STUDIES ON THE CHEMICAL TRANSFORMATION OF ROTENOIDS. I. RING TRANSFORMATION OF (-)-(6aS,12aS,2R)-ROTENONE INTO BENZOPYRANO[3,4-c]-PYRAZOLES

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Abstract——Rotenone (1) underwent the ring transformation into 3-substituted 1-(2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-1,9b,2,3,3a,4-hexahydro-[1]benzopyrano[3,4-c]pyrazol-1-enes (4a-e) when treated with hydrazines in the strong basic medium. The stereochemistry of the products was established by ^{1}H-NMR spectra confirming the cis B/C fusion.

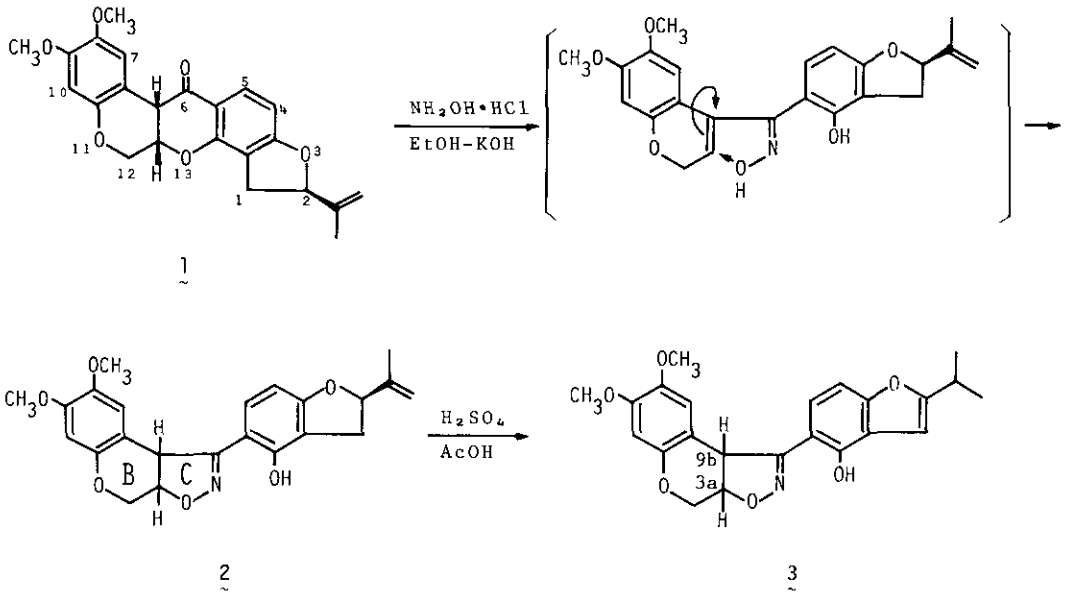
(-)-(6aS,12aS,2R)-Rotenone (1) is an abundant natural product, occurring in the roots of tropical plants belonging to Leguminosae family, and is known to be useful insecticide and nonpersistent in the environment.

As is obvious from its structure, the hetero atoms of rotenone are only oxygens. Therefore, it seemed interest from a pharmacological point of view to investigate the chemical transformation of rotenone into other heterocyclic ring systems containing nitrogens.

In this paper we wish to report our results concerning the ring convertion of rotenone into benzopyrano[4,3-d]isoxazol-1-enes (2 and 3) and benzopyrano[3,4-c]-pyrazol-1-enes (4a-e and 5a-b) involving the stereochemistry of B/C fusion.

An earlier study[1] of the reaction between rotenone and hydroxylamine in the presence of sodium hydroxide has reported an formation of 1-(4-hydroxy-2-methylethenyl-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-1,9b,3a,4-tetrahydro-2*H*-[1]-benzopyrano[4,3-d]isoxazol-1-ene (2), of which structure was determined by Crombie and co-workers[2] on the basis of infrared spectrum in 1961. However, the stereochemistry with regard to the B/C ring junction has not been mentioned. In order to

clarify the stereochemistry, we repeated the same reaction under a modified condition. A suspension of 1 (2.5 mM) and hydroxylamine hydrochloride (25 mM) in 50 ml of 2.8 % ethanolic potassium hydroxide was refluxed for 3.5 h and evaporated to dryness. The residue was washed with 5 % aqueous acetic acid and extracted with chloroform. Removal of chloroform deposited powders which were chromatographed on silica gel to provide product 2 as an isolable single compound. The formation of 2 could be arised from the initial cleavage between C-12a and O-13 linkage of 1 and subsequent ring closure via an intermediate as outlined in Chart 1.



1 2 3

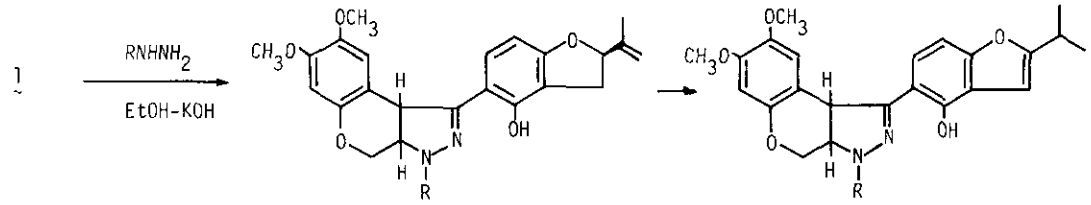
Chart 1

The approach to the stereochemistry by ^{1}H-NMR spectrum was uncertain because the multiplets from B/C ring system became partly obscured by signals from dihydropyran and isopropenyl substituent. Therefore, the dihydropyran ring was isomerized by treatment with a mixture of concentrated sulfuric acid and glacial acetic acid at 90°C for 5 min to give 1-(4-hydroxy-2-isopropylbenzofuran-5-yl)-7,8-dimethoxy-1,9b,3a,4-tetrahydro-2H-[1]benzopyrano[4,3-d]isoxazol-1-ene (3) (Table 1). ^{1}H-NMR spectrum of 3, as summarized in Table 2, showed the 9b-proton as a doublet centered at δ 4.86, coupled to the 3a-proton with J=8 Hz. The 3a-proton appeared at δ 5.04 and was coupled to the 9b-proton and broadened by the small couplings to C-4 methylene protons. The coupling constant for the ring junction was thus 8 Hz, which is clearly too small for a trans-diaxial arrangement of these hydrogens,

but is consistent with cis relationship[3].

The two 4-protons formed an AB quartet (J= 12 Hz). The low field doublet was split by coupling to the 3a-proton (J=2 Hz) and the higher field doublet was broadened by the small coupling to 3a-proton (J=1 Hz). In this conformation, the dihedral angles between 3a-proton and two 4-protons are calculated from the Karplus equation[4] to be approximately 68° and 52°, which were in good agreement with values read from a molecular model. In this manner, we concluded that compound 2 has a cis B/C fusion, and the intence steric hindrance between A ring and dihydrobenzofurano substituent resulted in the preferential formation of the cis isomer.

With these results in mind, we have next been engaged in the reactions of 1 with



4a: R=H
b: R=CH3
c: R=CH2CH2OH
d: R=phenyl
e: R=tolyl

5a: R=H
b: R=CH3

Chart 2

several hydrazines under the same conditions as shown in Chart 2.

A suspension of 1 (7.6 mM) and hydrazines (or hydrochloride)(76 mM) in 50 ml of 8.5 % ethanolic potassium hydroxide was refluxed for 3-5 h and worked up as described in the preparation of 2 to provide 3-substituted 1-(2-methylethenyl-4-hydroxy-2,3-dihydrobenzofuran-5-yl)-7,8-dimethoxy-1,9b,2,3,3a,4-hexahydro-[1]benzopyrano[3,4-c]pyrazol-1-enes (4a-e) (Table 1).

Compound 4a and 4b also easily underwent isomerization with sulfuric acid to give 1-(4-hydroxy-2-isopropylbenzofuran-5-yl)-7,8-dimethoxy- (5a) and 1-(4-hydroxy-2-isopropylbenzofuran-5-yl)-3-methyl-1,9b,2,3,3a,4-hexahydro-[1]benzopyrano[3,4-c]-pyrazol-1-ene (5b) respectively.

As is obvious from Table 2, the ^{1}H-NMR spectra of 4a-e and 5a-b exhibit the quite

Table 1 [1]Benzopyrano[4,3-d]isoxazol-1-enes (2-3) and [1]benzopyrano-[3,4-c]pyrazol-1-enes (4a-e and 5a-b)

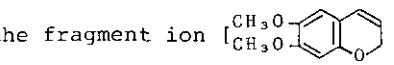
Comp. No	mp(°C) (recryst. solv.)	Appearance	Yield (%)	$[\alpha]_D^{24}$ in $CHCl_3$ (c)	MS m/z
2	215-217[a] (EtOH-Me_2CO)	colorless needles	66	-37.7 (0.72)	409(M^+) 192
3	199-201 (EtOH)	colorless prisms	98	———	409(M^+) 192
4a	242-244 (CH_2Cl_2)	colorless prisms	87	-34.6 (0.74)	408(M^+) 192
4b	254-256 (EtOAc-Et_2O)	colorless needles	84	-40.5 (0.54)	422(M^+) 192
4c	198-200 (EtOH)	colorless plates	71	-41.0 (0.54)	452(M^+) 192
4d	205-206 (EtOAc)	colorless prisms	85	-54.5 (0.60)	484(M^+) 192
4e	230-233 (EtOAc)	colorless prisms	70	-66.0 (0.52)	498(M^+) 192
5a	257-260 (EtOH)	colorless prisms	90	———	408(M^+) 192
5b	210-212 (EtOH)	colorless needles	95	———	422(M^+) 192

a) Lit[2], 210-211°

Table 2 ^{1}H-NMR spectra, δ ppm (Hz) in $CDCl_3$

Comp. No	H-3a	H-9b	H-4	H-4	OH	ΔOCH_3	Others
2	———	4.74 (d,8)	4.06 (dd,12,1)	4.58 (dd,12,2)	9.74	0.18	
3	5.04 (qq,8,2,1)	4.86 (d,8)	4.08 (dd,12,1)	4.62 (dd,12,2)	9.96	0.24	1.34($(CH_3)_2CH$) 6.50(furan)
4a	4.55 (qq,8,2,1)	4.21 (d,8)	4.15 (dd,12,1)	4.38 (dd,12,2)	11.06	0.22	5.70(NH)
4b	4.60 (qq,8,2,1)	———	4.15 (dd,12,1)	4.39 (dd,12,2)	11.08	0.22	2.55($N-CH_3$)
4c	4.68 (qq,8,2,1)	———	4.23 (dd,12,1)	4.50 (dd,12,2)	11.0	0.24	
4d	4.85 (qq,8,2,1)	4.37 (d,8)	4.16 (dd,12,1)	4.62 (dd,12,2)	10.92	0.19	7.20(phenyl)
4e	4.85 (qq,8,2,1)	4.27 (d,8)	4.20 (dd,12,1)	4.61 (dd,12,2)	10.96	0.20	2.32(CH_3) 7.12(phenyl)
5a	4.63 (qq,8,2,1)	4.21 (d,8)	4.15 (dd,12,1)	4.38 (dd,12,2)	11.06	0.29	1.32($(CH_3)_2CH$) 6.50(furan)
5b	4.72 (qq,8,2,1)	———	4.22 (dd,12,1)	4.39 (dd,12,2)	11.37	0.30	2.55($N-CH_3$) 6.52(furan)

identical coupling patterns and coupling constants of B/C ring junction as that of compound 2 and 3. Therefore, we decided that compounds 4a-e have the cis B/C fusions.

The noticeable characteristics in common with newly synthesized products are seen in the ^{1}H-NMR and mass spectra, that is, the chemical shift differences between two methoxy groups are separated by up to 0.30 ppm (rotenone: 0.04 ppm) on account of the magnetical unequivalency, and the mass spectra show the base ion peak at m/z 192 $[C_{11}H_{12}O_3]^+$, probably due to the fragment ion  .

The pharmacological investigations on the products are now in progress.

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