1 mmole), palladium(II) acetate (0.16 g, 0.7 mmole), triphenylphosphine (3.70 g, 14.1 mmole), potassium carbonate (4.87 g, 35.3 mmole) and anhydrous acetonitrile (100 ml) was refluxed under argon for 4.5h (glc monitoring). The mixture was filtrated and the filtrate evaporated. The residue was passed through a silica gel column (hexane-ethyl acetate 85:15 as eluent) to afford **15** (1.45 g, 53%), bp 90-100 ºC(oven temp.)/0.5 mmHg; IR(film): 1743, 1716, 891 cm^{-1}; ^{1}H-NMR: 2.15 (s, 3H), 2.95 (m, 4H), 3.70 (s, 3H), 4.95 (broad s, 2H), 5.35 (broad s, 2H); ^{13}C-NMR: 26.2; 39.9; 52.5; 63.9; 105.4; 144.5; 172.3; 202.8; MS(m/e): 194(M, 14), 151(100), 119(49), 91(70), 43(85).

4'-Acetyl-4'-methoxycarbonyl-5,6-cyclopenteno-1,3-dioxo-3aH,4H,7H,7aH-tetrahydroisoindoline, **16** (Mixture of isomers). A mixture of **15** (4.74 g, 24.4 mmole), maleimide (2.37 g, 24.4 mmole) and dichloromethane (100 ml) was refluxed for 24h (glc monitoring). The solvent was evaporated to afford a residue that upon washing with diethyl ether gave **16** (69%), mp 124-5ºC;

IR(KBr): 3207, 1767, 1716; ^{1}H-NMR: 2.10 (s, 3H, isomer A), 2.12 (s, 3H, isomer B), 2.25-2.50 (m, 4+4H, both isomers), 2.85 (m, 4+4H, both isomers), 3.12 (m, 2+2H, both isomers), 3.70 (s, 3H, isomer A or B), 3.72 (s, 3H, isomer B or A), 7.75 (broad s, 1+1H, both isomers); ^{13}C-NMR (both isomers): 23.2, 23.3, 25.5, 25.7, 39.4, 39.5, 41.8, 52.6, 64.1, 130.3, 130.6, 172.9, 173.1, 180.3, 202.0, 202.1; MS(m/e) (both isomers): 291(M, 4), 248(28), 216(33), 150(14), 117(41), 76(30), 43(100). Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.97; H, 5.86; N, 4.71.

1,2-bis(Ethoxycarbonyl)-4'-acetyl-4'-methoxycarbonyl-4,5-cyclopentene-1,2,3,6-tetrahydropyridazine, **17**. A mixture of **15** (1.08 g, 5.6 mmole), diethyl azodicarboxylate (0.97 g, 5.6 mmole) and dichloromethane (25 ml) was refluxed for 16h (glc monitoring). The solvent was evaporated to afford an oil that can not be distilled without decomposition. Washing the oil with diethyl ether gives **17** (1.87 g, 91% with a purity of 98% determined by glc); the analitical sample was chromatographed through a silica gel column, IR(film): 1715 cm^{-1}; ^{1}H-NMR: 1.30 (t, J = 7.3 Hz, 6H), 2.20 (s, 3H), 2.95 (m, 4H), 3.50-4.60 (m, 4H), 3.80 (s, 3H), 4.25 (q, J = 7.3 Hz, 4H); ^{13}C-NMR: 14.4, 25.7, 39.2, 44.2, 52.8, 62.3, 64.4, 129.2, 155.5, 172.9, 201.5. Anal. Calcd. for $C_{17}H_{24}N_2O_7$: C, 55.34; H, 6.56; N, 7.60. Found: C, 55.29; H, 6.50; N, 7.61.

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