UDC 547.655.6.07 : 547.659.1

159. **Tsutomu Momose and Shujiro Goya** : Studies on Tetralin Derivatives. XI.[*1] Synthesis of 5-Hydroxy-6-acyl-1,4-naphthoquinones.

(*Pharmaceutical Institute, Medical Faculty, University of Kyushu*[*2])

In the previous papers[1] of this series, 2-alkyl-8-hydroxy-1,4-naphthoquinones were shown to have some bacteriostatic activities *in vitro* and to form characteristic chelate compounds with some metallic ions. In the present wark, 5-hydroxy-6-acyl-1,4-naphthoquinones were synthesized to study their bacteriostatic activity and behavior to metallic ions. As a starting material 5,8-dimethoxy-1-naphthol, which was easily obtained by the dehydrogenation of 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalenone, was used. A schematic diagram of the synthesis is shown in Chart 1.

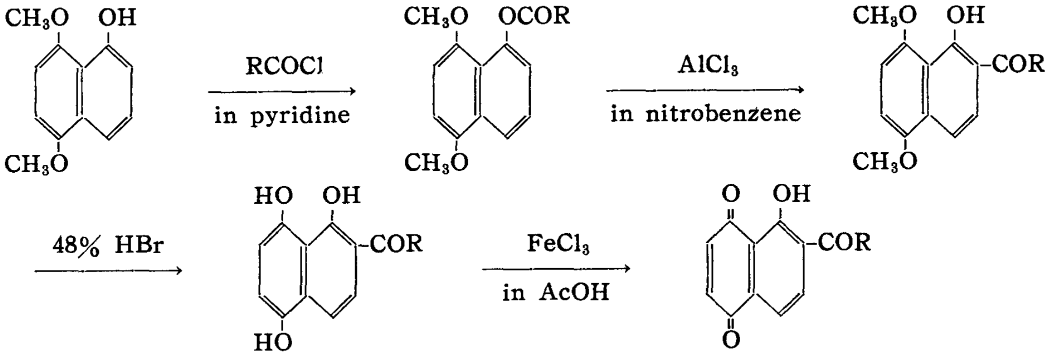
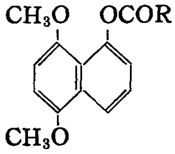


Chart 1.

Acylation of 5,8-dimethoxy-1-naphthol was easily carried out in pyridine with the corresponding acid chloride and the resulting acylates are listed in Table I. Only the acetyl derivative is found in the past literature[2] and it was synthesized by another method, checked by its melting point.

The Fries rearrangement at a room temperature of 5,8-dimethoxy-1-naphthol acylate gave only one crystalline acyl compound, though there are two possibilities of

Table I.



R	b.p. (°C/mm. Hg)	Formula	Analyses (%) Calcd. C	Calcd. H	Found C	Found H
C_2H_5	185/6	$C_{15}H_{16}O_4$	69.21	6.21	69.04	6.24
C_3H_7	168/4.5*	$C_{16}H_{18}O_4$	70.05	6.61	69.20	6.33
C_4H_9	175/3	$C_{17}H_{20}O_4$	70.81	6.99	70.58	7.05
C_5H_{11}	162/2	$C_{18}H_{22}O_4$	71.50	7.33	70.78	7.53
C_6H_{13}	165/2	$C_{19}H_{24}O_4$	72.12	7.65	71.99	7.79
C_7H_{15}	175/2	$C_{20}H_{26}O_4$	72.70	7.93	72.87	8.06
C_8H_{17}	212/2	$C_{21}H_{28}O_4$	73.22	8.19	72.46	8.17
C_9H_{19}	235/3	$C_{22}H_{30}O_4$	73.71	8.44	73.48	8.43

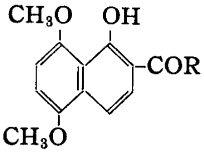
* m.p. 56.5° from petr. ether.

[*1] Part X. T. Momose, S. Goya : This Bulletin, **7**, 849(1959).
[*2] Katakasu, Fukuoka (百瀬 勉, 合屋周次郎).
1) T. Shoji : Yakugaku Zasshi, **79**, 1041, 1044(1959).
2) M. Asano, J. Hase : Yakugaku Zasshi, **63**, 88(1943).

migration of the acyl group, to the *ortho*- and *para*-positions. A few instances have been reported in the literature concerning the same reaction of substituted naphthol acylates. An acetyl group in 1,4-dihydroxynaphthalene diacetate migrated to the *ortho*-position[3] and the same group in 1-acetoxy-2-methoxynaphthalene migrated to the *para*-position.[4] In methyl 1- and 3-acetoxy-2-naphthoate, the acetyl group migrated to *para*- and *ortho*-positions,[5] respectively.

In the rearrangement of the present series, it was concluded from the infrared spectra of resulting acylated compounds that the acyl group migrates to the *ortho*-position. In acetyl compounds, for example, the carbonyl group exhibited its absorption band at 6.16 μ (1623 cm^{-1}) in Nujol mull, and the hydroxyl band was superimposed on the absorption of Nujol, indicating that the two groups were chelated. This conclusion was confirmed by the fact that 1-hydroxy-2-acetyl-5,6,7,8-tetrahydronaphthalene showed a carbonyl band at 6.14 μ (1629 cm^{-1}) without hydroxyl absorption in Nujol mull, whereas 1-hydroxy-4-acetyl-5,6,7,8-tetrahydronaphthalene showed its carbonyl and hydroxyl bands respectively at 6.06 μ (1650 cm^{-1}) and 2.94 μ (3401 cm^{-1}). The 2-acylated compounds so obtained are shown in Table II.

Table II.



R	m.p. (°C)	Crystal form (recrystd. from)	Yield (%)	Formula	Analyses (%) Calcd. C	H	Found C	H
CH_3	129	yellow prisms (benzene)	33	$C_{14}H_{14}O_4$	68.28	5.73	68.66	6.06
C_2H_5	146~147	〃	28	$C_{15}H_{16}O_4$	69.21	6.21	68.85	6.64
C_3H_7	120	yellow needles (EtOH)	34	$C_{16}H_{18}O_4$	70.05	6.61	70.37	6.84
C_4H_9	123~124	〃	47	$C_{17}H_{20}O_4$	70.81	6.99	71.03	7.24
C_5H_{11}	104	yellow needles (MeOH)	56	$C_{18}H_{22}O_4$	71.50	7.33	71.61	7.68
C_6H_{13}	87	〃	24	$C_{19}H_{24}O_4$	72.12	7.65	72.32	7.86
C_7H_{15}	83	〃	27	$C_{20}H_{26}O_4$	72.70	7.93	72.41	8.21
C_8H_{17}	80	〃	25	$C_{21}H_{28}O_4$	73.22	8.19	73.56	8.30
C_9H_{19}	80	〃	29	$C_{22}H_{30}O_4$	73.71	8.44	73.71	8.41

Demethylation of 2-acyl-5,8-dimethoxy-1-naphthols with hydriodic acid only gave a resinous substance. This result might be caused by the nature of the resulting triphenols which are easily oxidized. The same reaction with hydrobromic acid in the presence of phenol was successfully carried out except in the acetyl and propionyl derivatives, which gave resinous substances in all conditions tried. 2-Acyl-1,5,8-trihydroxynaphthalenes thus obtained are shown in Table III.

These trihydroxyl compounds were easily oxidized by ferric chloride to 5-hydroxy-6-acyl-1,4-naphthoquinones in acetic acid solution. The quinones obtained are shown in Table IV. It is of interest to note that the melting point of quinones of even number of carbons in the side chain was higher than those with odd numbers, in agreement with the results obtained in 2-alkyl-8-hydroxy-1,4-naphthoquinones.[1]

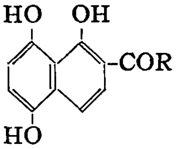
Bacteriostatic activitiy and metal chelate of the quinones will be reported in the near future.

The authors are indebted to Mr. M. Shido and Miss S. Tada for microanalyses. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education.

---

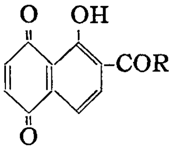
[3] C. J. P. Spruit: Rec. trav. chim., 66, 655(1947) (C. A., **42**, 1921(1948)).
[4] T. Bisanz: Roczniki Chem., **30**, 111(1956) (C. A., **51**, 323(1957)).
[5] G. G. Joshi, N. M. Shah: J. Indian Chem. Soc., **31**, 223(1954) (C. A., **49**, 9543(1955)).

Table III.



R	m.p. (°C)	Crystal form (recrystd. from)	Formula	Analyses (%)			
				Calcd.		Found	
				C	H	C	H
C_3H_7	189~190	orange yellow needles (benzene)	$C_{14}H_{14}O_4$	68.28	5.23	68.03	5.85
C_4H_9	141,5	〃	$C_{15}H_{16}O_4$	69.23	6.20	69.23	6.47
C_5H_{11}	136.5	orange yellow plates (benzene+petr. benzine)	$C_{16}H_{18}O_4$	70.05	6.61	70.07	6.64
C_6H_{13}	134	〃	$C_{17}H_{20}O_4$	70.81	6.99	70.96	7.08
C_7H_{15}	137	〃	$C_{18}H_{22}O_4$	71.50	7.33	71.60	7.44
C_8H_{17}	131	〃	$C_{19}H_{24}O_4$	72.12	7.65	71.88	7.67
C_9H_{19}	142	orange yellow needles (benzene+petr. benzine)	$C_{20}H_{25}O_4$	72.70	7.93	72.25	8.35

Table IV.



R	m.p. (°C)	Crystal form (recrystd. from)	Formula	Analyses (%)			
				Calcd.		Found	
				C	H	C	H
C_3H_7	88~89	orange needles (petr. ether)	$C_{14}H_{12}O_4$	68.85	4.95	68.56	5.13
C_4H_9	83~84	〃	$C_{15}H_{14}O_4$	69.77	5.46	69.79	5.47
C_5H_{11}	91~92	〃	$C_{16}H_{16}O_4$	70.57	5.92	70.49	6.07
C_6H_{13}	72~72.5	〃	$C_{17}H_{18}O_4$	71.31	6.34	71.52	6.35
C_7H_{15}	96~97	〃	$C_{18}H_{20}O_4$	71.97	6.71	71.69	6.90
C_8H_{17}	64~65	〃	$C_{19}H_{22}O_4$	72.59	7.05	72.61	7.31
C_9H_{19}	73~74	〃	$C_{20}H_{24}O_4$	73.14	7.36	73.36	7.32

Experimental

5,8-Dimethoxy-1-naphthol Esters (Table I)—To a solution of 5,8-dimethoxy-1-naphthol in dehyd. pyridine, excess acid chloride was added under cooling, and allowed to stand over night. The mixture was poured into 10% H_2SO_4 and extracted with ether. The ether solution was washed with 5% $NaHCO_3$, dried over anhyd. Na_2SO_4, and evaporated. The remaining acylate was distilled *in vacuo* to a colorless oil.

2-Acyl-5,8-dimethoxy-1-naphthol (Table II)—To a solution of 5,8-dimethoxy-1-naphthol acylate in 7 volumes of nitrobenzene, 1.2 times the calculated amount of $AlCl_3$ was added under cooling with ice and allowed to stand at room temperature (15~20°) for 24 hr. The reaction mixture was poured into ice and HCl, and the separated nitrobenzene was distilled off by steam. The benzene extract of the remaining solution was washed with H_2O, dried over anhyd. Na_2SO_4, and poured through a short column of Al_2O_3. The benzene eluate was evaporated and the remaining crystals were recrystallized from benzene or EtOH.

2-Acyl-1,5,8-trihydroxynaphthalene (Table III)—2-Acyl-5,8-dimethoxy-1-naphthol was boiled in CO_2 atmosphere for 40 min. with an excess of 48% HBr, to which a small amount of phenol was added. After dilution with H_2O, separated crystals were collected, washed successively with 5% $NaHCO_3$ and H_2O, and recrystallized from benzene or benzene+petr. benzine. Yield, 60~85%.

5-Hydroxy-6-acyl-1,4-naphthoquinone (Table IV)—To a solution of 2-acyl-1,5,8-trihydroxynaphthalene in AcOH, an aqueous solution of calculated amount of $FeCl_3$ was added and the mixture was heated on a water bath for 30 min. The mixture was diluted with H_2O, neutralized with $NaHCO_3$, and extracted with benzene. The benzene extract was passed through a short column of Al_2O_3, the effluent was evaporated, and the residue was recrystallized from petr. ether to orange crystals.

Infrared spectra were measured by a Koken Model DS-301 recording infrared spectrophotometer using NaCl prism.

Summary

The Fries rearrangement of 5,8-dimethoxy-1-naphthol acylate gave 2-acyl-5,8-dimethoxy-1-naphthol in a yield of 24~56%. These acyl compounds were demethylated and oxidized to 5-hydroxy-6-acyl-1,4-napthoquinones.

(Received May 15, 1959)