Studies on Antiatherosclerotic Agents.[1] Synthesis of 5-Substituted Derivatives of 7-Ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinone

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Several 5-substituted derivatives of 7-ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinone were prepared by means of nitration, reductive amination, and diazonium decomposition. The substituents introduced included NO_2, NH_2, F, Cl, CN. Among the derivatives, the fluorine compound was obtained only in poor yield because intramolecular cyclization occurred predominantly.

Keywords 7-ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinone derivative; antiatherosclerotic agent; diazonium decomposition; 5-fluorine compound

Several new 5-substituted derivatives of 7-ethoxycarbonyl-6,8-dimethyl-1(2*H*)-phthalazinones were synthesized starting from the previously prepared compounds (**1a—c**).[1,2] As the synthetic procedures included nitration,[3,4] subsequent reduction and conventional diazonium salt decomposition[5,6] were convenient to introduce substituents, such as F, Cl, and CN, at the 5-position. Fluorine was an especially attractive substituent from the viewpoint of our medicinal studies.[7,8] The derivatives were required for examination of their potential as antiatherosclerotic agents.

The starting compounds **1a—c** were efficiently nitrated at the 5-position to afford **2a—c** in good yields using a mixture of potassium nitrate and concentrated sulfuric acid as a nitrating agent. In the reaction of **1a**, the dinitro derivative (**2d**) was produced as a by-product in 8% yield. The structures of these derivatives were confirmed by their proton nuclear magnetic resonance (^{1}H-NMR) spectra, which showed no aromatic protons, and infrared (IR) spectra, with typical $-NO_2$ absorption bands near 1540, 1370, and 1260 cm^{-1}, as well as mass spectra (MS).

The other nitro derivatives (**2e—j**) listed in Table I were also prepared by the following modified methods. Compound **2f** was obtained by hydrolysis of **2c** and subsequent decarboxylation of **2e** on heating at 220 °C in 90% yield. Compound **2g** was prepared from **2a** by heating with phosphoryl chloride. Treatment of **2g** with morpholine or sodium ethoxide afforded the corresponding products, **2h** and **2i**, respectively. The N^2-methyl derivative **2j** was obtained when **2f** was reacted with methyl iodide in alcoholic KOH.

Reduction of the nitro compounds **2a**, **b**, **f**, **h**, and **j** was carried out by hydrogenation over a catalyst of 5% palladium on carbon (Pd–C) under normal pressure, affording the corresponding 5-amino derivatives (**3a—e**) in good yields. On the other hand, reduction of **2c** afforded

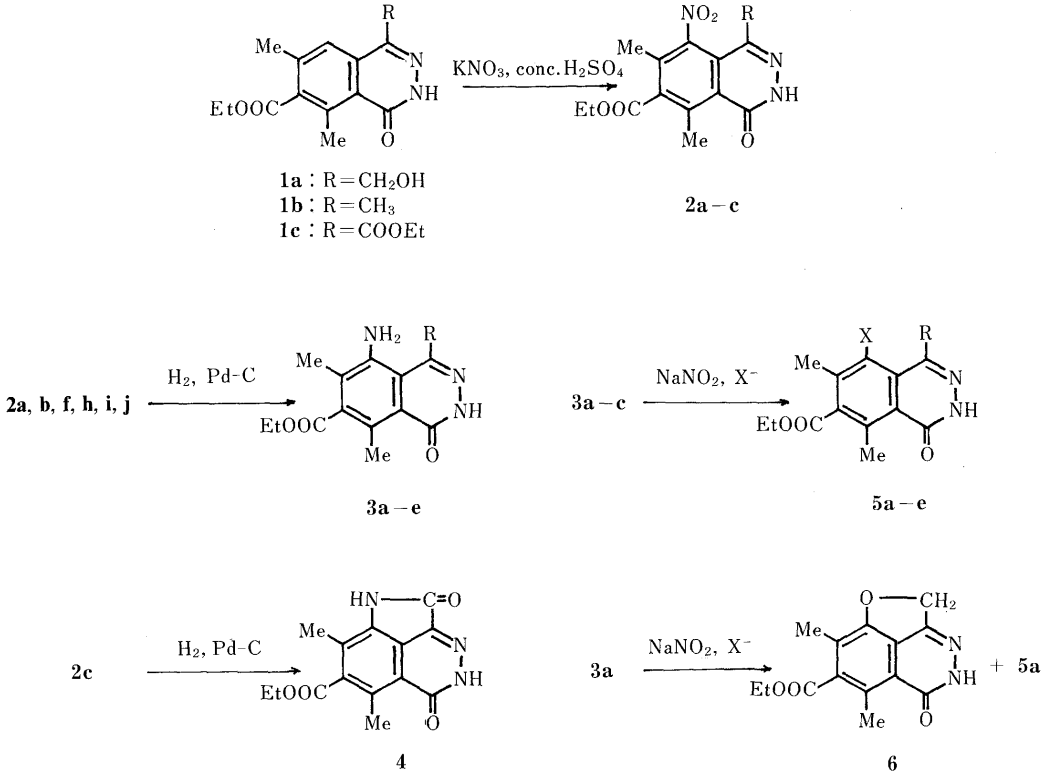
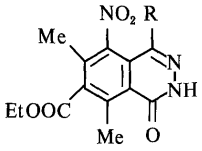


Chart 1

TABLE I



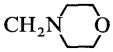
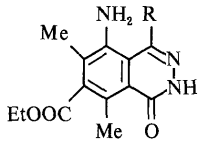
Compound	R	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd			Found		
				C	H	N	C	H	N
2a	CH_2OH	177—179 (MeOH)	$C_{14}H_{15}N_3O_6$	52.33	4.71	13.08	52.30	4.70	13.11
2b	CH_3	216—217 (MeOH)	$C_{14}H_{15}N_3O_5$	55.08	4.95	13.77	55.13	4.89	13.70
2c	$COOC_2H_5$	200—202 (MeOH)	$C_{16}H_{17}N_3O_7$	52.89	4.72	11.57	52.86	4.75	11.63
2d	CH_2ONO_2	183—185 (EtOAc–benzene)	$C_{14}H_{14}N_4O_8$	45.90	3.85	15.30	45.92	3.79	15.24
2e	COOH	212 (MeOH)	$C_{14}H_{13}N_3O_7$	50.15	3.91	12.53	50.18	3.95	12.48
2f	H	210 (MeOH)	$C_{13}H_{13}N_3O_5$	53.61	4.50	14.43	53.57	4.55	14.36
2g	CH_2Cl	207—209 (EtOH)	$C_{14}H_{14}ClN_3O_5$	49.45	4.12	12.36	49.42	4.11	12.44
2h		164—166 (MeOH)	$C_{18}H_{22}N_4O_6$	55.38	5.68	14.35	55.36	5.70	14.42
2i	$CH_2OC_2H_5$	150—152 (MeOH)	$C_{16}H_{19}N_3O_6$	55.01	5.48	12.03	55.05	5.50	12.08
2j	H, N^2–CH_3	137—138 (EtOAc–*n*-hexane)	$C_{14}H_{15}N_3O_5$	55.08	4.95	13.77	55.12	4.93	13.73

TABLE II



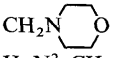
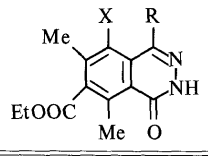
Compound	R	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd			Found		
				C	H	N	C	H	N
3a	CH_2OH	217—219 (MeOH)	$C_{14}H_{17}N_3O_4$	57.72	5.88	14.43	57.83	5.85	14.48
3b	CH_3	181—182 (MeOH)	$C_{14}H_{17}N_3O_3$	61.08	6.22	15.26	61.06	6.23	15.26
3c	H	205—206 (EtOAc–*n*-hexane)	$C_{13}H_{15}N_3O_3$	59.76	5.79	16.08	59.76	5.83	16.12
3d		204—206 (MeOH)	$C_{18}H_{24}N_4O_4$	59.93	6.71	15.55	59.87	6.73	15.60
3e	H, N^2–CH_3	178—179 (EtOAc–ether)	$C_{14}H_{17}N_3O_3$	61.08	6.22	15.26	61.11	6.24	15.30
3f	CH_2OH, N^5–$COCH_3$	235—240 (MeOH)	$C_{16}H_{19}N_3O_5$	57.65	5.75	12.61	57.66	5.73	12.67

TABLE III



Compound	X	R	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd			Found		
					C	H	N	C	H	N
5a	F	CH_2OH	187—188 (EtOAc)	$C_{14}H_{15}FN_2O_4$	57.14	5.10	9.52	57.07	5.14	9.42
5b	Cl	CH_2OH	202—203 (MeOH)	$C_{14}H_{15}ClN_2O_4$	54.07	4.82	9.01	54.09	4.80	9.05
5c	CN	CH_2OH	203—205 (MeOH–EtOAc)	$C_{15}H_{15}N_3O_4$	59.79	5.02	13.95	59.77	5.01	13.97
5d	Cl	CH_3	188—189 (MeOH)	$C_{14}H_{15}ClN_2O_3$	57.04	5.09	9.50	57.07	5.06	9.57
5e	CN	H	190—192 (EtOH)	$C_{14}H_{13}N_3O_3$	61.98	4.83	15.49	61.96	4.81	15.52

the lactam derivative (**4**) as a sole product. The ultraviolet (UV) spectra of **3a—e** exhibited characteristic absorptions near 365 nm, which were not observed in the nitro compounds. Upon heating in acetic anhydride, **3a** provided the N^5-acetyl derivative (**3f**). The 5-amino derivatives obtained are listed in Table II.

It has been reported that [9] tetrabutylammonium fluoride is a powerful fluoride ion source able to displace aromatic nitro groups to yield fluoroaromatics. But, in the case of **2a**, no fluorinated products were obtained under similar

reaction conditions. However, the 5-fluorine compound (**5a**) was prepared in 7% yield by the thermal decomposition of the diazonium fluoroborate derived from **3a**, by the classical method.[5,10] Owing to radical decomposition,[11] the serious side reaction in which the *peri*-methylhydroxy group of **3a** acts as a donor to the radical center occurred to give an intramolecular cyclization product (**6**) exclusively in 30% yield. The other diazonium substitution products (**5b—e**) listed in Table III were prepared from the corresponding amino compounds in yields of 40—65% by the conventional procedures.[6]

Preliminary biological tests of the prepared compounds showed rather decreased inhibitory activities on platelet aggregation induced by both adenosine diphosphate and arachidonic acid as compared with **1a**.

Experimental

All melting points were determined in a capillary tube and are uncorrected. IR spectra were determined with a Hitachi model 285 spectrometer, MS were recorded on a Hitachi RMU-7L spectrometer, UV spectra with a Hitachi model 323 spectrometer, and NMR spectra with a JEOL C-60HL machine. Merck Silica gel 60 was used for column chromatography.

General Procedure for Preparation of the 5-Nitro Compounds Potassium nitrate (3.0 g) was added portionwise to a solution of **1a** (6.0 g) in concentrated sulfuric acid (40 ml), and the mixture was stirred for 7 h at room temperature, then poured into water (1.5 l). The whole was stirred for 20 h at room temperature. Precipitates were filtered off and washed with water on the filter. Recrystallization from MeOH gave 3.9 g of **2a**, melted at 177—179 °C (55.9%). *Anal.* Calcd for $C_{14}H_{15}N_3O_6$: C, 52.33; H, 4.71; N, 13.08. Found: C, 52.30; H, 4.70; N, 13.11. IR ν_{max}^{KBr} cm^{-1}: 1740, 1660, 1540, 1370, 1260. UV λ_{max}^{EtOH} nm: 215, 254, 263, 306. NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz), 2.33 (3H, s), 2.92 (3H, s), 3.30 (1H, br), 4.50 (2H, q, J=7 Hz), 4.71 (2H, d, J=5 Hz), 10.92 (1H, s).

The mother liquor of **2a** was subjected to column chromatography with benzene–EtOAc (10 : 1) to give 640 mg of **2d** in 8.0% yield, mp 183—185 °C (EtOAc–benzene). *Anal.* Calcd for $C_{14}H_{14}N_4O_8$: C, 45.90; H, 3.85; N, 15.30. Found: C, 45.92; H, 3.79; N, 15.24. IR ν_{max}^{KBr} cm^{-1}: 1740, 1660, 1540, 1370, 1280, 1260. UV λ_{max}^{EtOH} nm: 213, 254, 264, 305, 313. NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7Hz), 2.36 (3H, s), 2.92 (3H, s), 4.51 (2H, q, J=7 Hz), 5.47 (2H, s), 11.03 (1H, s).

Preparation of 2f Tableted **2e** (25 g) was placed in a 100 ml round-bottomed flask, which was filled with argon gas. When the flask was heated gradually to 210—225 °C, the tablets began to melt with evolution of gas. When evolution of the gas had ceased, the flask was allowed to stand at room temperature. A part of the solid was recrystallized from MeOH to give **2f**, mp 208 °C. Yield: 21 g (96%). *Anal.* Calcd for $C_{13}H_{13}N_3O_3$: C, 53.61; H, 4.50; N, 14.43. Found: C, 53.57; H, 4.55; N, 14.36. IR ν_{max}^{KBr} cm^{-1}: 1730, 1660, 1530, 1360, 1260. UV λ_{max}^{EtOH} nm: 214, 260, 302. NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7 Hz), 2.41 (3H, s), 2.95 (3H, s), 4.82 (2H, q, J=7 Hz), 7.98 (1H, s), 10.72 (1H, s).

Compound **2g** was obtained from **2a** by reaction with $POCl_3$ under reflux for a short time (yield, 72%). Compounds **2h** and **2i** were obtained from **2g** in 65 and 57% yields by reaction with morpholine and EtONa, respectively. Compound **2j** was obtained from **2f** by reaction with CH_3I.

General Procedure for Preparation of the 5-Amino Compounds A solution of **2a** (1.3 g) in MeOH (40 ml) and EtOAc (20 ml) was shaken in H_2 on 5% Pd–C (0.3 g). After the theoretical amount of H_2 had been taken up, the catalyst was filtered off and the filtrate was concentrated to afford 1.0 g (85%) of **3a**. *Anal.* Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.43. Found: C, 57.83; H, 5.85; N, 14.48. IR ν_{max}^{KBr} cm^{-1}: 3420, 3350, 2980, 1740, 1700, 1640. UV λ_{max}^{EtOH} nm: 205, 224, 316, 367. NMR (DMSO-d_6) δ: 1.32 (3H, t, J=7 Hz), 2.12 (3H, s), 2.59 (3H, s), 4.38 (2H, d, J=7 Hz), 4.61 (2H, d, J=5 Hz), 5.65—6.30 (3H, m), 12.03 (1H, br).

Compound **4** was obtained from **2c** in 65% yield by a similar procedure. *Anal.* Calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.62; H, 4.58; H, 14.70. MS m/z: 287, 259, 242. NMR (DMSO-d_6) δ: 1.35 (3H, t, J=7 Hz), 2.20 (3H, s), 2.56 (3H, s), 4.39 (2H, q, J=7 Hz), 11.15 (1H, s), 13.19 (1H, s).

7-Ethoxycarbonyl-5-fluoro-4-hydroxymethyl-6,8-dimethyl-1(2*H*)-phthalazinone (5a) A solution of **3a** (1.0 g) in 42% fluoroboric acid (4 ml) and water (4 ml) was chilled at 0 °C and a solution of sodium nitrate (400 mg) in water (2 ml) was added with vigorous stirring. Stirring was continued for 30 min, yielding precipitates. The salts were collected and washed with a small amount of cold water, then air-dried. The salts were placed in an argon gas-filled flask and heated gently with a flame. Evolution of gas occurred and the resulting mass was taken up in chloroform. Purification by column chromatography with benzene–EtOAc–MeOH (50 : 20 : 1) afforded 78 mg of **5a** from the later fractions in 7.2% yield. *Anal.* Calcd for $C_{14}H_{15}FN_2O_4$: C, 57.14; H, 5.10; N, 9.52. Found: C, 57.07; H, 5.14; N, 9.42. MS m/z: 294, 265, 249, 237. UV λ_{max}^{EtOH} nm: 215, 264, 293, 316, 329. The early fractions gave 290 mg (30.7%) of **6** as off-white crystals. *Anal.* Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found; C, 61.34; H, 5.18; N, 10.31. MS m/z: 274, 245, 229, 200. UV λ_{max}^{EtOH} nm: 216, 234, 275, 338, 354.

Compounds **5b—e** were obtained in 35—52% yields in the manner described in the literature.[6]

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