STUDIES ON THE CHEMICAL TRANSFORMATIONS OF ROTENOIDS. III[1]. RING CONVERSIONS OF METHYL ROTENONONATE AND β-ROTENONONE

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Abstract —— Ring conversions of methyl rotenononate (2b) and β-rotenonone (3) into rotenonone (1) or 4H-furo[2,3-h][1]benzopyrans (5a-b) were investigated. The Beckmann rearrangement of 2b oxime (6) in PPA provided methyl 3-(benzofuran-5-yl)carbonylamino- (9), 3-(benzofuran-5-yl)amino-carbonyl-2-benzofurancarboxylate (10) and furo[2,3-g]benzoxazole (11), whereas 3 oxime (12) gave furo[2,3-g]benzoxazole (13) as a single product. Compound 2b underwent ring closure with hydrazines to provide benzofuro-[2,3-d]pyridazin-4(3H)-ones (14a-e).

(-)-(6aS,12aS,2R)-Rotenone is an abundant natural product and widely used as an agricultural insecticides. In a previous paper[1], we reported the ring transformations of rotenone and (-)-(2R)-rotenonone (1) into [1-(2,3-dihydrobenzofuran-5-yl)-1-(2H-chromen-4-yl)methylidene]alkylamines and 2-alkylcarbamoyl-4-alkylamino-4H-furo[2,3-h][1]benzopyrans. In continuation of our ongoing programs directed toward the chemical transformations of rotenoids and subsequent development of pharmacologically effective heterocycles, we will report in this paper some ring transformations of methyl rotenononate (2b) and β-rotenonone (3) by primary amines and hydrazines as well as the Beckmann rearrangements of the corresponding oximes (6 and 12). In addition, we will describe the conversion of 2b into 3-substituted benzofuro[2,3-d]pyridazin-4(3H)-ones (14a-e).

The preparations of 2a[2] and 3[3] were reported in the literature without detailed spectral evidences for their structures. We thus attempted the preparations of 2a and 3 according to the reported methods and confirmed their structures on the basis of the spectral data.

Hydrolysis of 1 with methanolic KOH gave rotenononic acid (2a) as light yellow prisms in 79% yield. IR spectrum exhibited OH, COOH and CO stretching vibrations at 3440, 1735 and 1640 cm^{-1}, respectively and MS showed the molecular ion peak at m/z 424. In ^{1}H-nmr spectrum, the signals for COOH and OH appeared at δ 5.93 and 12.38 ppm. Compound 2a, on treatment with diazomethane, was readily converted to methyl 3-[(2R-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)carbonyl]-5,6-dimethoxy-2-benzofurancarboxylate (methyl rotenononate: 2b), ^{1}H-nmr of which showed a new methyl signal at δ 3.81 ppm.

β-Rotenonone (3), isomeric with rotenonone (1), was prepared by the dehydration of 2a in 80% yield. Ir spectrum showed carbonyl and lactone carbonyl absorptions at 1640 and 1730 cm^{-1}. ^{1}H-nmr spectrum exhibited no signals exchangeable by D_2O and ms showed the molecular ion peak at m/z 406. These spectral data of 2a-b and 3 were in good agreement with their chemical structures.

Reaction of 2b with ethanolic ammonia or 40% methylamine in a sealed tube at 100°C provided no condensed products but rotenonone (1) as unusual product in 31% and 52% yield along with unidentified tarry products.

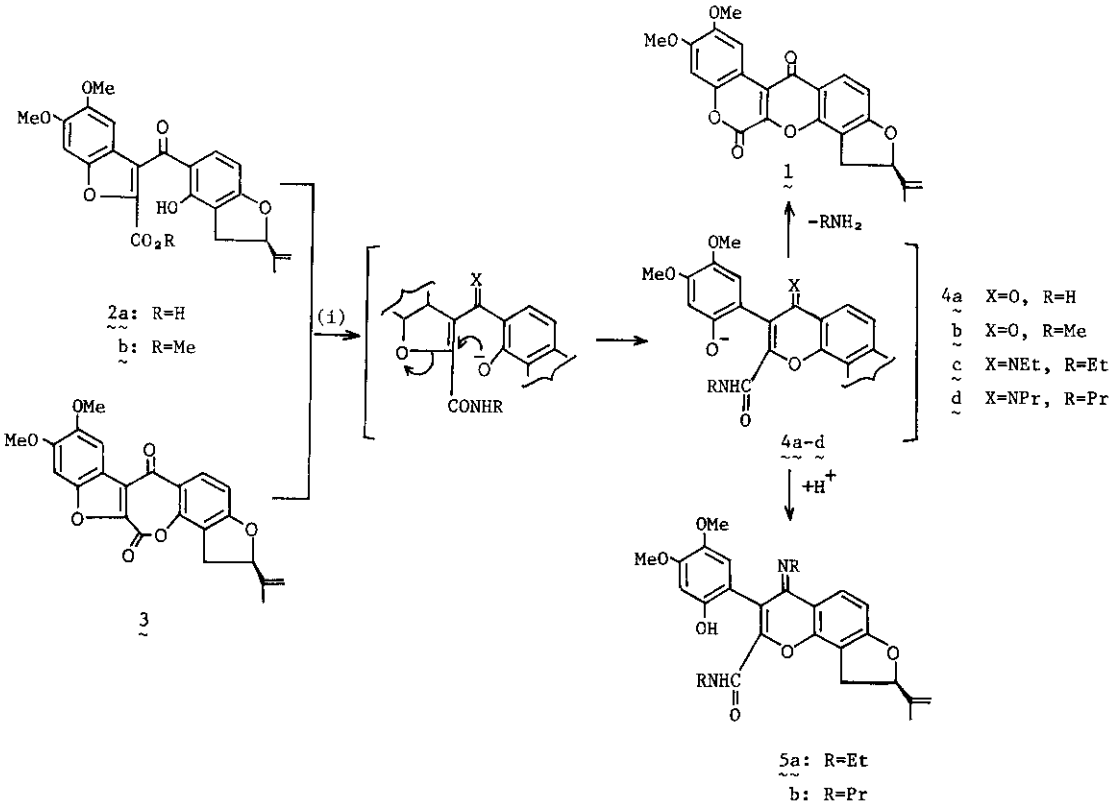


Chart 1. Reagent: (i) RNH_2

Rotenonone (1) was also formed in 40% or 59% yield when β-rotenonone (3) was boiled with ethanolic ammonia or 40% methylamine in a sealed tube. In contrast, treatment of 2b or 3 with ethylamine in ethanol provided yellow amorphous powders in 59% or 48% yield. Elemental and spectral analyses easily confirmed the structure to be 2-ethylcarbamoyl-4-ethylimino-8-methylethenyl-3-(2-hydroxy-4,5-dimethoxy)phenyl-8,9-dihydro-4H-furo[2,3-h][1]benzopyran (5a), which has been prepared by us previously[1] on the reaction of 1 with ethylamine. Similarly, 2-propylcarbamoyl-4-propylimino-4H-furo[2,3-h][1]benzopyran (5b) was obtained when 2b or 3 were treated with propylamine in boiling ethanol.

These unusual results may be rationalized considering that the isoflavone intermediates (4a-b) favor the ring closure to form rotenonone (1) involving the elimination of ammonia or methylamine, whereas the intermediates (4c-d) undergo the protonation of the phenolate anion to provide the corresponding 4H-furo[2,3-h][1]benzopyran (5a-b). These mechanisms might be supported by our previous findings[1] that ethylamine or propylamine readily condensed with rotenonone (1) to give 5a-b while neither ammonia or methylamine reacted with 1 to recover unchanged 1. Thus the reaction pathways probably depend on basicity of primary amines employed.

The oximes of 2b and 3 were then prepared for the investigations of Beckmann rearrangement. Treatment of 2b with hydroxylamine hydrochloride provided methyl (E)-3-[(2R-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)hydroxyimino]-5,6-dimethoxy-2-benzofurancarboxylate (6) as a single isomer in 74% yield. The E stereochemistry was estimated from ^{1}H-nmr spectrum which showed C-6'aromatic proton signal shifted 0.57 ppm upfield relative to the parent ketone (2b). Clearly, the proton responsible for this signal suffers an anisotropic effect of hydroxyimino group. In order to obtain more evidence regarding the stereochemistry about the C=N double bond, compound 6 was acetylated with acetic anhydride at room temperature to give methyl (E)-3-[(2R-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)acetoxyimino]-5,6-dimethoxy-2-benzofurancarboxylate (7a) and methyl (E)-3-[(2R-2-methylethenyl-4-acetoxy-2,3-dihydrobenzofuran-5-yl)acetoxyimino]-5,6-dimethoxy-2-benzofurancarboxylate (7b) in 52% and 28% yield, respectively. In ^{1}H-nmr spectrum, the C-6'proton of 7a appeared 0.16 ppm downfield compared to that of 6, whereas C-4 aromatic proton shifted only 0.07 ppm downfield. These observations were in accord with the E structure for 6. Further evidence was obtained from cyclization of 7a, which yielded (7R)-3-(2-methoxycarbonyl-5,6-

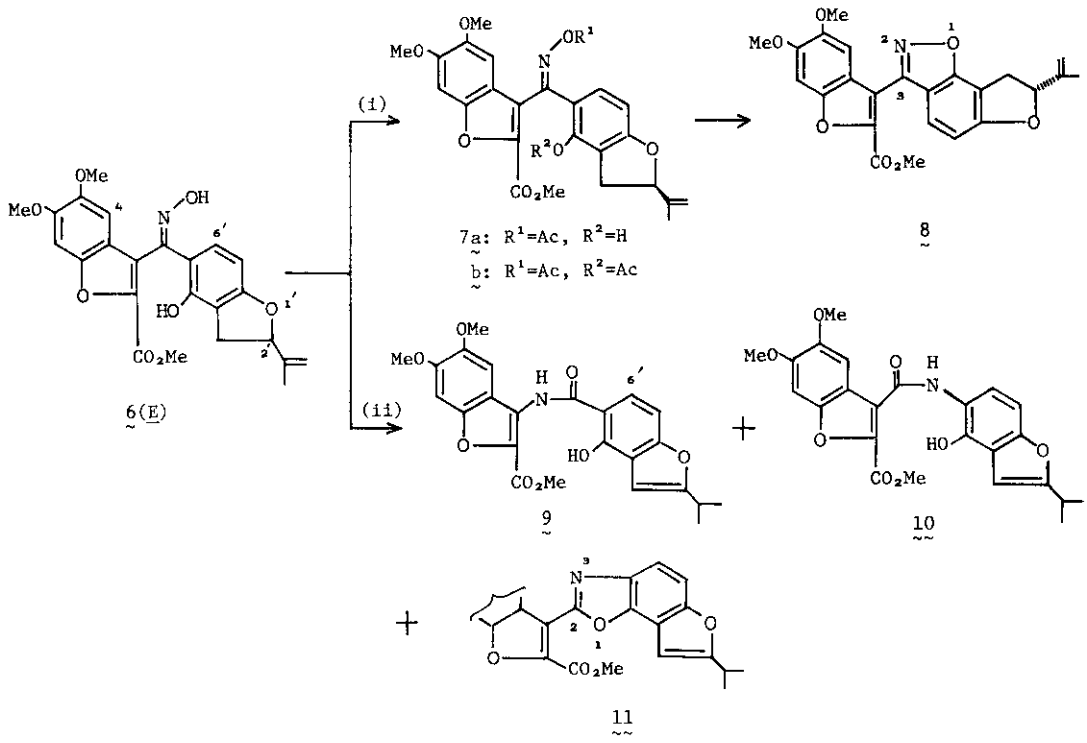


Chart 2. Reagents: (i) Ac_2O/pyridine; (ii) PPA

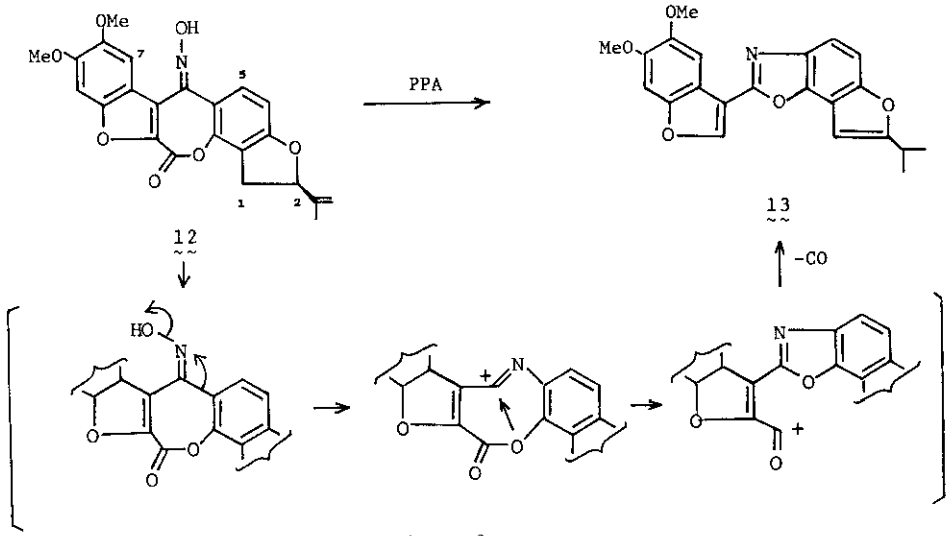


Chart 3

dimethoxybenzofuran-3-yl)-7-methylethenyl-7,8-dihydrofuro[2,3-g]-1,2-benzisoxazole (8) in 84% yield. Elemental and spectroscopic data were consistent with the structure 8.

Beckmann rearrangement of 6 was carried out in polyphosphoric acid (PPA) at 95°C for 1 h to give methyl 3-(2-isopropyl-4-hydroxybenzofuran-5-yl)carbonylamino-5,6-dimethoxy-2-benzofurancarboxylate (9), methyl 3-(2-isopropyl-4-hydroxybenzofuran-5-yl)aminocarbonyl-5,6-dimethoxy-2-benzofurancarboxylate (10) and 2-(2-methoxycarbonyl-5,6-dimethoxybenzofuran-3-yl)-7-isopropyl-furo[2,3-g]-benzoxazole (11) in 36%, 14% and 20% yield, respectively. Compound 9 and 10 were proved to have the same molecular formula on the basis of elemental and mass spectral analyses. Ir spectra of 9 and 10 showed the characteristic amido carbonyl absorptions at 1635 and 1630 cm^{-1}. The pairs of isomeric 9 and 10 could be recognized by ^{1}H-nmr spectra, in which C-6' aromatic proton of 9 was deshielded by the carbonyl group and appeared 1.03 ppm downfield compared to that of 10. Thus 9 was confirmed to be the normal Beckmann product derived from the stereospecific trans migration of the anti C-3 carbon of (E)-6.

In contrast, the formation of 10 would rationalize that (E)-6 underwent facile geometrical isomerization under the reaction condition to form a E-Z equilibrium mixture. In fact, the use of PPA or other protic solvent is known to often bring about geometrical isomerization of oximes[4]. On the other hand, compound 11 was unambiguously formed via the intramolecular dehydration of 10.

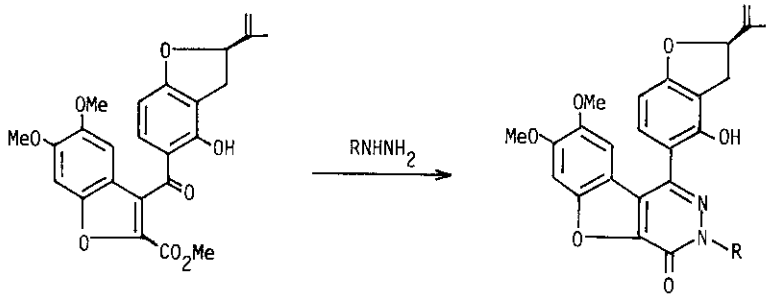
Elemental and spectropic data of 11 were in agreement with the proposed structure. ^{1}H-Nmr spectra of 9-11 also revealed the isomerization of methylethenyl group to the isopropyl group during the reaction in PPA.

β-Rotenonone oxime; (2R)-2-methylethenyl-6-hydroxyimino-8,9-dimethoxy-1,2-dihydro-6H,12H-furo[2,3-i]benzofuro[2,3-c][1]benzoxepin-12-one (12) was obtained as a single isomer by either the cyclization of 6 with sodium methoxide or the treatment of 3 with hydroxylamine hydrochloride in 93% or 32% yield, respectively. ^{1}H-Nmr spectrum showed the C-5 and C-7 aromatic protons at δ7.41 and δ7.49 ppm. which resonated 0.78 and 0.38 ppm upfield than the corresponding aromatic protons of the parent ketone (3). MS showed the molecular ion peak at m/z 421. The spectroscopic data were in consistent with the structure 12, however, the geometrical confirmation for 12 was not obtained because attempts to detect nuclear Overhauser effects between the hydroxyimino proton and C-5 or C-7 proton in ^{1}H-nmr spectrum, or to acetylate the hydroxyimino group of 12 were unsuccessful.

Beckmann rearrangement of 12 was carried out under the similar condition as 6 to afford exclusively 2-(5,6-dimethoxybenzofuran-3-yl)-7-isopropyl-furo[2,3-g]-benzoxazole (13) in 94% yield. ^{1}H-Nmr spectrum displayed the quite the same coupling patterns as compound 11 except one signal attributable to the aromatic hydrogen resonated at δ8.29 ppm, and ms showed the molecular ion peak at m/z 377. Accordingly, compound 13 was confirmed to be the assigned structure and obviously derived from E geometrical isomer of 12 via the reaction pathway as illustrated in Chart 3.

The remaining objective in this study is the chemical transformation of 2b into nitrogen-containing heterocycles using the 1,4-dicarbonyl functions in the molecule. Condensation reaction of 2b with hydrazine hydrate led to 1-(2R-2-methyl-ethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-3,4-dihydrobenzofuro-[2,3-d]pyridazin-4(3H)-one (14a) in 97% yield. Ir spectrum showed band at 3280 cm^{-1}(NH). ^{1}H-Nmr spectrum exhibited resonance signals at δ9.26(OH) and δ12.95 ppm(NH). Elemental analysis and ms coincided with the structure 14a.

In a similar manner, 2b was condensed with N-substituted hydrazines to give the corresponding 3-substituted 1-(2R-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-3,4-dihydrobenzofuro[2,3-d]pyridazin-4(3H)-ones (14b-e) as shown in Chart 4. Physicochemical and spectral data summarized in Table I and Table II were in accord with the structures 14b-e.



2b

14a: R=H
b: R=Me
c: R=$(CH_2)_2OH$
d: R=C_6H_5
e: R=C_6H_4Me-p

Chart 4

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Ei-ms was measured with a JEOL JMS DX-300 mass spectrometer, and IR spectra(KBr disk) with a JASCO IRA-2 spectrometer. ^{1}H-Nmr spectra were recorded with JEOL JNM-MH-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The following abbreviations are used; s, singlet; d, doublet; dd, doublet of doublets; sept, septet; br, broad. Column chromatography was carried out on silica gel BW-200(Fuji Davison Chemicals , Ltd.).

3-[(2R-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)carbonyl]-5,6-dimethoxy-2-benzofurancarboxylic acid; rotenononic acid (2a)

A mixture of 1(1.78g) and EtOH(25ml) containing 10% KOH(5ml) was refluxed for 2h, neutralized with 10% HCl and evaporated to dryness. The residue was washed with water and EtOH, and chromatographed on silica gel. Elution with $CHCl_3$ gave yellow solids. Recrystallization from EtOH gave light yellow prisms, mp 257-259°C(lit.[2] 249-251°C). Yield 1.41g(79%). Ir: 3440(OH), 1735(CO_2H), 1640(CO)cm^{-1}. ^{1}H-Nmr δ: 3.81 and 3.94(6H, s, 2xOCH_3), 5.93(1H, br s, CO_2H), 6.29(1H, d, J=8.8Hz, 7'-H), 6.77(1H, s, 7-H), 7.07(1H, s, 4-H), 7.26(1H, d, J=8.8Hz, 6'-H). 12.38(1H, s, 4'-OH). Ms m/z: 424(M^+). Anal. Calcd for $C_{23}H_{20}O_8$: C, 65.09; H, 4.75. Found: C, 65.32; H, 4.75.

Methyl 3-[(2R-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)carbonyl]-5,6-dimethoxy-2-benzofurancarboxylate; methyl rotenononate (2b)

To a solution of 2a(6.4g) and $CHCl_3$(300ml) was added CH_2N_2-Et_2O solution(100ml) prepared from N-nitroso-N-methylurea(4g). The mixture was stirred at room temperature for 0.5h, treated with AcOH and evaporated to dryness to give solids. Recrystallization from EtOH gave light yellow needles, mp 153°C. Yield 6.4g(97%). Ir: 3440(OH), 1730(CO_2CH_3), 1640(CO)cm^{-1}. ^{1}H-Nmr δ: 3.81(3H, s, CO_2CH_3), 3.83 and 3.94(6H, s, 2xOCH_3), 6.30(1H, d, J=8.8Hz, 7'-H), 6.81(1H, s, 7-H), 7.08(1H, s. 4-H), 7.26(1H, d, J=8.8Hz, 6'-H), 12.47(1H, s, 4'-OH). Ms m/z: 438(M^+), 379(M^+-CO_2CH_3). Anal. Calcd for $C_{24}H_{22}O_8$: C, 65.75; H, 5.06. Found: C, 65.46; H, 4.87.

(2R)-2-Methylethenyl-8,9-dimethoxy-1,2-dihydro-6H,12H-furo[2,3-i]benzofuro[2,3-c]-[1]benzoxepine-6,12-dione; β-rotenonone (3)

A solution of 2a(0.3g) and NaOAc(1.5g) in Ac_2O(8ml) was refluxed for 1h and evaporated to dryness. The residue was dissolved in $CHCl_3$, washed with water

and dried over $MgSO_4$. Removal of solvent gave yellow powders which were recrystallized from $CHCl_3$-EtOH to afford yellow needles, mp 285-287°C(lit.[3] 275-276°C). Yield 0.23g(80%). Ir: 1730(OC=O), 1640(CO)cm^{-1}. ^{1}H-Nmr δ: 1.81(3H, s, CH_3), 3.25(1H, dd, J=8,16Hz, 1-H), 3.64(1H, dd, J=8,16Hz, 1-H), 3.99 and 4.02 (6H, s, 2xOCH_3), 4.98(1H, s, =CH_2), 5.12(1H, S, =CH_2), 5.41(1H, t, J=9.2Hz, 2-H), 6.86(1H, d, J=8.4Hz, 4-H), 7.12(1H, s, 10-H), 7.87(1H, s, 7-H), 8.19(1H, d, J=8.4Hz, 5-H). Ms m/z: 406(M^+). Anal. Calcd for $C_{23}H_{18}O_7$: C, 68.04; H, 4.47. Found: C, 67.87; H, 4.47.

Reaction of 2b with Ammonia

A solution of 2b(0.15g) and EtOH(10ml) was saturated with ammonia. The mixture was heated in a sealed tube at 100°C for 12h and evaporated to dryness. The residue was chromatographed on silica gel($CHCl_3$) to give yellow solids. Recrystallization from $CHCl_3$-EtOH gave yellow needles, mp 298-300°C. Yield 0.43g (31%). Analytical and spectral data were identical in all respects with that of an authentic rotenonone(1)[5].

Reaction of 2b with 40% Methylamine

A solution of 2b(0.15g) and 40% methylamine(2ml) in EtOH(5ml) was heated and worked up as the reaction with ammonia to give 0.072g(52%) of rotenonone(1).

Reaction of 3 with Ammonia

A solution of 3(0.2g) and EtOH(10ml) was saturated with ammonia. The mixture was heated in a sealed tube at 100°C for 5h and evaporated to dryness. The residue was chromatographed on silica gel($CHCl_3$) to give yellow solids. Recrystallization from $CHCl_3$-EtOH gave yellow needles, mp 298-300°C. Yield 0.08g(40%). Analytical and spectral data were identical with that of an authentic rotenonone (1).

Reaction of 3 with 40% Methylamine

A solution of 3(0.2g) and 40% methyamine(4ml) in EtOH(10ml) was heated and worked up as the reaction with ammonia to give 0.118g(59%) of rotenonone(1).

Reaction of 2b or 3 with Ethylamine

A solution of 2b or 3(0.2g) and 70% ethylamine(2ml) in EtOH(5ml) was refluxed for 1.5h and evaporated to dryness. The residual oil was chromatographed on silica gel($CHCl_3$) to give yellow solids. Recrystallization from n-hexane gave yellow amorphous powderes, mp 111-114°C. Yield 0.129g(59%) or 0.113g(48%). Analytical and spectral data were identical with that of an authentic 5a[1].

Reaction of 2b or 3 with Propylamine

A solution of 2b or 3(0.2g) and propylamine(1ml) in EtOH(10ml) was refluxed for 2h and evaporated to dryness. The residual oil was chromatographed on silica gel($CHCl_3$) to give yellow powders. Recrystallization from Et_2O-petr. ether gave yellow amorphous powders, mp 163-166°C. Yield 0.095g(41%) or 0.184g(74%). Analytical and spectral data were identical with that of an authentic 5b[1].

Methyl (E)-3-[(2R-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)hydroxyimino]-5,6-dimethoxy-2-benzofurancarboxylate (6)

A solution of 2b(0.4g) and $NH_2OH \cdot HCl$(1g) in EtOH(10ml) was refluxed for 7 days and evaporated to dryness. To the residue was added $CHCl_3$, and insoluble material was filtered off. The filtrate was evaporated to dryness, and the residue was chromatographed on silica gel($CHCl_3$) to give white solids. Recrystallization from Et_2O-petr. ether gave colorless needles, mp 189-190°C. Yield 0.305g(74%). Ir: 3425(OH), 3375(NOH), 1725(CO)cm^{-1}. ^{1}H-Nmr δ: 3.88(6H, s, 2xOCH_3), 3.96(3H, s, CO_2CH_3), 6.23(1H, d, J=8.8Hz, 7'-H), 6.69(1H,d, J=8.8HZ, 6'-H), 6.72(1H, s, 7-H), 7.12(1H, s, 4-H), 7.50(1H, s, N-OH), 11.09(1H, s, 4'-H). Ms m/z: 453(M^+). Anal. Calcd for $C_{24}H_{23}NO_8$: C, 63.57; H, 5.11; N, 3.09. Found: C, 63.71; H, 5.27; N, 2.93.

Methyl (E)-3-[(2R-2-Methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)acetoxyimino]-5,6-dimethoxy-2-benzofurancarboxylate (7a) and Methyl (E)-3-[(2R-2-Methylethenyl-4-acetoxy-2,3-dihydrobenzofuran-5-yl)acetoxyimino]-5,6-dimethoxy-2-benzofurancarboxylate (7b)

A solution of 6(0.28g) and Ac_2O(0.5ml) in dry pyridine(4ml) was stirred at room temperature for 2.5h and evaporated to dryness below 30°C. The residue was chromatographed on silica gel($CHCl_3$). The fast moving band gave 0.158g(52%) of 7a and the slow moving band gave 0.092g(28%) of 7b. 7a: colorless crystalline powders, mp 104-106°C(Et_2O-n-hexane). ^{1}H-Nmr δ: 1.99(3H, s, $COCH_3$), 6.32(1H, d, J=8.8Hz, 7'-H), 6.74(1H, s, 7-H), 6.85(1H, d, J=8.8Hz, 6'-H), 7.19(1H, s, 4-H), 11.40(1H, s, 4'-OH). Ms m/z: 495(M^+). Anal. Calcd for $C_{26}H_{25}NO_9$: C, 63.03; H, 5.09; N, 2.83. Found: C, 63.15; H, 5.01; N, 2.72. 7b: light yellow crystalline powders, mp 85-87°C(Et_2O-n-hexane). ^{1}H-Nmr δ: 1.97(3H, s, $COCH_3$), 2.04(3H, s, $COCH_3$), 6.71(1H, d, J=8.4Hz, 7'-H), 6.86(1H, d, J=8.4Hz, 6'-H), 6.89(1H, s, 7-H), 7.34(1H, s, 4-H). Ms m/z: 537(M^+). Anal. Calcd for $C_{28}H_{27}NO_{10}$: C, 62.57; H, 5.06; N, 2.61. Found: C, 62.38; H, 4.98; N, 2.55.

(7R)-3-(2-Methoxycarbonyl-5,6-dimethoxybenzofuran-3-yl)-7-methylethenyl-7,8-

dihydrofuro[2,3-g]-1,2-benzisoxazole (8)

A solution of 7a(0.1g) and pyridine(2ml) was refluxed for 1h and evaporated to dryness. The residue was chromatographed on silica gel($CHCl_3$) to give light yellow powders. Recrystallization from Et_2O-n-hexane gave colorless crystalline powders, mp 106-108°C. Yield 0.074g(84%). Ir: 1710(CO_2CH_3)cm^{-1}. ^{1}H-Nmr δ: 3.85, 3.91 and 4.00(9H, s, 3xOCH_3), 6.95(1H, d, J=8.8Hz, 5-H), 7.13(1H, s, 7'-H), 7.20(1H, s, 4'-H), 7.37(1H, d, J=8.8Hz, 4-H). Ms m/z: 435(M^+). Anal. Calcd for $C_{24}H_{21}NO_7$: C, 66.20; H, 4.86; N, 3.22. Found: C, 65.99; H, 4.80; N, 3.08.

Beckmann Rearrangement of 6

A solution of 6(0.5g) and PPA(10ml) was stirred at 95°C for 1h and poured into ice-water. The precipitates were chromatographed on silica gel. Elution with $CHCl_3$ successively gave 0.182g(36%) of methyl 3-(2-isopropyl-4-hydroxybenzofuran-5-yl)-carbonylamino-5,6-dimethoxy-2-benzofurancarboxylate (9), 0.07g(14%) of methyl 3-(2-isopropyl-4-hydroxybenzofuran-5-yl)aminocarbonyl-5,6-dimethoxy-2-benzofuran-carboxylate (10) and 0.097g(20%) of 2-(2-methoxycarbonyl-5,6-dimethoxybenzofuran-3-yl)-7-isopropyl-furo[2,3-g]benzoxazole (11). 9: yellow crystalline powders, mp 255-257°C(EtOH). Ir: 3430(OH), 3240(NH), 1695(CO_2CH_3), 1635(CO)cm^{-1}. ^{1}H-Nmr δ: 1.40(6H, d, J=6.4Hz, $(CH_3)_2CH$), 3.12(1H, sept, J=6.4Hz, $(CH_3)_2CH$), 3.96 and 4.00(6H, s, 2xOCH_3), 4.11(3H, s, CO_2CH_3), 5.30(1H, s, NH), 6.44(1H, s, 3'-H), 6.58(1H, d, J=8.8Hz, 7'-H), 7.04(1H, s, 7-H), 7.95(1H, s, 4-H), 8.08(1H, d, J=8.8Hz, 6'-H), 10.95(1H, s, OH). Ms m/z: 453(M^+). Anal. Calcd for $C_{24}H_{23}NO_8$: C, 63.57; H, 5.11; N, 3.09. Found: C, 63.54; H, 5.17; N, 2.91. 10: brown crystalline powders, mp 205-208°C(EtOH). Ir: 3430(OH), 3230(NH), 1685(CO_2CH_3), 1630(CO)cm^{-1}. ^{1}H-Nmr δ: 1.36(6H, d, J=6.4Hz, $(CH_3)_2CH$), 3.06(1H, sept, J=6.4Hz, $(CH_3)_2CH$), 3.97 and 3.98(6H, s, 2xOCH_3), 4.09(3H, s, CO_2CH_3), 6.58(1H, s, 3'-H), 6.94(1H, d, J=8.8Hz, 6'-H or 7'-H), 6.98(1H, s, 7-H), 7.05(1H, d, J=8.8Hz, 6'-H, or 7'-H), 7.97(1H, s, 4-H), 9.99(1H, s, NH), 12.19(1H, s, OH). Ms m/z: 453(M^+). Anal. Calcd for $C_{24}H_{23}NO_8$: C, 63.57; H, 5.11; N, 3.09. Found: C, 63.47: H, 5.09; N, 2.99. 11: yellow needles, mp 162-164°C(Et_2O-petr. ether). Ir: 1720(CO_2CH_3) cm^{-1}. ^{1}H-Nmr δ: 1.40(6H, d, J=6.4Hz, $(CH_3)_2CH$), 3.15(1H, sept, J=6.4Hz, $(CH_3)_2CH$), 3.96(3H, s, OCH_3), 4.03(6H, s, OCH_3 and CO_2CH_3), 6.68(1H, s, 8-H), 7.12(1H, s, 7'-H), 7.51(1H, d, J=8.8Hz, 4-H or 5-H), 7.72(1H, d, J=8.8Hz, 4-H or 5-H), 7.76(1H, s, 4'-H). Ms m/z: 435(M^+). Anal. Calcd for $C_{24}H_{21}NO_7$: C, 66.20; H, 4.86; N, 3.22. Found: C, 66.09; H, 4.64; N, 3.15.

(2R)-2-Methylethenyl-6-hydroxyimino-8,9-dimethoxy-1,2-dihydro-6H,12H-furo-[2,3-i]benzofuro[2,3-c][1]benzoxepin-12one; β-rotenonone oxime (12)

a) A solution of 6 (0.58g) and Na (0.12g) in absolute methanol (35ml) was refluxed for 2h and evaporated to dryness. The residue was dissolved in water, neutralized with 5% AcOH and extracted with $CHCl_3$. Removal of $CHCl_3$ gave yellow solids. Recrystallization from EtOH-$CHCl_3$ gave yellow needles, mp 293-295°C. Yield 0.5g (93%). $[\alpha]_D^{25}$ -72.4° (c=0.2, $CHCl_3$). Ir: 3440 (OH), 1710 (CO) cm^{-1}. ^{1}H-Nmr δ: 3.91 and 4.01 (6H, s, 2xOCH_3), 6.94 (1H, s, 10-H), 6.95 (1H, d, J=8.8Hz, 4-H), 7.41 (1H, d, J=8.8Hz, 5-H), 7.49 (1H, s, 7-H), 15.64 (1H, br s, NOH). Ms m/z: 421 (M^+). Anal. Calcd for $C_{23}H_{19}NO_7$: C, 65.56: H, 4.54: N, 3.32. Found: C, 65.40; H, 4.59; N, 3.50.

b) A solution of 3 (0.15g) and $NH_2OH \cdot HCl$ (0.45g) in EtOH (10ml) was refluxed for 13h and evaporated to dryness. The residue was dissolved in $CHCl_3$, and the insoluble material was removed by filtration. The filtrate was evaporated to dryness and the residue was chromatographed on silica gel ($CHCl_3$) to give 0.05g (32%) of yellow needles, mp 293-295°C (EtOH-$CHCl_3$). Spectral data were identical with that of 12 prepared by method a).

Beckmann Rearrangement of 12

A solution of 12 (0.15g) and PPA (2ml) was stirred at 95°C for 1h and poured into ice-water. The precipitates were chromatographed on silica gel. Elution with $CHCl_3$ gave white solids. Recrystallization from EtOH gave 0.105g (94%) of 2-(5,6-dimethoxybenzofuran-3-yl)-7-isopropyl-furo[2,3-g]benzoxazole (13), as colorless needles, mp 164-165°C. ^{1}H-Nmr δ: 1.39 (6H, d, J=6.4Hz, $(CH_3)_2CH$), 3.12 (1H, sept, J=6.4Hz, $(CH_3)_2CH$), 3.95 and 4.06 (6H, s, 2xOCH_3), 6.63 (1H, s, 8-H), 7.10 (1H, s, 7'-H), 7.43 (1H, d, J=8.8Hz, 4-H or 5-H), 7.62 (1H, d, J=8.8Hz, 4-H or 5-H), 7.82 (1H, s, 4'-H), 8.29 (1H, s, 2'-H). Ms m/z: 377 (M^+). Anal. Calcd for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07; N, 3.71. Found: C, 69.77: H, 5.03; N, 3.99.

General Preocedure for the Preparation of 3-Substituted 1-(2R-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-3,4-dihydrobenzofuro[2,3-d]-pyridazin-4(3H)-ones (14a-e)

A solution of 2b (0.2g) and N-substituted hydrazines (0.2g) in EtOH (10ml) was refluxed for 2-48h and allowed to stand to give the corresponding 3,4-dihydrobenzofuro[2,3-d]pyridazin-4(3H)-ones (14a-e). Physicochemical and spectral data are summarized in Table I and Table II.

Table 1. Physicochemical Data for 3-Substituted 1-(2R-2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-3,4-dihydrobenzofuro[2,3-d]pyridazin-4-(3H)-ones (14a-e)

Compd.	Reaction time (h)	mp(°C) (recryst. solvent)	Appearance	Formula	Analysis(%) Calcd(Found) C	H	N	Yield (%)
14a	2	>300 ($EtOH-CHCl_3$)	colorless needles	$C_{23}H_{20}N_2O_6$	65.71 (65.78	4.80 4.62	6.66 6.65)	97
14b	16	220-222 (EtOH)	colorless needles	$C_{24}H_{22}N_2O_6$	66.35 (66.20	5.10 4.95	6.45 6.37)	32
14c	10	192-194 (EtOH)	colorless needles	$C_{25}H_{24}N_2O_7$	64.65 (64.30	5.21 5.01	6.03 5.80)	32
14d	20	226-227 (EtOH)	light brown prisms	$C_{29}H_{24}N_2O_6$	70.15 (70.02	4.87 4.68	5.64 5.67)	36
14e	48	135-137 (petr.ether-Et_2O)	light brown prisms	$C_{30}H_{26}N_2O_6$	70.58 (70.32	5.13 4.93	5.49 5.69)	36

Table II. Spectroscopic Data for 14a-e

Compd.	IR(KBr) cm^{-1}	^{1}H-NMR($CDCl_3$)δ	MS m/z (M^+)
14a	3430(OH), 3280(NH) 1675(CO)	9.26(1H,br s,OH), 12.95(1H,br s,NH)	420
14b	3430(OH), 1660(CO)	3.96(3H,s,NCH_3), 9.38(1H,s,OH)	434
14c	3420(OH), 1660(CO)	3.40(1H,br s,CH_2CH_2OH), 4.16(2H,t,CH_2CH_2OH), 4.54(2H,t,CH_2CH_2OH), 9.34(1H,s,OH)	464
14d	3430(OH), 1685(CO)	7.30-7.70(5H,m,phenyl protons), 9.63(1H,s,OH)	496
14e	3430(OH), 1675(CO)	2.40(3H,s,$C_6H_4CH_3$), 9.64(1H,s,OH)	510

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