

STUDIES ON THE CHEMICAL TRANSFORMATION OF ROTENOIDS. II¹.

REACTIONS OF ROTENONE AND ROTENONONE WITH PRIMARY AMINES

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Abstract—The ring transformations of rotenone and rotenonone by primary amines were investigated. The improved synthetic methods for rotenonone were also developed. Rotenone (1) underwent cleavage of C-12a and O-13 linkage to give [1-(4-hydroxy-2-methylethenyl-2,3-dihydro-benzofuran-5-yl)-1-(6,7-dimethoxy-2H-chromen-4-yl)methylidene]alkylamines (2a-b), while rotenonone (5) gave 2-alkylcarbamoyl-4-alkylimino-8-methylethenyl-3-(2-hydroxy-4,5-dimethoxy)phenyl-8,9-dihydro-4H-furo[2,3-h]-[1]benzopyrans (7a-d) as a result of nucleophilic attack on C-12 carbon. Compound 1 was oxidized by nitrosyl chloride or dimethyl sulfoxide in the presence of iodine and sulfuric acid to provide rotenonone (5) in improved yields respectively.

(-)-(6a_S,12a_S,2R)-Rotenone (1) is an abundant natural product and widely used as a useful insecticide. In a previous paper¹, we reported the ring transformation of 1 into 3-substituted 1-(4-hydroxy-2-methylethenyl-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-1,9b,2,3,3a,4-hexahydro-[1]benzopyrano[3,4-c]pyrazol-1-enes by the reaction with monosubstituted hydrazines in the strong basic medium, and discussed on the stereochemistries of the products. In continuation of our study on the chemical transformation of rotenoids and subsequent development of pharmacologically effective compounds, we wish to report in this paper some ring transformations of rotenone (1) and rotenonone (5) by primary amines.

Treatment of 1 with excess of ethylamine solution in boiling ethanol resulted in cleavage of C-12a and O-13 linkage to provide [1-(4-hydroxy-2-methylethenyl-2,3-dihydrobenzofuran-5-yl)-1-(6,7-dimethoxy-2H-chromen-4-yl)methylidene]ethylamine

(2a) after repeated chromatography on silica gel. This compound was confirmed as the assigned structure 2a on the basis of ^1H -NMR spectrum which showed an methine proton of 2H-pyran ring as a triplet centered at δ 5.61 and phenolic hydroxy proton at δ 16.40 respectively. Similarly, 1 was converted to [1-(4-hydroxy-2-methyl-ethenyl-2,3-dihydrobenzofuran-5-yl)-1-(6,7-dimethoxy-2H-chromen-4-yl)methylidene]-propylamine (2b) with propylamine. Compounds 2a-b were fairly unstable, and the reactions of 1 with other primary amines gave no stably isolable compounds.

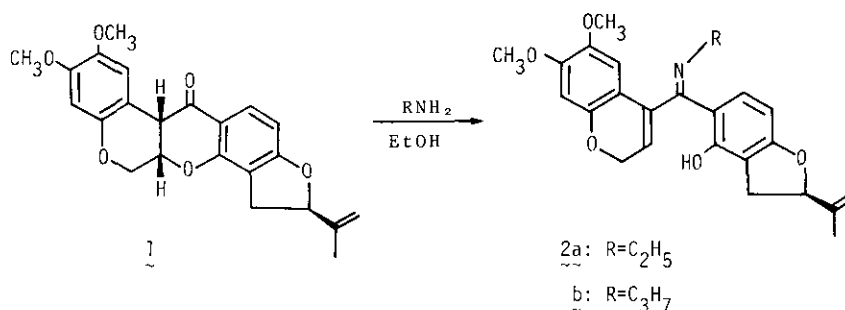


Chart 1

Table 1. [1-(2,3-Dihydrobenzofuran-5-yl)-1-(2H-chromen-4-yl)methylidene]-alkylamines (2a-b)

Compd.	Yield (%)	mp(°C) (recryst. solvent)	Appearance	Formula	Analysis(%) Calcd(Found)		
					C	H	N
2a	73	52-54 (n-hexane)	yellow amorphous powders	C ₂₅ H ₂₇ NO ₅	71.24 (71.55)	6.46 6.64	3.32 3.51
2b	52	69-74 (n-hexane-Et ₂ O)	yellow amorphous powders	C ₂₆ H ₂₉ NO ₅	71.70 (71.59)	6.71 6.87	3.22 3.50

Table 2. ^1H -NMR and MS Data for 2a-b

Compd.	^1H -NMR (CDCl ₃) δ	MS m/z
2a	4.88(2H, d, J=4 Hz, C(2)-H ₂ of 2H-chromene) 5.61(1H, t, J=4 Hz, C(3)-H of 2H-chromene) 16.40(1H, br s, OH)	421(M ⁺), 392(M ⁺ -C ₂ H ₅)
2b	4.90(2H, d, J=4 Hz, C(2)-H ₂ of 2H-chromene) 5.64(1H, t, J=4 Hz, C(3)-H of 2H-chromene) 16.50(1H, br s, OH)	435(M ⁺), 392(M ⁺ -C ₃ H ₇)

Under the same condition, we investigated analogous condensation of rotenonone (5) with primary amines. Compound 5 has been synthesized by a few methods², however, these methods were unsatisfactory in terms of chemical yield and reaction time. Therefore, we attempted two kinds of reactions in order to develop the improved synthetic methods for 5 as shown in Chart 2.

Rotenone (1) was suspended in a saturated solution of nitrosyl chloride in dichloromethane and stirred overnight at room temperature to give an inseparable mixture of (2R)-6a,12a-dehydrorotenone (3) and (2R)-12-ethoxy-6a,12a-dehydrorotenone (4). Successive exposure of nitrosyl chloride over a mixture of 3 and 4 completed oxidation to provide 56.5 % yield of rotenonone (5) and 3 % yield of compound 4. As reported by Crombie³, the formation of 5 was rationalized by the initial oximation at C-12 of 3 followed by the hydrolysis to ketone 5. However, a possible mechanism for the formation of 4 is not clear at present.

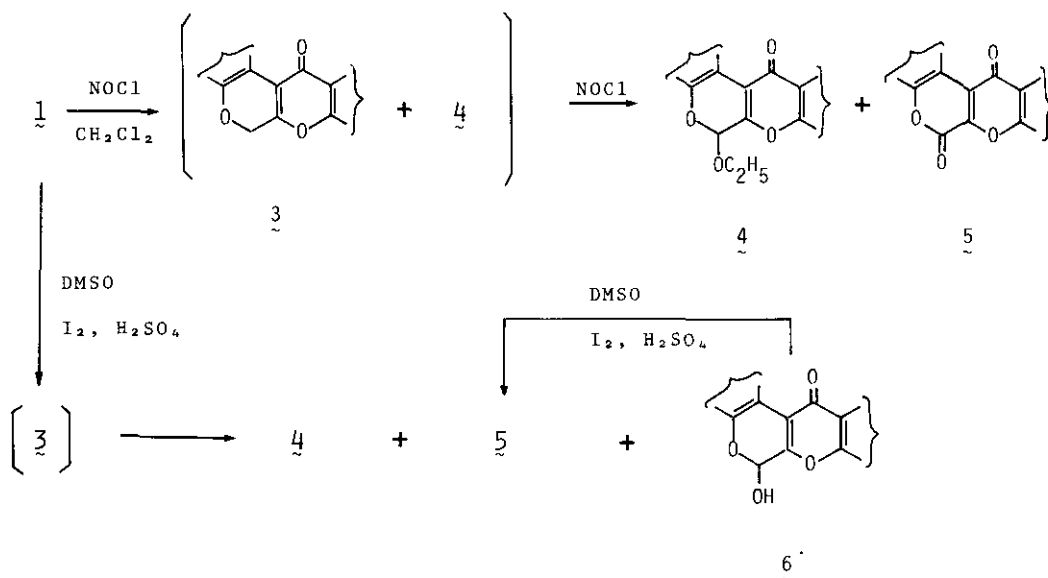


Chart 2

Another attempted oxidation was carried out by a modification of Kornblum oxidation⁴, that is, compound 1 was heated under reflux for 15 h with iodine and concentrated sulfuric acid in dimethyl sulfoxide. After separation by column chromatography, 5 was isolated as a major product in 45.8 % yield, accompanying with 4.6 % yield of 4 and 1.9 % yield of (2R)-12-hydroxy-6a,12a-dehydrorotenone (6).

12-Hydroxy compound 6 was readily converted to 5 under the same oxidative condition

and confirmed as the proposed structure 6 because ^1H -NMR spectrum has been found to be identical with that of amorpholone 1 isolated by Sorensen and co-workers⁵. Although the isolation of 4 seemed to be strange, we speculated that the formation of 4 was resulted from a reaction between compound 6 and ethoxide ion since it seemed reasonable that rotenone (1) solvated by ethanol during the period of extraction from plants, liberated ethanol into the reaction medium when 1 was converted to 3. This speculation was proved chemically under Kornblum condition as follows; namely, rotenone recrystallized in advance from carbon tetrachloride, has never produced compound 4, while compound 4 has been obtained as a major product in more than 50 % yield when freshly prepared 6a,12a-dehydrorotenone (3)⁶ was oxidized in the presence of excess ethanol.

12-Ethoxy compound (4) obtained each time through the oxidative reactions was unknown product and confirmed as the assigned structure 4 on the basis of the following spectral data. ^1H -NMR spectrum showed the appearance of new signals attributed to ethoxy and C-12 methine protons, and ^{13}C -NMR spectrum exhibited the existence of ethoxy group at δ 15.21 and δ 64.53. In addition, mass spectrum showed the molecular ion peak at m/z 436 and the base ion peak at m/z 391 ($\text{M}^+ - \text{OC}_2\text{H}_5$). Rotenonone (5) obtained in this manner was then subjected to condensation with ethylamine in boiling ethanol, however, the reaction proceeded in a different manner from rotenone to afford 2-ethylcarbamoyl-4-ethylimino-8-methylethenyl-3-

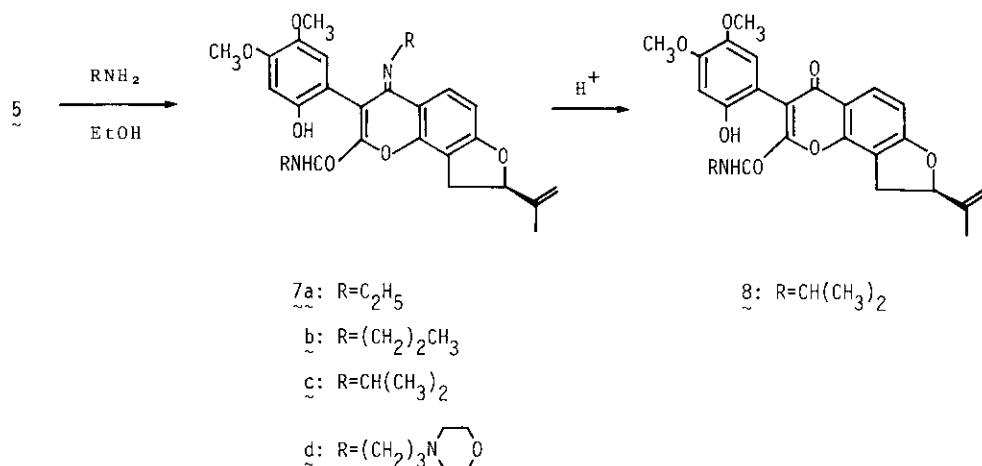


Chart 3

Table 3. 2-Alkylcarbamoyl-4-alkylimino-8-methylethenyl-3-(2-hydroxy-4,5-dimethoxy)phenyl-8,9-dihydro-4H-furo[2,3-h][1]benzopyrans (7a-d)

Compd.	Reaction time (h)	mp(°C) (recryst. solvent)	Appearance	Formula	Analysis(%) Calcd(Found)			Yield (%)
					C	H	N	
7a ~~	4	110-114 (n-hexane)	yellow amorphous powders	C ₂₇ H ₃₀ N ₂ O ₆	67.77 (68.00)	6.32 6.45	5.85 5.78	59
7b ~~	5	163-166 (petr.ether-Et ₂ O)	yellow amorphous powders	C ₂₉ H ₃₄ N ₂ O ₆	68.76 (68.93)	6.77 6.59	5.53 5.41	60
7c ~~	8	130-134 (petr.ether-Et ₂ O)	yellow amorphous powders	C ₂₉ H ₃₄ N ₂ O ₆	68.76 (68.57)	6.77 6.60	5.53 5.39	33
7d ~~	4	112-114 (petr.ether-Et ₂ O)	yellow amorphous powders	C ₃₁ H ₄₈ N ₄ O ₈	65.66 (65.91)	7.15 6.98	8.28 8.41	79

Table 4. ¹H-NMR and MS Data for 7a-d

Compd.	¹ H-NMR(CDCl ₃) δ	MS m/z
7a ~~	1.20 and 1.25(6H, t, 2 x CH ₃ CH ₂), 6.46(1H, br s, NH), 16.44(1H, br s, OH)	478(M ⁺) 406(M ⁺ -CONHC ₂ H ₅)
7b ~~	0.96(6H, t, 2 x CH ₃ CH ₂), 1.67(4H, m, 2 x CH ₃ CH ₂ CH ₂ N), 3.34(4H, t, 2 x CH ₂ N), 6.63(1H, br s, NH), 16.57(1H, br s, OH)	506(M ⁺) 420(M ⁺ -CONH(CH ₂) ₂ CH ₃)
7c ~~	1.18 and 1.20(12H, d, 2 x (CH ₃) ₂ CHN) 3.52 and 4.12(2H, sept, 2 x (CH ₃) ₂ CHN), 6.28(1H, br s, NH), 16.64(1H, br s, OH)	506(M ⁺) 420(M ⁺ -CONHCH(CH ₃) ₂)
7d ~~	8.50(1H, br s, NH), 16.26(1H, br s, OH)	676(M ⁺) 505(M ⁺ -CONH(CH ₂) ₃ N ₂ )

(2-hydroxy-4,5-dimethoxy)phenyl-8,9-dihydro-4H-furo[2,3-h][1]benzopyran (7a) as outlined in Chart 3. The spectral data of 7a were sufficient to assign the structure 7a because ¹H-NMR spectrum showed phenolic hydroxy proton at δ 16.44, and mass spectrum showed the molecular ion peak at m/z 478 and the base ion peak at m/z 406. Similarly, rotenonone (5) was condensed with other primary amines to

Compound 7b and 7c were less toxic and exhibited collagen-induced platelet aggregation as well as aspirin.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Mass spectra were measured with a Hitachi M-52 mass spectrometer. ^1H -NMR spectra were measured with a Japan Electron Optics Laboratory Co., JNM-100 spectrometer using tetramethylsilane as an internal standard. ^{13}C -NMR spectra were obtained with JEOL Model FX Fourier transform nuclear magnetic resonance spectrometer. Abbreviations are as follows; s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; br, broad. Rotenone (1) was offered by Dr. Kengo Kagei, Eisai Tsukuba Research Laboratory and used without recrystallization. General Procedure for the Preparation of [1-(4-Hydroxy-2-methylethenyl-2,3-dihydro-benzofuran-5-yl)-1-(6,7-dimethoxy-2H-chromen-4-yl)methylidene]alkylamines (2a-b) A solution of 1 and 10-15 times molar of amines in 20 ml of EtOH (or CHCl_3) was refluxed for 45-60 h under nitrogen until TLC indicated the disappearance of 1. After removal of solvent, the oily residues were chromatographed on silica gel with CHCl_3 . Analytical, physical and spectral data are summarized in Table 1 and Table 2.

Rotenonone (5)

a) To a suspension of 20 g of 1 in 60 ml of CH_2Cl_2 was added dropwise a solution of 80 ml of CH_2Cl_2 containing 10 g of NOCl at room temperature during 1 h. After the addition was over, the reaction mixture was then stirred for 24 h and evaporated in vacuo below 30°C . On trituration of the residue with Et_2O , 18.3 g of light yellow solids were obtained which were proved to be a mixture of 3 and 12-ethoxy-6a,12a-dehydrorotenone (4) by ^1H -NMR spectrum. Since the R_f values of two products were very close each other, the mixture of two products was used for the subsequent oxidation without isolation. A solution of 18.3 g of the mixture in 60 ml of CH_2Cl_2 was treated with 13 g of NOCl in 90 ml of CH_2Cl_2 for 23 h at room temperature, evaporated in vacuo and chromatographed on silica gel with CHCl_3 as an eluate. Elution of fast moving band afforded (2R)-12-ethoxy-6a,12a-dehydrorotenone (4). Recrystallization from n-hexane- Me_2CO gave 0.66 g (3 %) of light yellow needles, melted at $201-202^\circ\text{C}$. Anal. Calcd for $\text{C}_{25}\text{H}_{24}\text{O}_7$: C, 68.80; H, 5.54. Found: C, 68.71; H, 5.36. IR(KBr) cm^{-1} : 1645(C=O). ^1H -NMR(CDCl_3) δ : 1.26(3H, t, $\text{J}=8$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 3.82(2H, q, $\text{J}=8$ Hz, $\text{CH}_3\text{CH}_2\text{O}$), 5.89(1H, s, C(12)-H).

^{13}C -NMR(CDCl_3) δ : 15.21(q, $\text{CH}_3\text{CH}_2\text{O}$), 64.53(t, $\text{CH}_3\text{CH}_2\text{O}$), 94.49(d, $\text{CH}(\text{OC}_2\text{H}_5)$). MS m/z : 436(M^+), 391($\text{M}^+ - \text{OC}_2\text{H}_5$). Elution of slow moving band afforded rotenonone (5). Recrystallization from $\text{EtOH}-\text{CHCl}_3$ gave 12.5 g (56.5 %) of fine yellow needles, melted at 298-300°C. Spectral data were identical in all respects with authentic 5⁷.

b) A mixture of 5 g (12.7 mM) of 1, 478 mg (1.88 mM) of I_2 , 0.1 ml (1.88 mM) of $\text{c.H}_2\text{SO}_4$ in 40 ml of DMSO was heated at 140°C for 15 h and poured into ice-water. The resulting precipitates were filtered, dissolved in CHCl_3 and chromatographed on silica gel. From the fast moving band, 0.25 g (4.6 %) of 4 and 2.36 g (45.8 %) of 5 were isolated successively. The slow moving band gave 0.1 g (1.9 %) of (2R)-12-hydroxy-6a,12a-dehydrorotenone (6). Recrystallization from CHCl_3 gave fine yellow needles, melted at 227-230°C (decomp.) (lit.⁵ 255-260°C (decomp.)).

General Procedure for the Preparation of 2-Alkylcarbamoyl-4-alkylimino-8-methylethenyl-3-(2-hydroxy-4,5-dimethoxy)phenyl-8,9-dihydro-4H-furo[2,3-h][1]benzopyrans (7a-d).

A suspension of 5 (5.1 mM) and primary amines (10 mM) in 10 ml of EtOH was refluxed under nitrogen for 4-8 h until reactants have dissolved completely. After removal of solvent, the residual oils were chromatographed on silica gel using CHCl_3 as an eluate. Analytical, physical and spectral data are summarized in Table 3 and Table 4.

2-Isopropylcarbamoyl-8-methylethenyl-3-(2-hydroxy-4,5-dimethoxy)phenyl-8,9-dihydro-4H-furo[2,3-h][1]benzopyran-4-one (8)

A solution of 0.1 g of 7c and 10 ml of 5 % HCl was heated at 80°C for 16 h and evaporated in vacuo. The residue was washed with water and recrystallized from n-hexane- CHCl_3 to give colorless prisms, melted at 110-111°C. Yield 1.03 g (95 %). Anal. Calcd for $\text{C}_{26}\text{H}_{27}\text{NO}_7$: C, 67.09; H, 5.85; N, 3.01. Found: C, 67.31; H, 5.69; N, 3.25. IR(KBr) cm^{-1} : 1660(C=O). ^1H -NMR(CDCl_3) δ : 1.24(6H, d, $(\text{CH}_3)_2\text{CHNH}$), 4.16(1H, sept, $(\text{CH}_3)_2\text{CHNH}$), 6.72(1H, br s, NH), 12.36(1H, s, OH). MS m/z : 465(M^+), 379($\text{M}^+ - \text{CONHCH}(\text{CH}_3)_2$).

Catalytic Hydrogenation of 7b

A solution of 0.28 g of 7b in 80 ml of EtOH was hydrogenated over 0.6 g of Raney nickel at 80°C under the pressure of 100 kg/cm^2 . After 20 h, the catalyst was removed by suction and the filtrate was evaporated in vacuo to give light yellow powders which were chromatographed on silica gel with CHCl_3 as an eluate. From

the fast moving band, the major and more polar product was obtained as colorless prisms (0.053 g, 42.3 %), and this product was confirmed as 8-isopropyl-3-(2-hydroxy-4,5-dimethoxy)phenyl-2-propylcarbamoyl-8,9-dihydro-4H-furo[2,3-h][1]benzopyran (9), mp 221-224°C (EtOH). Anal. Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09. Found: C, 69.06; H, 6.98; N, 3.15. 1H -NMR ($CDCl_3$) δ : 1.0 (6H, d, $(CH_3)_2CH$), 4.24 (2H, s, C(4)-H₂), 4.45 (1H, m, C(8)-H), 6.80 (1H, br s, NH), 9.65 (1H, s, OH). MS m/z : 453 (M^+), 367 ($M^+ - CONHC_3H_7$). The minor and slow moving product was obtained as fine colorless needles (0.015 g, 11.9 %) and confirmed as 7-hydroxy-8-isopentyl-3-(2-hydroxy-4,5-dimethoxy)phenyl-2-propylcarbamoyl-3,4-dihydro-2H-chromen-2-ene (10), mp 190-191°C (n-hexane- $CHCl_3$). Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.32; H, 7.49; N, 3.25. 1H -NMR ($CDCl_3$) δ : 0.36-1.80 (5H, m, 2 $\times$ CH_2 and $(CH_3)_2CH$), 0.92 (6H, d, $J=7$ Hz, $(CH_3)_2CH$), 2.60 (2H, t, $CH_2CH_2CH(CH_3)_2$), 4.26 (2H, s, C(4)-H₂), 6.72 (1H, s, NH), 6.80 (1H, br s, C(7)-OH), 9.20 (1H, s, OH of 4,5-dimethoxyphenyl). MS m/z : 455 (M^+), 369 ($M^+ - CONHCH_2CH_2CH_3$).

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