[Chem. Pharm. Bull.
36(5)1685—1691(1988)]

Studies on the Chemical Transformations of Rotenoids. IV.[1] Synthesis of Novel Benzofuro[2,3-*d*]pyridazines Fused with Tetrazole, 1,2,4-Triazole and 1,2,4-Triazine

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(Received October 7, 1987)

Benzofuro[2,3-*d*]pyridazin-4(3*H*)-one (**1**) was converted into 4-chloro-(**3**) and 4-ethoxy-benzofuro[2,3-*d*]pyridazine (**4**). Reaction of **1** with phosphorus pentasulfide provided benzofuro-[2,3-*d*]pyridazine-4-thione (**2**), which underwent S-methylation to give the 4-thiomethyl derivative (**5**). Hydrazinolysis of **2** or **3** proceeded efficiently to give the corresponding 4-hydrazino compound (**6**). Compound **6** was cyclized with nitrous acid to afford benzofuro[2,3-*d*]tetrazolo[1,5-*b*]-pyridazine (**7**), which was alternatively prepared from **3** or **4** with sodium azide.

3-Substituted benzofuro[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazines (**8**—**12**) were prepared by cyclization of **6**. Refluxing **6** with ethyl pyruvate in ethanol followed by cyclization in acetic acid provided a novel 4*H*-benzofuro[2′,3′: 4,5]pyridazino[3,2-*c*][1,2,4]triazin-4-one (**14**).

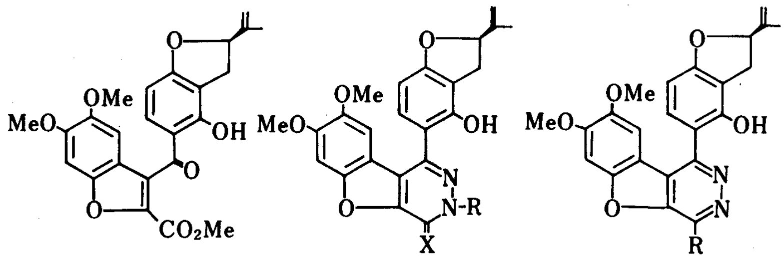
Keywords——rotenoid; methyl rotenononate; transformation; hydrazinobenzofuropyridazine; benzofurotetrazolopyridazine; benzofuro[1,2,4]triazolopyridazine; benzofuropyridazino[1,2,4]-triazine

(−)-(6a*S*,12a*S*,2*R*)-Rotenone, derived from derris roots, has been used as an agricultural insecticide and fish toxicant, and is an attractive heterocyclic ring system for stereochemical and synthetic investigations. In a previous paper,[1] we reported some ring transformations of methyl rotenononate, obtained by alkaline degradation of rotenonone, into furo[2,3-*g*]benzoxazole and 3-substituted benzofuro[2,3-*d*]pyridazin-4(3*H*)-ones (**1**; R = H, CH_3, CH_2CH_2OH, C_6H_5 and $C_6H_4CH_3$-*p*).

As a continuation of our programs directed towards the chemical transformations of rotenoids and evaluation of pharmacological activities, we will describe in this paper the preparations of novel benzofuro[2,3-*d*]pyridazines fused with tetrazole, 1,2,4-triazole and 1,2,4-triazine (**7**—**12** and **14**) starting from 4-hydrazino-benzofuro[2,3-*d*]pyridazine (**6**), since tetrazolo[1,5-*b*]pyridazines[2] and [1,2,4]triazolo[4,3-*b*]pyridazines[3] are known to possess interesting pharmacological activities.

Heterocyclic hydrazines are excellent intermediates for the preparations of fused heterocyles with tetrazole, triazole and triazine nuclei. Therefore, we began with the preparation of 1-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-hydrazino-7,8-dimethoxy-benzofuro[2,3-*d*]pyridazine (**6**) according to Chart 1.

Heating of **1** with phosphorus oxychloride under reflux for 0.5 h followed by treatment with boiling dioxane–potassium hydroxide provided 1-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-chloro-7,8-dimethoxy-benzofuro[2,3-*d*]pyridazine (**3**) in 53% yield. The 4-ethoxy compound (**4**) was isolated in 69% yield when the reaction product was



methyl rotenononate

1 : R=H, X=O
2 : R=H, X=S

3 : R=Cl
4 : R=OEt
5 : R=SMe
6 : $R=NHNH_2$

Chart 1

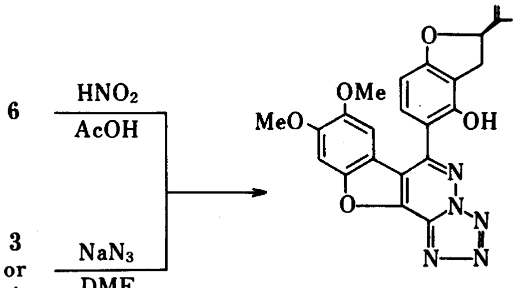


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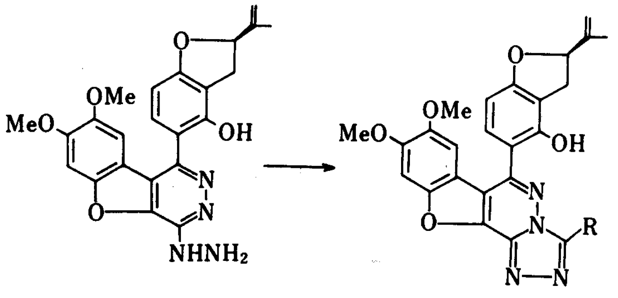
Chart 2



6

8 : R=H
9 : R=Me
10 : $R=CH=CH_2$
11 : $R=NH_2$
12 : R=Ph

Chart 3

worked up with ethanolic potassium hydroxide instead of dioxane–potassium hydroxide. Similar work-up with sodium ethoxide in ethanol provided compound **4** quantitatively. On the other hand, reaction of **1** with phosphorus pentasulfide in pyridine gave 1-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-3,4-dihydro-3*H*-benzofuro[2,3-*d*]pyridazine-4-thione (**2**) in 73% yield. The proposed thione structure for **2** was supported by the infrared (IR) spectrum which showed absorption bands at 3430 (OH), 3250 (NH) and 1260 (C=S) cm^{-1}. Compound **2** readily underwent methylation with methyl iodide to afford the 4-methylthio compound (**5**). The proton nuclear magnetic resonance (^1H-NMR) spectrum showed a methyl signal at δ 2.87 ppm, confirming the thiomethyl structure, not the N-methyl structure.

Compounds **3**, **4** and **5** were then subjected to hydrazinolysis. However, only the chloro compound (**3**) underwent hydrazinolysis to give the expected hydrazino intermediate **6** in 65% yield when **3** was heated with hydrazine hydrate in ethanol. Elementary analysis and spectral data were in agreement with the structure **6**. In contrast, hydrazinolysis of the pyridazinethione (**2**) was found to proceed easily to give **6** in 76% yield. Treatment of **6** with nitrous acid under cooling gave 6-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-benzofuro[2,3-*d*]tetrazolo[1,5-*b*]pyridazine (**7**) in 70% yield. Compound **7** was confirmed to be the tetrazole form as indicated in Chart 2, because the IR spectrum (recorded in KBr disk) showed no characteristic azide stretching at about 2150 cm^{-1}. Compound **7** was also obtained through alternative routes which involved condensations of **3** or **4** with sodium azide in boiling dimethyl formamide. However, the former method is superior to the latter in terms of yields and reaction conditions.

TABLE I. 3-Substituted 6-(2*R*-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-benzofuro[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazines (**8**—**12**)

Compd.	Reagent/solvent	Reaction conditions	Yield (%)
8	$CH(OEt)_3$	Reflux/1 h	78 (from **6**)
	$CH(OEt)_3$, 35% HCl	r.t./20 h	79 (from **6**)
	HCOOH	Reflux/1 h	52 (from **6**)
9	AcOH	Reflux/0.5 h	59 (from **6**)
	$NH_2NHCOCH_3$/BuOH	Reflux/28 h	84 (from **4**)
10	1) $CH_2=CHCOCl$/THF	1) r.t./1 h	
	2) Na_2CO_3/2-butanone	2) Reflux/18 h	63 (from **6**)
11	BrCN/75% MeOH	r.t./12 h	50 (from **6**)
	$NH_2NHCSNH_2$/BuOH	Reflux/6 h	37 (from **4**)
12	$NH_2NHCOC_6H_5$/BuOH	Reflux/14 h	85 (from **4**)

r.t. = room temperature.

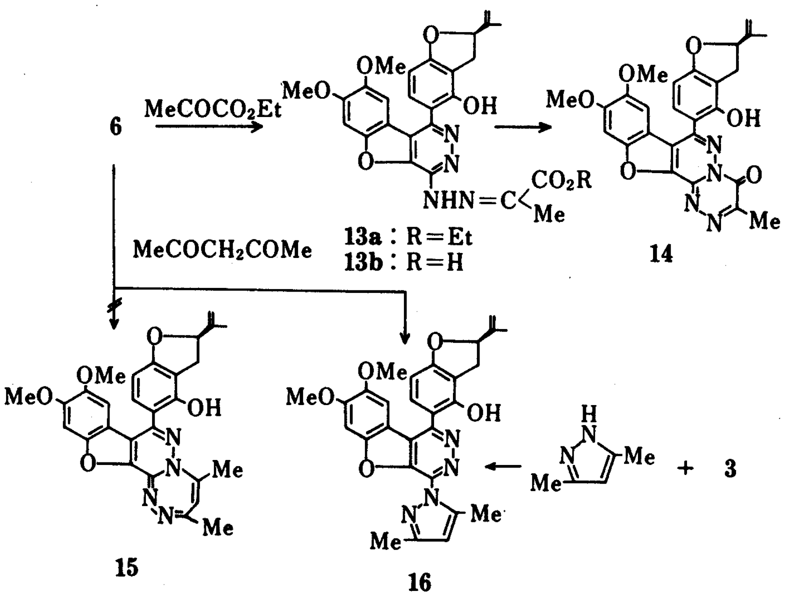


Chart 4

Conversions of the hydrazino compound (**6**) into 3-substituted 6-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-benzofuro[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazines (**8**—**12**) were accomplished efficiently by employing the appropriate reagents, as shown in Chart 3 and Table I. When **6** was treated with triethyl orthoformate either under reflux or at room temperature in the presence of concentrated hydrochloric acid, benzofuro-[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyridazine (**8**) was obtained; it could be alternatively prepared by heating **6** with formic acid. The ^{1}H-NMR spectrum exhibited a new signal at δ9.18 ppm corresponding to the triazole proton. Similarly, other 3-substituted benzofuro[2,3-*d*][1,2,4]-triazolo[4,3-*b*]pyridazines (**9**—**11**) were prepared by condensations of **6** with the corresponding reagents indicated in Table I. On the other hand, compounds **9**, **11** and **12** were formed when **4** was condensed with hydrazine derivatives. All the new compounds (**8**—**12**) gave elementary analyses (Table II) and spectral data (Table III) consistent with the assigned structures.

The synthesis of benzofuro[2′,3′:4,5]pyridazino[3,2-*c*][1,2,4]triazin-4-one (**14**), a novel heterocyclic ring system, was accomplished by condensation of **6** with ethyl pyruvate followed by ring closure of the carboxyethylidenehydrazino compound (**13b**) as illustrated in Chart 4.

Heating of **6** with ethyl pyruvate in ethanol for 2 h provided 1-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-[*N*′-(1-ethoxycarbonylethylidene)hydrazino]-7,8-dimethoxy-benzofuro[2,3-*d*]pyridazine (**13a**) in 78% yield. Compound **13a** readily underwent hydrolysis to give 4-[*N*′-(1-carboxyethylidene)hydrazino]-7,8-dimethoxy-benzofuro[2,3-*d*]-pyridazine (**13b**), which was subsequently cyclized to 3-methyl-7-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-9,10-dimethoxy-4*H*-benzofuro[2′,3′-4,5]pyridazino-[3,2-*c*][1,2,4]triazin-4-one (**14**) in 56% yield. The structure was confirmed by elementary analysis and spectral data. On the other hand, prolonged heating of **6** with ethyl pyruvate resulted in direct ring closure to yield compound **14** in 60% yield. A report by El-Kashef and co-workers[4] described the synthesis of [1]benzothieno[2′,3′: 5,6]pyrrolo[1′,2′: 1,2]pyrazino-[3,4-*c*][1,2,4]triazepine by condensation of hydrazino-[1]benzothieno[2,3-*e*]pyrrolo[1,2-*a*]-pyrazine with 2,4-pentanedione. We have prepared the triazepine derivative (**15**) according to the procedure described by these authors. Compound **6** was heated with 2,4-pentanedione for 2 h to afford 64% yeild of colorless needles as a single product. The ^{1}H-NMR spectrum displayed a new signal at δ 6.19 ppm, which was in agreement with the value (δ 6.16 ppm) assigned to the proton of 1,2,4-triazepine by these authors. However, it is well-known[5] that 2,4-pentanedione reacts with hydrazine to give 3,5-dimethylpyrazole. In order to establish the structure of the obtained product, 4-chloro-benzofuro[2,3-*d*]pyridazine (**3**) was reacted with 3,5-dimethylpyrazole in the presence of sodium amide to afford 1-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)-7,8-dimethoxy-benzofuro[2,3-*d*]pyridazine (**16**) in 82% yield. Spectral examination revealed that compound **16** was identical with the compound obtained by reaction of **6** with 2,4-pentanedione. Therefore, it is evident that the compound obtained by El-Kashef and co-workers is the pyrazine substituted with pyrazole rather than pyrazine fused with triazepine.

Pharmacological investigations on the obtained products are in progress.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The electron impact-mass spectra (EI-MS) were measured with a JEOL JMS DX-300 mass spectrometer and IR spectra with a JASCO IRA-2 spectrometer. The ^{1}H-NMR spectra were recorded with a JEOL JNM-MH-100 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used; s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Column chromatography was carried out on Silica gel BW-200 (Fuji Davison Chem. Co., Ltd.).

1-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-3*H*-benzofuro[2,3-*d*]pyridazine-4-thione (2)——A solution of **1** (1 g) and P_2S_5 (1.4 g) in pyridine (10 ml) was refluxed for 16 h and evaporated to dryness. The residual oil was mixed with H_2O to give a white solid, which was chromatographed on silica gel. Elution with $CHCl_3$ gave a yellow solid. Recrystallization from EtOH gave a yellow crystalline powder, mp 255—256°C. Yield 0.76 g (73%). $[\alpha]_D^{25}$ $-27.4°$ ($c=0.2$, $CHCl_3$). IR (KBr): 3430 (OH), 3250 (NH), 1260 (C=S) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.98 (1H, br s, OH), 12.69 (1H, br s, NH). MS *m*/*z*: 436 (M^+). *Anal.* Calcd for $C_{23}H_{20}N_2O_5S$: C, 63.29; H, 4.62; N, 6.42. Found: C, 63.03; H, 4.64; N, 6.54.

1-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-chloro-7,8-dimethoxy-benzofuro[2,3-*d*]-pyridazine (3)——A suspension of **1** (0.2 g) and $POCl_3$ (2 ml) was refluxed for 0.5 h, and then excess $POCl_3$ was evaporated off. The residue was dissolved in dioxane (10 ml), and 20% KOH (4 ml) was added dropwise to the dioxane solution under reflux with stirring. After 1 h, the mixture was shaken with a mixture of $CHCl_3$ and H_2O. The chloroform layer was separated and evaporated to dryness to give a yellow solid. Recrystallization from EtOH gave yellow prisms, mp 165—166 °C. Yield 0.11 g (53%). IR (KBr): 3430 (OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 11.88 (1H, s, OH). MS *m*/*z*: 438 (M^+), 440 ($M^+ +2$). *Anal.* Calcd for $C_{23}H_{19}ClN_2O_5$: C, 62.95; H, 4.36; N, 6.38. Found: C, 63.06; H, 4.28; N, 6.11.

1-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-ethoxy-7,8-dimethoxy-benzofuro[2,3-*d*]-pyridazine (4)——a) A suspension of **1** (0.3 g) and $POCl_3$ (2 ml) was refluxed for 0.5 h and evaporated to dryness. The residue was dissolved in EtOH (10 ml)–20% KOH (5 ml) and refluxed for 2 h. The mixture was evaporated and shaken with a mixture of EtOAc and H_2O. The organic layer was evaporated to give a white solid. Recrystallization from EtOH gave colorless needles, mp 174—175 °C. Yield. 0.22 g (69%). IR (KBr): 3430 (OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, t, $OCH_2C\underline{H}_3$), 4.80 (2H, q, $OC\underline{H}_2CH_3$). MS *m*/*z*: 448 (M^+). *Anal.* Calcd for $C_{25}H_{24}N_2O_6$: C, 66.95; H, 5.39;

N, 6.25. Found: C, 66.71; H, 5.18; N, 6.46.

b) A solution of **3** (0.1 g), Na (0.02 g) and absolute ethanol (4 ml) was refluxed for 1 h and evaporated to dryness. The residue was taken up in H_2O, and the mixture was neutralized with 10% HCl and extracted with $CHCl_3$. Removal of $CHCl_3$ gave a solid. Recrystallization from EtOH gave colorless needles, mp 174—175 °C. Yield 0.1 g (99%). Analytical and spectral data were identical with those of **4** prepared by method a).

1-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-methylthio-7,8-dimethoxy-benzofuro[2,3-*d*]-pyridazine (5)——A mixture of **2** (0.3 g), CH_3I (0.1 g), powdered KOH (0.075 g) in EtOH (5 ml) was refluxed for 1 h and evaporated to dryness. The residue was dissolved in H_2O, neutralized with 5% HCl and extracted with $CHCl_3$. Removal of $CHCl_3$ gave a solid. Recrystallization from EtOH gave colorless needles, mp 190—191 °C. Yield 0.176 g (57%). IR (KBr): 3440 (NH) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.87 (3H, s, SCH_3), 12.08 (1H, br s, OH). MS *m/z*: 450 (M^+). *Anal.* Calcd for $C_{24}H_{22}N_2O_5S$: C, 63.99; H, 4.92; N, 6.22. Found: C, 64.03, H, 4.91; N, 6.22.

1-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-hydrazino-7,8-dimethoxy-benzofuro[2,3-*d*]-pyridazine (6)——a) A solution of **3** (0.2 g) and $NH_2NH_2 \cdot H_2O$ (0.5 ml) in EtOH (4 ml) was refluxed for 2 h and allowed to stand to precipitate a yellow crystalline powder. Recrystallization from EtOH gave yellow needles, mp 184—185 °C. Yield 0.128 g (65%). IR (KBr): 3430 (OH) cm^{-1}. ^1H-NMR (pyridine-d_5) δ: 5.64 (3H, br s, $NHNH_2$). MS *m/z*: 434 (M^+). *Anal.* Calcd for $C_{23}H_{22}N_4O_5$: C, 63.59; H, 5.10; N, 12.90. Found: C, 63.85; H, 5.23; N, 12.67.

b) A solution of **2** (0.2 g) and $NH_2NH_2 \cdot H_2O$ (1 ml) in pyridine (2 ml) was refluxed for 2 h and evaporated to dryness. The residue was taken up in H_2O, and the precipitates were collected. Recrystallization from EtOH gave yellow needles, mp 184—185 °C. Yield 0.151 g (76%). Analytical and spectral data were identical with those of **6** prepared by method a).

6-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-benzofuro[2,3-*d*]tetrazolo[1,5-*b*]-pyridazine (7)——a) A solution of $NaNO_2$ (0.32 g) in H_2O (1 ml) was added to a solution of **6** (0.3 g) and AcOH (4 ml) under cooling. The mixture was stirred for 1 h and the precipitate was collected. Recrystallization from $CHCl_3$–EtOH gave colorless plates, mp 250—251 °C. Yield 0.216 g (70%). $[\alpha]_D^{25}$ $-19.9°$ ($c=0.2$, $CHCl_3$). IR (KBr): 3390 (OH) cm^{-1}. ^1H-NMR ($CDCl_3$–DMSO-d_6) δ: 9.77 (1H, s, OH). MS *m/z*: 445 (M^+), 389 ($M^+ - N_4$). *Anal.* Calcd for $C_{23}H_{19}N_5O_5$: C, 62.02; H, 4.30; N, 15.72. Found: C, 61.89; H, 4.29; N, 16.00.

b) A solution of **3** (0.1 g) and NaN_3 (0.04 g) in dimethylformamide (DMF) (2 ml) was refluxed for 6 h and evaporated to dryness. The residue was chromatographed on silica gel. Elution with $CHCl_3$–MeOH (50 : 1) gave a white solid which was recrystallized from $CHCl_3$–EtOH to give 0.063 g (62%) of colorless plates, mp 250—251 °C. Analytical and spectral data were identical with those of **7** prepared by method a).

c) A mixture of **4** (0.1 g) and NaN_3 (0.04 g) in DMF (2 ml) was refluxed for 1 h. After the same work-up as in method b), 0.063 g (63%) of colorless plates, mp 250—251 °C, was obtained. Analytical and spectral data were identical with those of **7** prepared by method a).

6-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-benzofuro[2,3-*d*][1,2,4]triazolo-[4,3-*b*]pyridazine (8)——a) A solution of **6** (0.2 g) and $CH(OC_2H_5)_3$ (2 ml) was refluxed for 1 h and then evaporated to dryness. The residue was chromatographed on silica gel ($CHCl_3$). $[\alpha]_D^{25}$ $-14.4°$ ($c=0.2$, $CHCl_3$). Physicochemical, analytical and spectral data are summarized in Tables II and III.

b) A solution of **6** (0.2 g) and $CH(OC_2H_5)_3$ (2 ml) containing 2 drops of concentrated HCl was stirred at room temperature for 20 h and poured into H_2O. The resulting solution was extracted with $CHCl_3$. The organic layer was separated and evaporated to give a solid, which was purified by silica gel chromatography ($CHCl_3$). Analytical and spectral data were identical with those of **8** prepared by method a).

c) A solution of **6** (0.2 g) and HCOOH (2 ml) was refluxed for 1 h and evaporated to dryness. The residue was purified by silica gel chromatography ($CHCl_3$). Analytical and spectral data were identical with those of **8** prepared by method a).

3-Methyl-6-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-benzofuro[2,3-*d*][1,2,4]-triazolo[4,3-*b*]pyridazine (9)——a) A solution of **6** (0.1 g) and AcOH (2 ml) was refluxed for 0.5 h and evaporated to dryness. The residue was purified by silica gel chromatography ($CHCl_3$: MeOH = 50 : 1). Physicochemical, analytical and spectral data are summarized in Tables II and III.

b) A solution of **4** (0.1 g) and acetylhydrazine (0.17 g) in BuOH (2 ml) was refluxed for 28 h and allowed to stand at room temperature to give a light yellow precipitate. Analytical and spectral data were identical with those of **9** prepared by method a).

3-Ethenyl-6-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-benzofuro[2,3-*d*][1,2,4]-triazolo[4,3-*b*]pyridazine (10)——A solution of acryloyl chloride (0.074 g) in tetrahydrofuran (THF) (10 ml) was added dropwise to a solution of **6** (0.25 g) and THF (20 ml) with stirring. The mixture was stirred for 1 h, then the precipitate was collected and dissolved in a suspension of 2-butanone (4 ml) and powdered anhydrous Na_2CO_3 (0.15 g). After being refluxed for 18 h, the mixture was filtered, and the filtrate was evaporated to dryness to give a white solid, which was purified by silica gel chromatography ($CHCl_3$). Physicochemical, analytical and spectral data are summarized in Tables II and III.

3-Amino-6-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-benzofuro[2,3-*d*][1,2,4]-triazolo[4,3-*b*]pyridazine (11)——a) A solution of **6** (0.1 g) and BrCN (0.1 g) in 75% MeOH (5 ml) was stirred at room

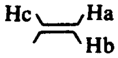
Table II. Physicochemical Data for 3-Substituted 6-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-benzofuro[2,3-*d*][1,2,4]-triazolo[4,3-*b*]pyridazines (**8**—**12**)

Compd.	mp (°C) (Recryst. solvent)	Appearance	Formula	Analysis (%) Calcd (Found)		
				C	H	N
8	250—251	Colorless	$C_{24}H_{20}N_4O_5$	64.86	4.54	12.61
	(CH_3CN)	needles		(64.87	4.50	12.42)
9	291—292	Light yellow	$C_{25}H_{22}N_4O_5$	65.49	4.84	12.22
	(EtOH–$CHCl_3$)	prisms		(65.30	4.99	12.03)
10	149—150	Colorless	$C_{26}H_{22}N_4O_5$	66.38	4.71	11.91
	(EtOH)	crystalline powder		(66.15	4.57	11.74)
11	280	Yellow	$C_{24}H_{21}N_5O_5$	62.74	4.61	15.24
	(EtOH)	crystalline powder		(62.42	4.45	15.42)
12	271—272	Colorless	$C_{30}H_{24}N_4O_5$	69.22	4.65	10.76
	(EtOH–$CHCl_3$)	needles		(68.99	4.64	10.58)

Table III. Spectral Data for **8**—**12**

Compd.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ	MS *m*/*z* (M^+)
8	3430 (OH)	9.18 (1H, s, triazole proton), 9.24 (1H, s, OH)	444
9	3340 (OH)	2.84 (3H, s, triazole CH_3), 9.50 (1H, s, OH)	458
10[a]	3420 (OH)	5.78 (1H, dd, $J_{a,b}=3$ Hz, $J_{a,c}=11$ Hz, Ha), 6.98 (1H, dd, $J_{a,b}=3$ Hz, $J_{b,c}=18$ Hz, Hb), 7.26 (1H, dd, $J_{a,c}=11$ Hz, $J_{b,c}=18$ Hz, Hc), 12.01 (1H, br s, OH)	470
11	3430 (OH), 3350, 3250 (NH_2)	6.24 (2H, s, NH_2), 9.47 (br s, OH)	459
12	3430 (OH)	7.40—7.70 and 8.40—8.60 (5H, m, phenyl protons), 9.43 (1H, br s, OH)	520

a) The ^{1}H-NMR spectrum was taken in pyridine-d_6 solution.



temperature for 12 h and evaporated to dryness to give a yellow powder, which was purified by silica gel chromatography ($CHCl_3$: MeOH = 20 : 1). Physicochemical, analytical and spectral data are summarized in Tables II and III.

b) A solution of **4** (0.1 g) and thiosemicarbazide (0.15 g) in BuOH (2 ml) was refluxed for 6 h and then evaporated to dryness. The residue was purified by silica gel chromatography ($CHCl_3$: MeOH = 20 : 1). Analytical and spectra data were identical with those of **11** prepared by method a).

3-Phenyl-6-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-8,9-dimethoxy-benzofuro[2,3-*d*][1,2,4]-triazolo[4,3-*b*]pyridazine (12)——A solution of **4** (0.1 g) and benzoyl hydrazine (0.13 g) in BuOH (2 ml) was refluxed for 14 h and allowed to stand at room temperature to give a white solid. Physicochemical, analytical and spectral data are summarized in Tables II and III.

1-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-[*N*′-(1-ethoxycarbonylethylidene)hydrazino]-7,8-dimethoxy-benzofuro[2,3-*d*]pyridazine (13a)——A solution of **6** (0.2 g) and ethyl pyruvate (0.38 g) in EtOH (5 ml) was refluxed for 2 h and allowed to stand to provide a yellow precipitate. Recrystallization from EtOH gave a yellow crystalline powder, mp 216—217 °C. Yield 0.133 g (78%). IR (KBr): 3440 (OH), 3250 (NH), 1705 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, $OCH_2C\underline{H}_3$), 2.26 (3H, s, CH_3–C=), 4.18 (2H, q, $OC\underline{H}_2CH_3$), 10.49 (1H, br s, NH). MS *m*/*z*: 532 (M^+), 459 ($M^+ - CO_2C_2H_5$). *Anal.* Calcd for $C_{28}H_{28}N_4O_7$: C, 63.15; H, 5.30; N, 10.52. Found: C, 62.98; H, 5.28; N, 10.33.

1-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-[*N*′-(1-carboxyethylidene)hydrazino]-7,8-dimethoxy-benzofuro[2,3-*d*]pyridazine (13b)——A suspension of **13a** (0.18 g), 6% KOH (3 ml) and EtOH (5 ml) was refluxed for 1 h. After being neutralized with 5% HCl, the mixture was extracted with $CHCl_3$. Evaporation of the extract gave a colorless crystalline powder, mp 217—218 °C. IR (KBr): 3440 (OH), 3250 (NH), 1693 (CO) cm^{-1}. This compound was used for the next experiment without further purification.

3-Methyl-7-(2*R*-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-9,10-dimethoxy-4*H*-benzofuro[2′,3′:4,5]pyridazino[3,2-*c*][1,2,4]triazin-4-one (14)——a) A solution of **13b** (0.12 g) and AcOH (5 ml) was refluxed for 2 h and evaporated to dryness. The residue was chromatographed on silica gel. Elution with $CHCl_3$ gave a yellow-white solid. Recrystallization from EtOH–$CHCl_3$ gave a yellow crystalline powder, mp 290 °C (dec.). Yield 0.062 g (56%). $[\alpha]_D^{25}$ $-7.6°$ ($c=0.2$, $CHCl_3$). IR (KBr): 3440 (OH), 1705 (CO) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.70 (3H, s, CH_3–C=), MS *m*/*z*: 486 (M^+). *Anal.* Calcd for $C_{26}H_{22}N_4O_6$: C, 64.19; H, 4.56; N, 11.52. Found: C, 63.94; H, 4.37; N, 11.70.

b) A solution of **6** (0.4 g) and ethyl pyruvate (0.76 g) in EtOH (10 ml) was refluxed for 14 h and allowed to stand at room temperature. The solid precipitated was collected and recrystallized from EtOH–$CHCl_3$ to give 0.27 g (60%) of yellow crystalline powder, mp 290 °C (dec.). Analytical and spectral data were identical with those of **14** prepared by method a).

1-(2*R*-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-(3,5-dimethyl-1*H*-pyrazol-1-yl)-7,8-dimethoxybenzofuro[2,3-*d*]pyridazine (16)——a) A solution of **6** (0.2 g) and 2,4-pentanedione (2 ml) was refluxed for 2 h and evaporated to dryness. The residue was chromatographed on silica gel. Elution with $CHCl_3$ gave a white solid. Recrystallization from EtOH gave colorless needles, mp 227—228 °C. Yield 0.147 g (64%). $[\alpha]_D^{25}$ $-12.2°$ ($c=0.2$, $CHCl_3$). IR (KBr): 3440 (OH) cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.44 (3H, s, C_3-CH_3 of pyrazole), 2.61 (3H, s, C_5-CH_3 of pyrazole), 6.19 (1H, s, pyrazole proton). 12.23 (1H, br s, OH). MS *m*/*z*: 498 (M^+). *Anal.* Calcd for $C_{28}H_{26}N_4O_5$: C, 67.46; H, 5.26; N, 11.24. Found: C, 67.43; H, 5.26; N, 11.02.

b) A solution of **3** (0.2 g) in dry benzene (2 ml) was added to a stirred suspension of 3,5-dimethylpyrazole (0.1 g) and $NaNH_2$ (0.1 g) in dry benzene (2 ml). The mixture was refluxed for 1 h and poured into H_2O. The benzene layer was separated and evaporated to dryness. The residue was recrystallized from EtOH to give 0.186 g (82%) of colorless needles, mp 227—228 °C. Analytical and spectral data were quite identical with those of **16** prepared by method a).

Acknowledgement This work was supported in part by a grant from the Research Foundation for Oriental Medicine. We are grateful to Dr. Kengo Kagei, Eisai Tsukuba Research Laboratory, for a generous gift of rotenone.

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