[Chem. Pharm. Bull. 21(9)1885—1893(1973)]

UDC 547.793.4.057 : 615.22.011.5.015.11

Studies on the Syntheses of N-Heterocyclic Compounds. IV.[1] Hypocholesterolemic 1,2,4-Oxadiazole Derivatives. (2)

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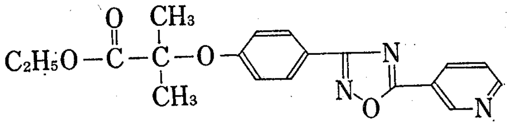
(Received October 24, 1972)

The derivatives of 3-[4-(1-ethoxycarbonyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (I), which showed considerable hypocholesterolemic activities, were synthesized. Among them, 3-[4-(1-ethoxycarbonyl-1-methylethoxy)phenyl]-5-(2- or 3-chlorophenyl)-1,2,4-oxadiazole (**13**, **14**) and their amide derivatives (**29**, **30**) showed nearly equal activity to I. Two alternative synthetic routes of I were developed.

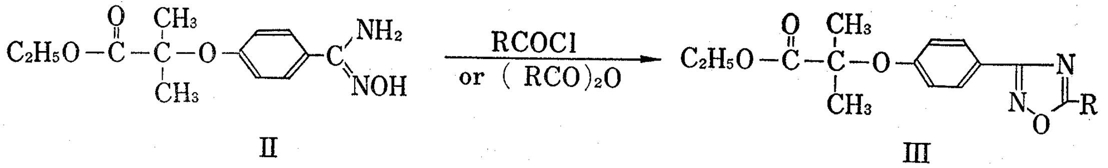
In the preceding paper,[1] we reported that 3-[4-(1-ethoxycarbonyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (I) possesses a significant hypocholesterolemic activity. The present paper is concerned with the effects of modifications of the substituents at 3 and 5 positions of the oxadiazole ring in I on hypocholesterolemic activity as well as with alternative synthetic methods of I.

First of all we undertook the modification of the substituent at the 5 position of the 1,2,4-oxadiazole ring confining the 3 position to 4-(1-ethoxycarbonyl-1-methylethoxy)phenyl group. For this purpose, 4-(1-ethoxycarbonyl-1-methylethoxy)benzamidoxime (II) was reacted with a variety of acid anhydrides or acylchlorides in pyridine to afford 3-[4-(1-ethoxycarbonyl-1-methylethoxy)phenyl]-5-substituted-1,2,4-oxadiazoles (III). The obtained compounds and their biological activities are listed in Table I.



I

Chart 1



II III

Chart 2

From the above result it became clear that the compounds (**6**, **8**, **9**, **10**, and **11**) possess considerable hypocholesterolemic activities, which suggested that the substitution by a phenyl, benzyl or a heteroaromatic group rather than an alkyl group at the 5 position might be essential to the activity. Among them, **6** was discarded because of the uncrystallizability in spite of its potent activity. The result, however, prompted us to the further syntheses of 5-substituted phenyl-1,2,4-oxadiazole derivatives (**12**—**21**) by the reaction of II with substituted benzoylchlorides (Table II). Although, among them, compounds (**13** and **14**) showed nearly equal activity to I, none of the compounds were found to exceed the activity of I.

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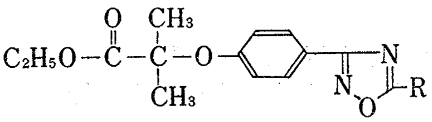
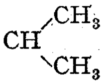
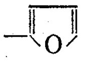
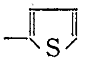
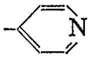
1) Part III: S. Yurugi, A. Miyake, T. Fushimi, E. Imamiya, H. Matsumura, and Y. Imai, *Chem. Pharm. Bull.* (Tokyo), 21, 1641 (1973).

2) *a,b*) Location: *Juso, Higashiyodogawa-ku, Osaka.*

TABLE I. 3-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]-5-substituted-1,2,4-oxadiazole (III)



III	R	Yield (%)	mp (°C)	Formula	Analysis % Calcd. C	H	N	Found C	H	N	Efficacy[a)] plasma total cholesterol A	B
1	H	60	oil	$C_{14}H_{16}O_4N_2$	60.86	5.84	10.14	60.90	6.03	10.28	+ ↑	−
2	CH_3	82	oil	$C_{15}H_{18}O_4N_2$	62.05	6.25	9.65	62.36	6.26	9.43	⧺ ↑	
3	 $CH(CH_3)_2$	89	oil	$C_{17}H_{22}O_4N_2$	64.13	6.97	8.80	64.37	6.91	9.08	+ ↓	+ ↓
4	$(CH_2)_6CH_3$	93	oil	$C_{21}H_{30}O_4N_2$	67.35	8.08	7.48	67.36	8.46	7.20	+ ↑	+ ↓
5	$(CH_2)_{14}CH_3$	73	35—37	$C_{29}H_{30}O_4N_2$	71.57	9.53	5.76	71.56	9.86	5.69	±	±
6	$CH_2C_6H_5$	90	oil	$C_{21}H_{22}O_4N_2$	68.83	6.05	7.65	68.71	6.22	7.61	⧻ ↓	+ ↓
7	CH_2- 	88	oil	$C_{21}H_{28}O_4N_2$	67.72	7.58	7.52	67.45	7.56	7.32	⧺ ↓	+ ↑
8	C_6H_5	61	43—45	$C_{20}H_{20}O_4N_2$	68.17	5.79	7.95	67.92	5.78	7.45	⧺ ↓	+ ↓
9		37	41—43	$C_{18}H_{18}O_5N_2$	63.71	5.50	12.38	64.13	5.19	12.20	⧺ ↓	+ ↓
10		86	89—91	$C_{18}H_{18}O_4N_2S$	60.33	5.06	7.82	60.41	5.23	7.54	⧺ ↓	+ ↓
11		50	131—133	$C_{19}H_{19}O_4N_3 \cdot (COOH)_2$	60.30	5.18	10.79	60.09	4.97	10.51	⧺ ↓	+ ↓

a) A: hypocholesterolemic activity in hypercholesterolemic rats
B: hypocholesterolemic activity in normocholesterolemic rats[1)]
A: (−)<10%, (+)10—30%, (++)30—50%, (+++)> 50%
B: (−)<5%, (+)5—15%, (++)15—30%, (+++)> 30%
↑: hypercholesterolemic activity
↓: hypocholesterolemic activity

Secondly, the modification of 1-methyl-1-ethoxycarbonylethyl moiety of I was carried out by the scheme shown in Chart 3. Base catalized condensation of *p*-cyanophenol (IV) with a variety of ethyl α-bromoacetate derivatives afforded V, which were reacted with hydroxylamine to give amidoxime (VI). The reaction of VI with nicotinoyl chloride in pyridine or in dioxane containing triethylamine yielded VII. Hypocholesterolemic activities of VII together with their analytical data are summarized in Table III. It has been shown by the Table III that compounds (**22**, **23**, and **25**) were inactive, while compound (**24**), which is substituted with normal octyl group, showed considerable hypocholesterolemic activity although less active than I. This result suggests that substitution with alkyl groups with greater than eight carbon atoms might be effective.

The third modification was carried out by replacing the 1,2,4-oxadiazole ring of I with 1,3,4-oxadiazole ring. Thus, employing the method of Huisgen,[3)] 4-(1-ethoxycarbonyl-1-methylethoxy)benzonitrile (VIII) was reacted with sodium azide to give a tetrazole derivative (IX), the reaction of which with nicotinoyl chloride afforded 2-[4-(1-ethoxycarbonyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,3,4-oxadiazole (X) in 43% yield. While Witiak, *et al.*[4)] reported that VIII showed no hypocholesterolemic activity, it was also found that niether the compound (IX nor X), which was derived from VIII, was active.

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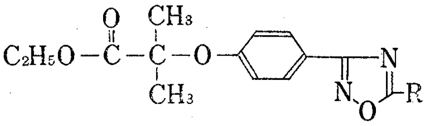
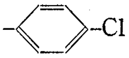
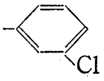
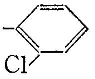
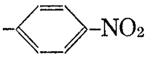
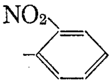
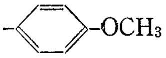
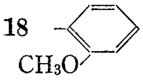
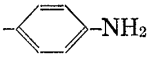
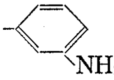
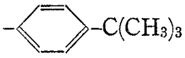
3) *a*) R. Huisgen, J. Sauer, and H.J. Sturm, *Angew. Chem.*, **70**, 272 (1958); *b*) J. Sauer, R. Huisgen, and H.J. Sturm, *Tetrahedron Letters*, **1960**, 241; *c*) R. Huisgen, J. Sauer, H.J. Sturm, and J.H. Morkigret, *Chem. Ber.*, **93**, 2106 (1960).
4) D.T. Witiak, J. Chun-Lun-Ho, and R.E. Hackney, *J. Med. Chem.*, **11**, 1086 (1968).

Although VIII, the key intermediate for the synthesis of I and its derivatives, had been prepared by the condensation of *p*-cyanophenol (IV) and ethyl α-bromoisobutylate, it was assumed that this method was unsuitable for a large scale synthesis because it required longer reaction time and ethyl α-bromoisobutylate is not readily available. Therefore, investigations on the improved alternative synthetic routes of I were subsequently undertaken.

TABLE II. 3-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]-5-substituted Phenyl-1,2,4-oxadiazole (III)



III	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Efficacy[a] plasma total cholesterol A	B
12		62	93—94	$C_{20}H_{19}O_4N_2Cl$	62.09	4.95	7.24	62.35	4.93	7.24	++↓	–
13		90	oil	$C_{20}H_{19}O_4N_2Cl$	62.09	4.95	7.24	62.39	4.89	6.95	+++↓	
14		69	oil	$C_{20}H_{19}O_4N_2Cl$	62.09	4.95	7.24	61.83	4.87	6.85	+++↓	+↓
15		74	91	$C_{20}H_{19}O_6N_3$	60.45	4.82	10.58	60.53	4.83	10.33	+↓	
16		74	112—114	$C_{20}H_{19}O_6N_3$	60.45	4.82	10.58	60.48	4.77	10.37	++↓	
17		63	83—85	$C_{21}H_{22}O_5N_2$	65.95	5.80	7.33	66.04	5.89	7.05	+↓	
18		70	79—80	$C_{21}H_{22}O_5N_2$	65.95	5.80	7.33	66.07	5.78	6.84	+↓	
19		92	109—111	$C_{20}H_{21}O_4N_3$	65.38	5.76	11.44	65.02	5.65	11.71	++↓	
20		54	oil	$C_{20}H_{21}O_4N_3$	65.38	5.76	11.44	65.41	5.91	11.03	–	
21		65	69—70	$C_{20}H_{28}O_4N_2$	70.56	6.91	6.86	70.67	6.79	6.42	++↓	

a) See footnote for Table I.

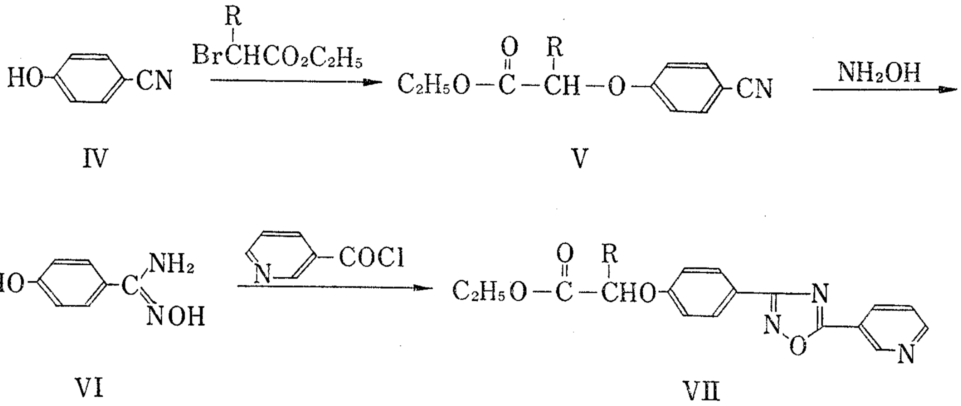
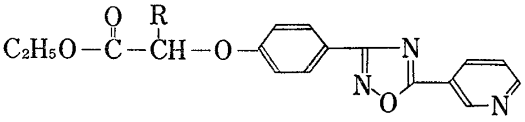


Chart 3

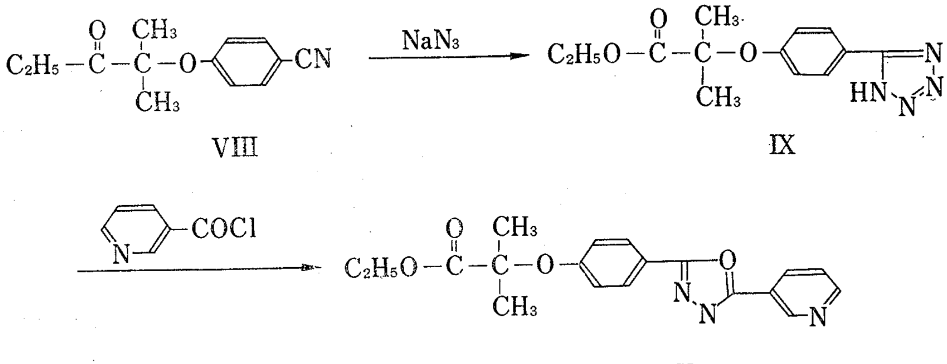
Employing the method of Bargellini[5a)] and Julia[5b)] *p*-(1-carboxy-1-methylethoxy)-benzonitrile (XI) was prepared by the reaction of IV with acetone and chloroform in the presence of sodium hydroxide. The chlorination of IX followed by the reaction with ethanol gave VIII which, after being led to amidoxime (II), was reacted with nicotinoyl chloride to give I in a total yieldof 34% (Method A).

TABLE III. 3-[4-(Ethoxycarbonyl-1-substituted methoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (VIII)



VIII	R	Yield (%)	mp (°C)	Formula	Analysis (%) Cacld. C	H	N	Found C	H	N	Efficacy[a)] plasma total cholesterol A	B
22	CH_3	40	103—105	$C_{18}H_{17}O_4N_3$	63.71	5.50	12.38	64.13	5.19	12.30	+ ↑	
23	$CH_3(CH_2)_3$	70	oil	$C_{21}H_{23}O_4N_3$	65.12	6.08	11.02	65.74	6.20	10.85	±	
24	$CH_3(CH_2)_7$	43	oil	$C_{25}H_{31}O_4N_3$	68.63	7.14	9.61	68.30	7.01	9.30	⧺ ↓	+ ↓
25		24	105—107	$C_{23}H_{25}O_4N_3$	67.79	6.18	10.31	67.46	6.08	10.42	—	
26	C_6H_5	67	89—91	$C_{23}H_{19}O_4N_3$	68.81	4.77	10.47	68.47	4.65	10.18	⧻ ↑	

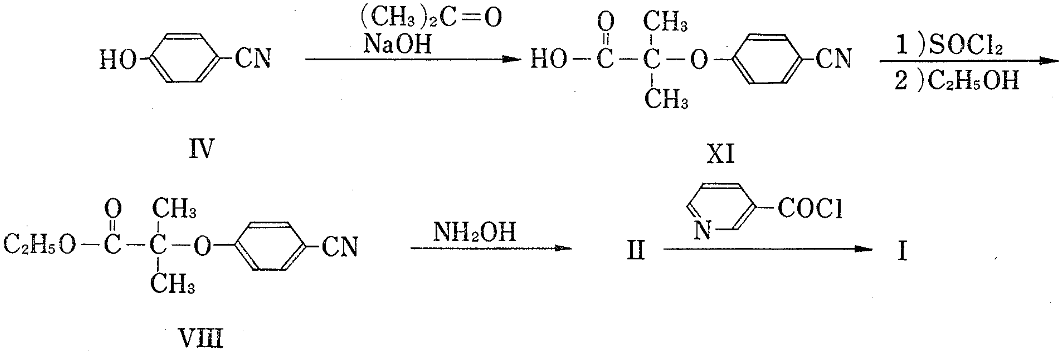
a) See footnote for Table I.



VIII IX X

Chart 4

Method A



IV XI VIII

Chart 5

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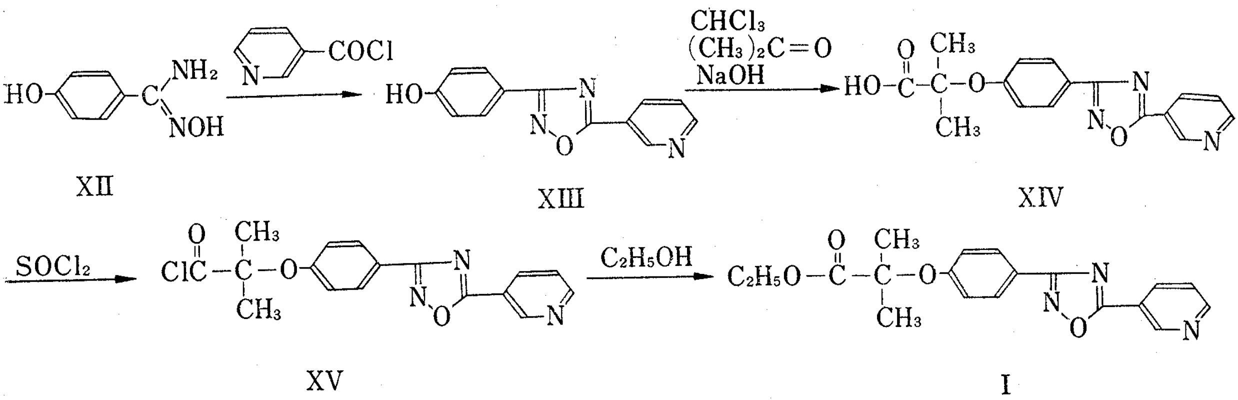
5) *a*) G. Bargellini, *Gazz. Chim. Ital.*, **36**, 334 (1906); *b*) P.M. Julia, *Bull. Soc. Chim. France*, **1956**, 776.

This method, however, was found to have a drawback that the obtained compound (I) was inevitable from the contamination with the intermediates of the procedure due to the difficulty in the purification of VIII. Accordingly, an attempt was made to introduce the 1-ethoxycarbonyl-1-methylethoxy group at the final stage of the procedure (Method B). Thus, *p*-hydroxybenzamidoxime (XII), obtained in an excellent yield from IV, were reacted with nicotinoyl chloride to afford XIII, which was reacted with acetone and chloroform in the presence of sodium hydroxide to yield 3-[4-(1-carboxy-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (XIV). XIV was successfully led to I by way of the acyl chloride (XV). In this method intermediates XII, XIII, XIV and XV were obtained all in crystalline form, facilitating the purification at each stage.

Method B

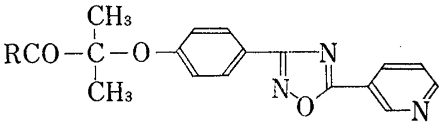


XII XIII XIV

XV I

Chart 6

TABLE IV. 3-[4-(1-Substituted carbonyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole



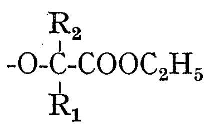
No.	R	Yield (%)	mp (°C)	Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Efficacy[a] plasma total cholesrteol A	B
27	C_4H_9O	51	82—84	$C_{21}H_{23}O_4N_3$	66.12	6.08	11.02	66.01	5.88	10.84	++ ↓	
28	$C_6H_5CH_2O$	23	72—73	$C_{24}H_{21}O_4N_3$	69.38	5.10	10.12	69.41	4.78	9.62	++ ↓	
29	NH_2	46	174—175	$C_{17}H_{16}O_3N_4$	62.95	4.97	17.28	62.83	4.74	17.40	+++ ↓	+ ↓
30	$HO(CH_2)_2NH$	66	131	$C_{19}H_{20}O_4N_4$	61.94	5.47	15.21	62.16	5.36	15.51	+++ ↓	—

a) See footnote for Table I.

Several ester and amide derivatives of I could also be obtained by the reactions of XV with a variety of alcohols and amines, which are listed in Table IV.

Finally, the clarified structure-activity relationships in the hypocholesterolemic activities of the 1,2,4-oxadiazole derivatives are summarized:

1) The partial structure that is important to the activity is (1-ethoxycarbonyl-1-methylethoxy)phenyl moiety just in the case of clofibrate.[6]



2) As for the substituents, R_1 and R_2, in the $-O-\overset{R_2}{\underset{R_1}{C}}-COOC_2H_5$ group, the compound

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[6] J.M. Throp and W.S. Waring, *Nature*, **194**, 948 (1962).

(R_1=R_2=CH_3) was the most active. When R_1 was H, only the compound with R_2=C_8H_{17} was considerably active, while compounds with smaller R_2 groups such as cyclohexyl, *n*-C_4H_9, or CH_3 showed virtually no activity.

3) Among the varieties of the substituents at 5-position of the 1,2,4-oxadiazole ring, aromatic, heteroaromatic and aralkyl group were effective, while alkyl groups were inactive. In particular, the compounds substituted with *m*-chloro or *o*-chlorophenyl group showed nearly equal activity to 3-[4-(1-ethoxycarbonyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (I).

Experimental

General Procedures for the Synthesis of 3-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]-5-substituted-1,2,4-oxadiazole (III) (Table I)——i) To a solution of 4-(1-ethoxycarbonyl-1-methylethoxy)benzamidoxime (II)[1)] (0.01 mole) in pyridine (5 ml) was added 0.015 mole of an acyl chloride. After the initial exothermic reaction ceased, the reaction mixture was refluxed for 2 to 4 hr, and the solvent was evaporated *in vacuo*. The residue was poured into ice-water whereby the products separated as an oily substance, which was extracted with $CHCl_3$ or AcOEt. The extract was washed with 10% NaOH and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel, eluted with C_6H_6–acetone (4: 1) to afford III.

ii) The mixture of II (0.01 mole) and an acid anhydride (5 ml) was heated at 100—130° for 5 to 6 hr. After cooling, the reaction mixture was poured into ice-water. The aqueous layer was made alkaline with 10% NaOH. The separated oily material was extracted with AcOEt. The extract was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue purified by column chromatography on silica gel, eluted with C_6H_6 or C_6H_6–acetone (9: 1), to afford III.

3-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]-5-substituted Phenyl-1,2,4-oxadiazoles (III) (Table II)——General Procedure: To a solution of II (0.01 mole) in pyridine (5 ml) was added substituted benzoyl chloride (0.015 mole). After the initial exothermic reaction ceased, the reaction mixture was refluxed for 3 to 5 hr, and evaporated *in vacuo*. The residue was poured into ice-water whereby the product separated as an oily substance, which was extracted with $CHCl_3$ or AcOEt. The extract was washed with 10% NaOH and H_2O, dried over anhydrous Na_2SO_4 and evaporated to dryness to give III, which was recrystallized from MeOH in the case that the residue was a solid or purified by column chromatography on silica gel before recrystallization in the case that it was a syrup.

4-(1-Ethoxycarbonyl-1-substituted methoxy)benzonitriles (V)——General Procedure: To a mixture of *p*-cyanophenol[7)] (0.1 mole) and NaOEt, prepared from 0.12 mole of Na in 150 ml of EtOH, was added an alkyl halide (0.2 mole). The reaction mixture was refluxed for 5 to 24 hr. EtOH was removed *in vacuo* and the residue was poured into water and extracted with ether. The extract was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to give the crude V which was used for the subsequent step without further purification.

4-(1-Ethoxycarbonyl-1-substituted methoxy)benzamidoximes (VI) (Table V)——General Procedure: To a solution of $NH_2OH \cdot HCl$ (0.075 mole) and Na_2CO_3 (0.038 mole) in H_2O (15 ml) was added the solution of V (0.05 mole) in EtOH (90 ml). The reaction mixture was refluxed for 2 to 5 hr. EtOH was removed *in vacuo* and the residue was poured into H_2O (50 ml) and extracted with AcOEt. The extract was washed with 10% HCl (50 ml). The aqueous layer was adjusted to pH 9 with 20% NaOH and the separated oily substance was extracted with AcOEt. The extract was washed with H_2O and evaporated *in vacuo*. The residue was recrystallized from C_6H_6 or a mixture of C_6H_6 and petroleum ether to give VI.

3-[4-(1-Ethoxycarbonyl-1-substituted methoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazoles (VII)——General Procedure: i) To a solution of VI (0.01 mole) in pyridine (5 ml) was added nicotinoyl chloride hydrochloride (0.015 mole). After the initial exothermic reaction ceased, the reaction mixture was refluxed for 3 to 5 hr and evaporated *in vacuo*. The residue was poured into ice-water whereby the products was separated as an oily substance, which was extracted with AcOEt. The extract was washed with H_2O, and dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (9: 1) to afford VII.

ii) To a solution of VI (0.01 mole) in the mixture of Et_3N (2 ml) and dioxane (10 ml) was added nicotinoyl chloride hydrochloride (0.015 mole) at 90—100° with stirring. The reaction mixture was heated at 120—130° for 5 hr. After cooling, $Et_3N \cdot HCl$ was filtered off and the filtrate was evaporated to dryness. The residue was purified by column chromatography on silica gel eluted with C_6H_6–acetone (9: 1) to give VII.

5-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]tetrazole (IX)——A stirred mixture of DMF (8 ml),

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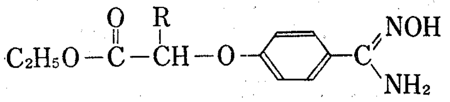
7) *a*) J.N. Ashley, H.J. Burber, A.J. Ewins, G. Newberg, and A.D.H. Shelf, *J. Chem. Soc.*, **1942**, 103; *b*) A. Findly and C.S. Tang, *Can. J. Chem.*, 45, 1014 (1967).

Table V. 4-(1-Ethoxycarbonyl-1-substituted methoxy)benzamidoxime (VI)



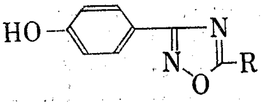
VI	R	Yield (%)	mp (°C)	Formula	Analysis %					
					Calcd.			Found		
					C	H	N	C	H	N
a	CH_3	43	oil	$C_{12}H_{16}O_4N_2$	57.01	6.07	11.08	57.13	6.39	11.11
b	$CH_3(CH_2)_3$	66	62—64	$C_{15}H_{22}O_4N_2$	61.20	7.53	9.52	61.49	7.55	9.44
c	$CH_3(CH_2)_7$	68	75—76	$C_{19}H_{30}O_4N_2$	65.25	8.40	7.69	65.11	5.63	7.99
d		70	109—110	$C_{17}H_{24}O_4N_2$	64.68	5.45	8.78	64.95	5.77	8.91
e	C_6H_5	42	133—134	$C_{17}H_{18}O_4N_2$	63.58	7.88	8.66	63.73	7.55	8.74

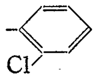
4-(1-ethoxycarbonyl-1-methylethoxy)benzonitrile (VIII)[4] (2.4 g), NaN_3 (0.79 g), NH_4Cl (0.59 g) and LiCl (0.01 g) was heated at 125° for 9 hr. After cooling to room temperature, the solution was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in H_2O (14 ml), and the solution was adjusted to pH 4 with 10% HCl. The crystals were collected by filtration and dried to give 2.7 g (95%) of IX, mp 80—83°. Recrystallization from aqueous MeOH gave colorless needles, mp 83—85°. *Anal.* Calcd. for $C_{13}H_{16}O_3N_4$: C, 56.51; H, 5.84; N, 20.89. Found: C, 56.56; H, 5.84; N, 19.87.

2-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,3,4-oxadiazole (X)——To a solution of IX (1.0 g) in pyridine (10 ml) was added nicotinoyl chloride hydrochloride (1.3 g). The reaction mixture was heated at 90° for 1 hr, during which time the solution turned dark brown with the evolution of N_2 gas. After removal of pyridine *in vacuo* the residue was poured into H_2O (50 ml) and the resulting precipitate was collected by filtration, (0.7 g, 55%). Recrystallization from MeOH gave 0.55 g (43%) of X, mp 123—125°. *Anal.* Calcd. for $C_{19}H_{19}O_4N_3$: C, 64.59; H, 5.42; N, 11.89. Found: C, 64.31; H, 5.39; N, 11.92.

3-(4-Hydroxyphenyl)-5-(3-pyridyl)-1,2,4-oxadiazole (XIII)——To a solution of 4-hydroxybenzamidoxime (XII)[8] (4.5 g) in pyridine (50 ml) was added nicotinoyl chloride hydrochloride (6.0 g). The reaction mixture was refluxed for 3 hr. After removal of pyridine *in vacuo*, the residue was poured into ice-water. The separated solid was collected by filtration to give 6.0 g (85%) of XIII. The recrystallization from MeOH afforded pale yellow needles. *Anal.* Calcd. for $C_{13}H_9O_2N_3$: C, 65.25; H, 3.79; N, 17.57. Found: C, 65.08; H, 3.64; N, 17.28. The derivatives of XIII which were prepared by the same procedure with XIII are listed in Table VI.

Table VI. 3-(4-Hydroxyphenyl)-5-substituted -1,2,4-oxadiazole (XIII)



XIII	R	Yield (%)	mp (°C)	Formula	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
a	CH_3	76	114—116	$C_9H_8O_2N_2$	61.36	4.58	15.10	61.37	4.49	15.57
b	C_6H_5	60	140—141	$C_{14}H_{10}O_2N_2$	70.58	4.23	11.76	70.51	4.20	11.53
c	$CH_2C_6H_5$	42	129—131	$C_{15}H_{12}O_2N_2$	71.41	4.80	11.11	71.07	4.85	11.15
d		37	130—132	$C_{14}H_9O_2N_2Cl$	61.66	3.33	10.28	61.60	2.94	10.50

3-[4-(1-Carboxyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (XIV)——Procedure: i) A solution of XIII (2.3 g) in acetone (20 ml) was heated to gentle reflux with stirring in the presence of 2.0 g

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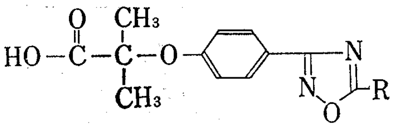
[8] W. Krone, *Chem. Ber.*, **24**, 834 (1891).

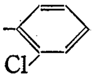
of NaOH pellet, while 1.3 g of $CHCl_3$ was added dropwise. After the addition was completed (0.5 hr), the solution was further refluxed with stirring for 2 hr. After removal of the solvent *in vacuo* the residue was dissolved in water and acidified with AcOH. The resulting precipitate was collected by filtration and dissolved in aqueous $NaHCO_3$.

By filtrating the insoluble substance, 1.5 g (65%) of XIII was recovered. The filtrate was acidified with AcOH and the separated precipitate was collected by filtration to give crude XIV. Recrystallization from MeOH gave 0.5 g of colorless needles, mp 198—199° (decomp.). *Anal.* Calcd. for $C_{17}H_{15}O_4N_2$: C, 62.72; H, 4.65; N, 12.92. Found: C, 62.54; H, 4.38; N, 12.95.

ii) Hydrolysis of 3-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (I): The solution of 1 g of I in EtOH (50 ml) and 10% aqueous NaOH (10 ml) was refluxed for 2 hr and poured into H_2O (300 ml). The solution was made acidic with AcOH and resulting precipitate was collected by filtration to give 0.8 g (84%) of crude XIV. Recrystallization from MeOH gave 0.7 g of colorless needles, mp 198—199° (decomp.), which showed complete identity with an authentic sample of XIV obtained in the procedure i) in the mixed melting point and IR spectrum. Compounds (XIV) which were prepared using the procedure i) are listed in Table VII.

TABLE VII. 3-[4-(1-Carboxy-1-methylethoxy)phenyl]-5-substituted-1,2,4-oxadiazole (XIV)

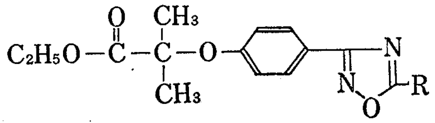


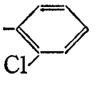
XIV	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	CH_3	58	130—132	$C_{13}H_{14}O_4N_2$	59.53	5.38	10.68	59.29	5.28	10.78
b	C_6H_5	30	140—142	$C_{18}H_{16}O_4N_2$	66.66	4.97	8.64	67.73	4.91	8.72
c	$CH_2C_6H_5$	93	oil	$C_{19}H_{18}O_4N_2$	67.44	5.36	8.28	67.69	5.43	7.79
d		76	oil	$C_{18}H_{15}O_4N_2Cl$	60.26	4.22	7.82	60.36	4.16	7.51

3-[4-(1-Chloroformyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (XV)——A mixture of XIV (14.7 g) and $SOCl_2$ (30 ml) was refluxed for 3 hr. The excess $SOCl_2$ was removed by evaporation to give crude XV, mp 165°, which was used for the subsequent reaction without purification, being susceptible of decomposition in the atmosphere.

3-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (I)——A solution of XV (3.0 g) and EtOH (20 ml) was refluxed for 3 hr and evaporated *in vacuo*. The residue was dissolved in H_2O and the solution was made alkaline with $NaHCO_3$. The separated substance was extracted with AcOEt. Dried over anhydrous Na_2SO_4, the extract was evaporated and the residue was recrystallized from MeOH

TABLE VIII. 3-[4-(Ethoxycarbonyl-1-methylethoxy)phenyl]-5-substituted-1,2,4-oxadiazole (III)



III	R	Yield (%)
2	CH_3	91
6	$CH_2C_6H_5$	93
8	C_6H_5	83
14		93

to give 2.7 g (91%) of I, mp 75—77°, which showed complete identity with an authentic sample in the mixed melting point and IR spectrum. The derivatives (III) which were prepared by the same procedure are listed in Table VIII.

3-[4-(1-Butoxycarbonyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (27)——A solution of XV (3.0 g) and BuOH (10 ml) was heated at 130—140° for 3 hr. After evaporation of BuOH *in vacuo*, to the residue was added 10% aqueous $NaHCO_3$ (10 ml). The resulting crystals were filtrated and recrystallized from EtOH to give 1.7 g (51%) of **27**.

3-[4-(Benzyloxycarbonyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (28)——A solution of XV (2.0 g) and benzylalcohol (10 g) was heated at 130—140° for 3 hr. After evaporation of benzylalcohol *in vacuo*, 10% aqueous $NaHCO_3$ (10 ml) was to the residue. The separated substance was extracted with AcOEt. The extract was evaporated and the residue was submitted to column chromatography on silica gel, eluted with C_6H_6–acetone (9: 1) to give 0.55 g (23%) of **28**.

3-[4-(1-Carbamoyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (29)——Ammonia was bubbled through the solution of XV (3.0 g) and $CHCl_3$ (200 ml) for 0.5 hr at room temperature. After evaporation of $CHCl_3$ *in vacuo*, H_2O was added to the residue. The separated substance was collected by filtration and recrystallized from EtOH to give **29**, 1.3 g (46%).

3-[4-(2-Hydroxyethylcarbamoyl-1-methylethoxy)phenyl]-5-(3-pyridyl)-1,2,4-oxadiazole (30)——To a solution of XV (1.5 g) in $CHCl_3$ (50 ml) ethanolamine (2.0 g) was added dropwise. The reaction mixture was refluxed for 1 hr and evaporated *in vacuo*. H_2O was added to the residue and the separated substance was collected by filtration and recrystallized from EtOH to give 1.0 g (66%) of **30**.

Hypocholesterolemic Activity——The biological tests for the hypocholesterolemic activity were carried out according to the method described in the preceding paper.[1]

Acknowledgement The authors express their deep gratitude to Dr. S. Tatsuoka, Director of this Division, for his encouragement and permission for publication of this work. Thanks are also due to the members who undertook the elemental analysis and NMR measurements.