Studies on Antiatherosclerotic Agents.[1] Synthesis of 7-Ethoxycarbonyl-4-formyl-6,8-dimethyl-1(2*H*)-phthalazinone Derivatives and Related Compounds

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Derivatives of 7-ethoxycarbonyl-4-formyl-6,8-dimethyl-1(2*H*)-phthalazinone and closely related compounds were synthesized using Wittig and epoxidation reactions. Ring opening amination of the epoxides were carried out using dimethylaluminum amide reagents under mild reaction conditions. β-Keto ester and β-diketone moieties were introduced through diazo derivatives. These moieties were reacted with hydrazine hydrate to produce 4-pyrazolyl derivatives. The derivatives were tested for their inhibitory effect on platelet aggregation, and their relaxing effect on blood vessels.

Keywords synthesis; 7-ethoxycarbonyl-4-formyl-6,8-dimethyl-1(2*H*)-phthalazinone; Wittig reaction; epoxidation; dimethylaluminum amide reagent; rhodium(II) acetate; inhibitory effect; platelet aggregation

In the preceding paper,[1] we reported the synthesis of 7-ethoxycarbonyl-4-hydroxymethyl-6,8-dimethyl-1(2*H*)-phthalazinone (**1**) which showed potent inhibitory activities both on platelet aggregation and edematous arterial reaction, and compared the activity to closely related compounds, such as 4-formyl (**2**) and 4-methyl (**3**) in order to obtain insights into the structure–activity relationship.

We wish to report herein on the synthesis of derivatives of **1**, starting from **2** and **3** by applying the known methods to construct the expected bioactive side chain.

First of all, introduction of a cinnamic moiety[2,3] in the compound was carried out by Wittig reaction, with carboethoxymethylene triphenylphosphorane in tetrahydrofuran (THF), **2**, gave 4-unsaturated ester (**4**) in a 68% yield. The transformed structure of **4** was predominant according to the determination of proton nuclear magnetic resonance (^{1}H-NMR) assignments: each vinyl proton resonated at 6.80 and 8.00 ppm with a coupling constant of 16 Hz. Although **4** reacted with hydrazine hydrate to afford acid hydrazide (**5**), when direct aminolysis on **4** with secondary amines was performed, no corresponding products were obtained. However by means of trimethylaluminum with amines,[4] **4** produced amides (**6**—**8**) in moderate yields.

In order to construct a β-blocking side chain, an amino alcohol moiety which was often familiar to cardiovascular agents was introduced by ring opening amination of the epoxide. As reported,[5] **2** reacted with dimethylsulfonium methylide at −10 °C to afford a 4-epoxidated product (**9**).

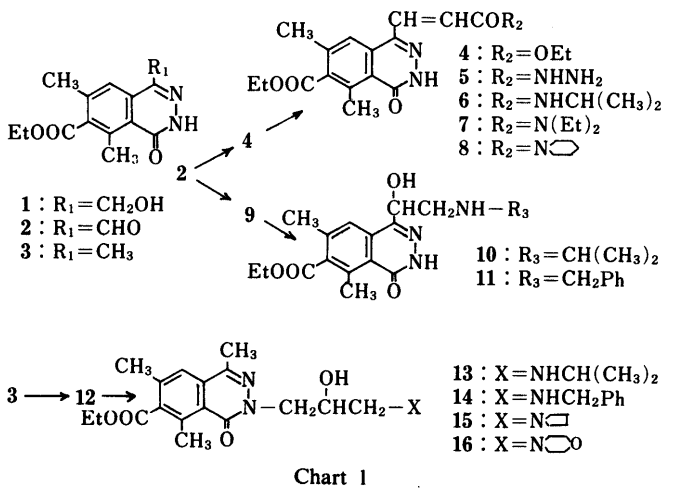
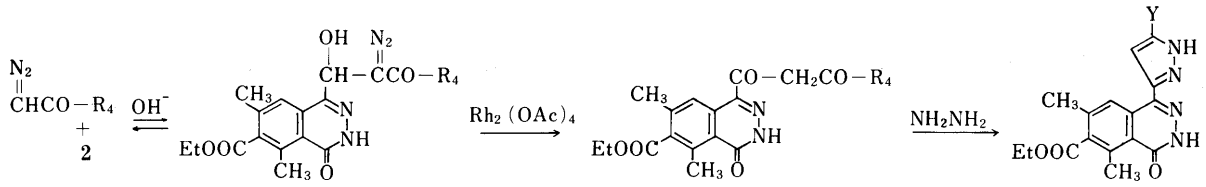


Chart 1

Upon refluxing the epoxide in benzene with amines, the corresponding aminoethyl alcohols (**10**, **11**) were obtained without any difficulty. On the other hand, the sodium salt of **3** was reacted with epichlorohydrin in dimethylformamide (DMF) to afford a sole product of *N*-epoxypropyl compound (**12**). Unfortunately, **12** was inert to secondary amines under refluxing conditions in benzene to open the ring, but was converted following treatment with dimethylaluminum amides in methylenechloride at room temperature to the corresponding products (**13**—**16**). Dimethylaluminum amide reagents[4] functioned well to produce ring opened compounds under very mild reaction conditions in this case.

Meanwhile, they reported[6–8] a condensation reaction of acyldiazomethanes with aldehydes or ketones to provide α-diazo-β-hydroxycarbonyl compounds, as well as an efficient procedure for the transformation of α-diazo-β-hydroxy esters into the corresponding β-keto esters using $Rh_2(OAc)_4$.[9] Keeping these reports in mind, we carried out condensation reactions of **2** with ethyl diazoacetate[10] and diazoacetone[11] under cooled conditions in a similar manner,[7] followed by treatment with $Rh_2(OAc)_4$ in dimethoxyethane in the same way.[8] Upon condensation of **2** with ethyl diazoacetate in ethanolic KOH at around 5 °C, a pale yellow crystalline product of diazo compound (**17**) was obtained. The infrared (IR) spectrum showed a typical absorption band due to a N≡N group at 2100 cm^{-1}. While carrying out the reaction in methanolic KOH, considerable trans esterification (ethyl to methyl) of the product at the 4 position was observed. Through reaction with diazoacetone, **2** was converted to diazoacetyl compound (**18**) in a 48% yield. In the reaction, an equilibration depicted in Chart 2 may have occured, depending on the reaction temperature. The yield lowered drastically when the temperature of the reaction mixture was not maintained at less than −10 °C. Addition of a catalytic amount of $Rh_2(OAc)_4$ to a stirred solution of **17** or **18** at room temperature resulted in rapid and quantitative evolution of nitrogen with a formation of β-keto ester (**19**) and β-diketone (**20**) in good yields, respectively. Hydrolysis accompanied with decarboxylation while refluxing in alcoholic KOH, converted **19** to 4-acetyl derivative (**19a**), whose ^{1}H-NMR spectrum displayed acetyl methyl protons at 2.88 ppm. Compound **19** was easily reacted with hydrazine hydrate in ethanol to afford a 4-pyrazolyl



17 : R_4=OEt
18 : R_4=CH_3

19 : R_4=OEt
20 : R_4=CH_3

21 : Y=OH
22 : Y=CH_3

Chart 2

TABLE I. Biological Activities of Compounds

Compd.	Inhibition of platelet aggregation (%) ADP (10 μM)	AA (137 μM)	Relaxing effect of blood vessel (%) Concentration 3×10^{-5} M
Papaverine			62
1	70	92	
3	72	88	
4	20	12	
5	14	42	
6	16	20	
7	13	32	
8	8	16	
10	8	16	34
11	10	18	42
13	27	45	48
14	18	30	30
15	17	18	37
16	20	32	48
21	22	40	
22	42	70	

derivative (**21**). Analysis of the ^{1}H-NMR spectra suggested almost exclusively the enolized structure of **21** shown in Chart 2, in which appeared the pyrazolyl ring proton at 5.76 ppm and the enolized hydroxy proton at 8.26 ppm. From β-diketone, **20** afforded a 4-(5-methyl-3-pyrazolyl) derivative (**22**), which was converted to HCl salt with high solubility in water.

Biological Results The biological activities assessed in this study were inhibitory effects on platelet aggregation[1,12] induced by both adenosine diphosphate (ADP) (10 μM) and arachidonic acid (AA) (137 μM). In addition, several compounds were tested for hypotensive activity for relaxing effects[13] on the blood vessels of spontaneously hypertensive rats.

In the results listed in Table I, compounds **5**, **13** and **22** showed high activity in the platelet aggregation test, especially **22**, whose pyrazolyl ring exhibited relatively potent activity. On the other hand, compounds having amino alcohol in their side chains, such as **13** and **16**, showed modest activity compared to its papaverine. Consequently, compounds **13**, **16** and **22** showed a relatively good balance of biological activity for further pharmacological evaluation.

Experimental

All melting points were determined in a capillary tube and were uncorrected. IR spectra were determined with a Hitachi model 285 spectrometer, mass spectra (MS) were recorded by a Hitachi RMU-7L spectrometer, ultraviolet (UV) spectra with a Hitachi model 323 spectrometer, and ^{1}H-NMR spectra with a JEOL-C-60HL machine. Merck Silica gel 60 was used for column chromatography.

7-Ethoxycarbonyl-4-(2-ethoxycarbonylethenyl)-6,8-dimethyl-1(2*H*)-phthalazinone (4) A mixture of NaH (54%, 400 mg) and dimethyl sulfoxide (DMSO) (7 ml) was warmed at 70 °C under nitrogen until evolution of the gas had ceased. The mixture was diluted with THF (50 ml) then treated with carboethoxymethylene triphenylphosphonium bromide (3.8 g) at 0 °C. To the stirred mixture was added **2** (2.44 g) at room temperature, and the new mixture was refluxed for 2 h. Decomposition by water and working-up afforded 1.6 g of **4**, mp 170—172 °C (EtOAc). *Anal.* Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.14. Found: C, 62.77; H, 5.82; N, 8.11. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7 Hz), 1.40 (3H, t, J=7 Hz), 2.45 (3H, s), 2.90 (3H, s), 4.30 (2H, q, J=7 Hz), 4.45 (2H, q, J=7 Hz), 6.80 (1H, d, J=16 Hz), 7.65 (1H, s), 8.00 (1H, d, J=16 Hz), 11.25 (1H, s).

Compound **5** was obtained from **4**: mp 235—237 °C (EtOH). ^{1}H-NMR (DMSO-d_6) δ: 1.35 (3H, t, J=7 Hz), 2.41 (3H, s), 2.77 (3H, s), 4.48 (2H, q, J=7 Hz), 7.63 (1H, d, J=10 Hz), 7.87 (1H, d, J=10 Hz), 9.01 (1H, s), 11.12 (1H, s), 12.26 (1H, s).

Compounds **6**—**8** were obtained from **4** in the described manner.[4]

6: mp 285—287 °C (MeOH). ^{1}H-NMR (DMSO-d_6) δ: 1.08 (3H, s), 1.17 (3H, s), 1.48 (3H, t, J=7 Hz), 2.48 (3H, s), 2.75 (3H, s), 3.94 (1H, br), 4.40 (2H, q, J=7 Hz), 6.82 (1H, d, J=15 Hz), 7.76 (1H, d, J=15 Hz), 7.86 (1H, s), 12.70 (1H, s).

7: mp 193—195 °C (MeOH). IR ν_{max}^{KBr} cm^{-1}: 3400, 2910, 1730, 1650, 1430, 1260, 1140.

8: mp 186—188 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.84 (3H, t, J=7 Hz), 1.63—1.88 (6H), 2.47 (3H, s), 2.90 (3H, s), 3.67 (4H, br), 4.47 (2H, q, J=7 Hz), 7.75 (1H, s), 7.58 (1H, d, J=16 Hz), 8.03 (1H, d, J=16 Hz), 10.82 (1H, br).

7-Ethoxycarbonyl-4-epoxyethyl-6,8-dimethyl-1(2*H*)-phthalazinone (9) A mixture of NaH (54%, 800 mg) and DMSO (12 ml) was heated at 65 °C under nitrogen, then was diluted with THF (40 ml) and cooled to −10 °C. To the stirred mixture was added dropwise a solution of trimethylsulfonium iodide (3.68 g) in THF (20 ml) and DMSO (10 ml), followed by **2** (2.74 g) in THF (20 ml) and DMSO (5 ml). The mixture was stirred vigorously at −10 °C for 30 min then allowed to warm at room temperature. The mixture was decomposed by addition of water, and acidified by dil. H_2SO_4 to afford an oil, which was purified by column chromatography with benzene : EtOAc (12 : 3). Yield: 1.46 g. mp 154—156 °C (acetone). *Anal.* Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.44; H, 5.54; N, 9.80. MS *m/z*: 288, 273, 260, 243, 232. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7 Hz), 2.50 (3H, s), 2.90 (3H, s), 3.25 (2H, br), 4.20 (1H, t, J=3 Hz), 4.45 (2H, q, J=7 Hz), 7.75 (1H, s), 10.80 (1H, s).

Compounds **10** and **11** were obtained from **9**.

10: mp 235—237 °C (acetone). MS *m/z*: 316, 302, 288. ^{1}H-NMR (DMSO-d_6) δ: 1.25 (3H, s), 1.40 (3H, s), 1.40 (3H, t, J=7 Hz), 2.45 (3H, s), 2.75 (3H, s), 3.25 (2H, br), 4.40 (2H, q, J=7 Hz), 5.45 (1H, s), 8.05 (1H, s), 12.55 (1H, s), HCl salt: mp 242—244 °C (acetone).

11: 155—157 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 2.45 (3H, s), 2.80 (3H, s), 3.10 (2H, d, J=5 Hz), 3.80 (2H, s), 4.45 (2H, q, J=7 Hz), 5.10 (1H, t, J=5 Hz), 7.30 (5H, s), 7.65 (1H, s). HCl salt: mp 248—250 °C (acetone).

7-Ethoxycarbonyl-2-(2,3-epoxypropyl)-4,6,8-trimethyl-1(2*H*)-phthalazinone (12) A clear solution of **3** (5.2 g), NaOH (800 mg) in water (12 ml) and MeOH (20 ml) was dried *in vacuo* to make sodium salt. To a stirred solution of epichlorohydrin (2.2 g) in DMF (20 ml) was added portionwise the salt (5.5 g) at 70 °C over a period of 2 h. The reaction mixture was poured into water. Working-up with EtOAc gave an oil. Purification by chromatography with benzene : EtOAc (4 : 1) afforded 3.2 g of **12**. mp 80—82 °C (EtOH). *Anal.* Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.54; H, 6.34; N, 8.88. IR ν_{max}^{KBr} cm^{-1}: 3450, 3000, 1740, 1640, 1430. MS *m/z*: 316, 287, 285, 273, 271. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7 Hz), 2.44 (3H, s), 2.51 (3H, s), 2.75 (2H, m),

2.89 (3H, s), 3.45 (1H, br), 4.25 (2H, m), 4.48 (2H, q, $J=7$ Hz), 7.40 (1H, s), 11.32 (1H, s).

7-Ethoxycarbonyl-2-(2-hydroxy-3-isopropylaminopropyl)-4,6,8-trimethyl-1(2*H*)-phthalazinone (13) To a stirred solution of isopropylamine (260 mg) in CH_2Cl_2 was added trimethylaluminum in hexane (25%, 0.8 ml) (Alfa Inorganics) under nitrogen. After 30 min, **12** (316 mg) was added and the mixture was stirred at room temperature for 10 h. The mixture was decomposed by careful addition of water and extracted with CH_2Cl_2. Working-up afforded semi-solid crystals, which were recrystallized from EtOAc–ether to give **13**, mp 111—112 °C in 210 mg. *Anal.* Calcd for $C_{20}H_{29}N_3O_4$: C, 63.97; H, 7.79; N, 11.19. Found: C, 63.90; H, 7.83; N, 11.23. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, s), 1.11 (3H, s), 1.41 (3H, t, $J=7$ Hz), 2.46 (3H, s), 2.53 (3H, s), 2.72 (2H, s, 1H, s), 2.87 (3H, s), 4.25 (2H, s), 4.45 (2H, q, $J=7$ Hz), 7.41 (1H, s).

Compounds **14**—**16** were obtained from **12** in a similar manner.

14: mp 135—136 °C (EtOAc–ether). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, $J=7$ Hz), 2.45 (3H, s), 2.51 (3H, s), 2.79 (2H, br), 2.86 (3H, s), 3.35 (2H, s), 3.84 (2H, s), 4.27 (2H, s), 4.44 (2H, q, $J=7$ Hz), 7.29 (5H, s), 7.40 (1H, s).

15: mp 115—116 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, $J=7$ Hz), 1.75 (4H, m), 2.47 (3H, s), 2.55 (3H, s, 4H, m), 3.86 (3H, s), 3.87 (1H, br), 4.25 (4H, m), 4.45 (2H, q, $J=7$ Hz), 7.40 (1H, s).

16: mp 137—138 °C (EtOAc–ether). ^{1}H-NMR ($CDCl_3$) δ: 1..41 (3H, t, $J=7$ Hz), 2.45 (3H, s), 2.53 (10H, s), 2.87 (3H, s), 3.71 (4H), 4.24 (2H, s), 4.43 (2H, q, $J=7$ Hz), 7.40 (1H, s).

4-(2-Diazo-2-ethoxycarbonyl-1-hydroxyethyl)-7-ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinone (17) To a mixture of **2** (1.64 g) and ethyl diazoacetate (1.37 g) in EtOH (30 ml) was added dropwise aq. NaOH [(480 mg) in water (10 ml)] at 0 °C. It was then allowed to stir at 0—5 °C for 5 h. While stirring, the reaction mixture became clear and crystals began to fall. Crystals were filtered and washed with cold EtOH on a filter to afford 1.3 g of **17**. mp 155—156 °C (EtOAc–ether). *Anal.* Calcd for $C_{18}H_{20}N_4O_6$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.53; H, 5.22; N, 14.21. MS *m/z*: 350 ($M^+ - N_2$), 331, 316. IR ν_{max}^{KBr} cm^{-1}: 3380, 2100, 1720, 1650. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, $J=7$ Hz), 1.39 (3H, t, $J=7$ Hz), 2.38 (3H, s), 2.85 (3H, s), 4.27 (2H, q, $J=7$ Hz), 4.40 (2H, q, $J=7$ Hz), 4.41 (1H, br), 6.11 (1H, d, $J=6$ Hz), 7.52 (1H, s), 10.76 (1H, s).

Compound **18**: mp 157—158 °C (EtOAc). IR ν_{max}^{KBr} cm^{-1}: 3350, 2100, 1730, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, $J=7$ Hz), 2.25 (3H, s), 2.38 (3H, s), 2.81 (3H, s), 4.36 (1H, s), 4.47 (2H, q, $J=7$ Hz), 6.25 (1H, d, $J=5$ Hz), 7.50 (1H, s), 10.56 (1H, s).

7-Ethoxycarbonyl-4-(2-ethoxycarbonyl-1-oxoethyl)-6,8-dimethyl-1(2*H*)-phthalazinone (19) To a stirred solution of **17** (388 mg) in dimethoxyethane (10 ml) was added portionwise $Rh_2(OAc)_4$ (8.0 mg). Nitrogen (about 23 ml) evolved. Inorganics were filtered off and the filtrate was concentrated at reduced pressure to afford semi-solid. Recrystallization from EtOAc–ether afforded 260 mg of **19** as pale yellow needles melted at 137—138 °C. *Anal.* Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.87; H, 5.60; N, 7.64. IR ν_{max}^{KBr} cm^{-1}: 3150, 3000, 1740, 1660, 1650. MS *m/z*: 360, 331, 315. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, $J=7$ Hz), 1.44 (3H, t, $J=7$ Hz), 2.48 (3H, s), 2.86 (3H, s), 4.10 (2H, s), 4.19 (2H, q, $J=7$ Hz), 4.48 (2H, q, $J=7$ Hz), 8.69 (1H, s), 10.73 (1H, s).

Compound **20**: mp 154—155 °C (EtOAc–ether). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, $J=7$ Hz), 2.15 (3H, s), 2.42 (3H, s), 2.87 (3H, s), 4.18 (1H, s), 4.41 (2H, q, $J=7$ Hz), 6.25 (1H, s), 8.41 (1H, s), 10.41 (1H, br).

Compound **19a**: mp 158—159 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, $J=7$ Hz), 2.47 (3H, s), 2.66 (3H, s), 2.88 (3H, s), 4.44 (2H, q, $J=7$ Hz), 8.67 (1H, s), 10.87 (1H, s).

Compounds **21** and **22** were obtained from **19** and **20**, respectively.

21: Did not melt at 280 °C. UV λ_{max}^{EtOH} nm: 228, 305. ^{1}H-NMR (DMSO-d_6) δ: 1.31 (3H, t, $J=7$ Hz), 2.30 (3H, s), 2.75 (3H, s), 4.38 (2H, d, $J=7$ Hz), 5.76 (1H, s), 8.20 (1H, br), 10.30 (1H, br), 12.68 (1H, s).

22: mp 230—231 °C (EtOH). UV λ_{max}^{EtOH} nm: 229, 306. ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) δ: 1.37 (3H, t, $J=7$ Hz), 2.31 (3H, s), 2.34 (3H, s), 2.79 (3H, s), 4.38 (2H, q, $J=7$ Hz), 6.29 (1H, s), 8.48 (1H, s), 12.22 (1H, s). HCl salt: mp 239—240 °C (EtOH–acetone).

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