STUDIES ON MITOMYCINS. V

SYNTHESIS OF INDOLEQUINONE AND THEIR ACTIVITIES

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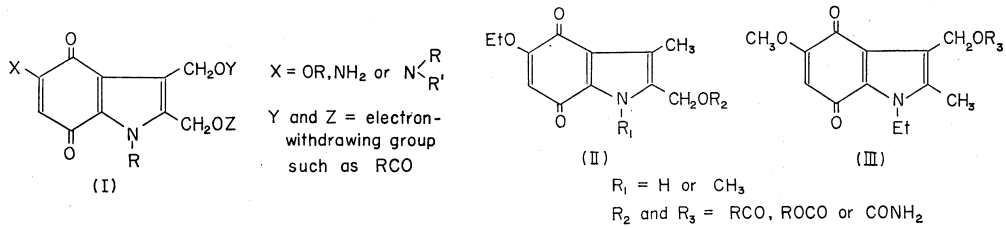
Indolequinones postulated as essential structure for activity of mitomycin were synthesized and examined for their antibacterial activities. Acyl esters of 3-hydroxymethylindole(4, 7)dione showed strong activity against Gram-positive bacteria but those of 2-hydroxymethylindolequinone did not.

In the previous paper[1], we postulated that the essential structure for activity of the mitomycins was the indolequinone as shown in I. In this paper, we wish to report the synthesis of 2-hydroxymethylindolequinone (4,7) derivatives (II) and 3-hydroxymethylindolequinone (4,7) derivatives (III) and their antibacterial activities.



TEUBER and THALER[2] has already reported the preparation of indolequinone and recently ALLEN *et al.*[3], used it in the synthesis of mitomycin antibiotics. In both two, indolequinone (4,7) was prepared by oxidation with FREMY's salt.

Authors prepared the 2-hydroxymethylindolequinone (4,7) derivatives (II) and 3-hydroxymethylindolequinone (4,7) derivatives (III) as shown in Charts 1 and 2.

I. Synthesis of 2-Hydroxymethylindolequinone (4,7) Derivatives

Ethyl-3-methyl-5-ethoxy-indole-2-carboxylate (**IVa**) was prepared from *p*-nitrophenetol and ethylacetoacetate by FISCHER's indole synthesis. Nitration of **IVa** was accomplished in good yield with quantitative fuming nitric acid in a mixture of acetic acid and acetic anhydride. If only an acetic acid was used as solvent, unreacted compound remained and purification of **V** was difficult. The location of the nitro group was established by the presence of two doublets, typical of ortho aromatic protons, in the NMR spectrum.

Selective reduction of ethyl carboxylate of **V** was achieved by using a limited amount of $LiAlH_4$. If excess $LiAlH_4$ was used, it gave several by-products formed by the reduction of nitro group. Catalytic hydrogenation of **VI** with Pd-C gave **VII**,

Chart 1.

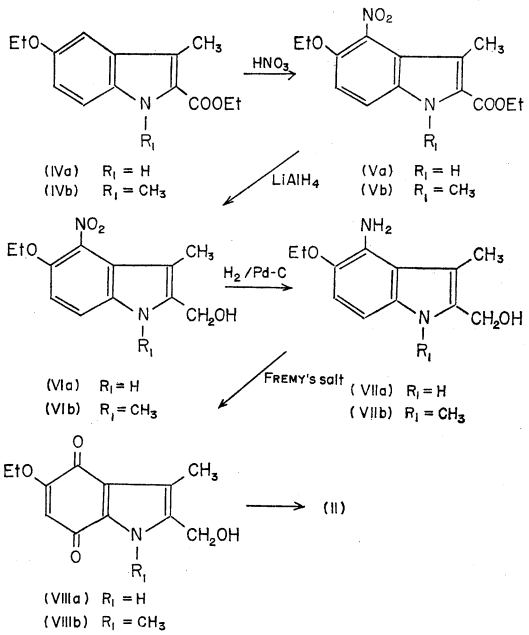
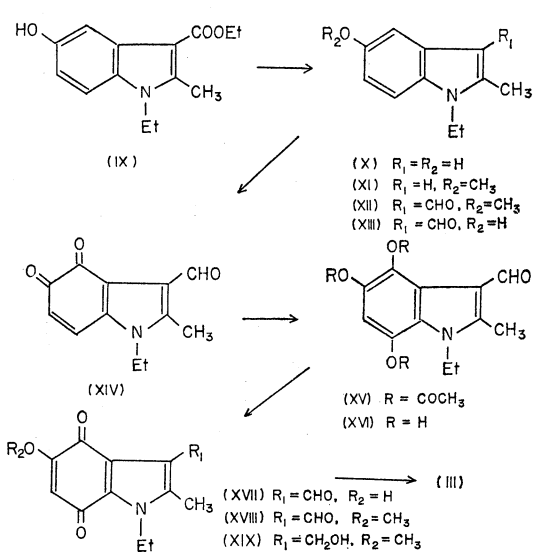


Chart 2.



which was unstable and oxidized with potassium nitrosodisulfonate to produce *p*-quinone (**VIIIa**). 1-Methyl-quinone (**VIIIb**) was prepared by the same procedure from **IVb** which was obtained by the methylation of **IVa** with dimethylsulfate.

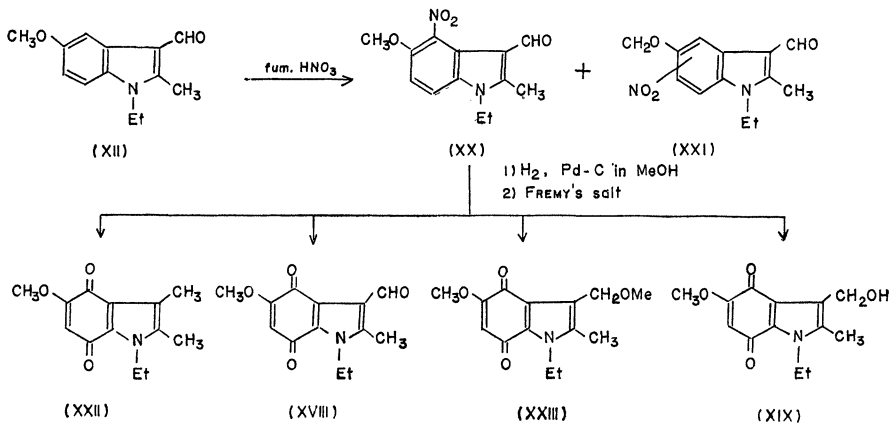
II. Synthesis of 3-Hydroxymethylindolequinone (4,7) Derivatives

3-Hydroxymethylindolequinone (4,7) derivatives were prepared as shown in Chart 2 by the method of ALLEN *et al.*[3c], who had prepared 2,3-dihydro-9-hydroxymethyl-7-methoxy-6-methyl-1-H. pyrrolo (1,2a) indole 5,8 dione.

Starting material **IX** of this series was prepared from *p*-benzoquinone and ethyl β-aminocrotonate by the method of NENITZESCU[4]. When boiled with conc. HCl or 4 N NaOH, **IX** was decarboxylated to form **X**, which was transformed into methyl derivatives (**XI**). Pure **XI** (m.p. 21°C) was identical with that of GRINEV'S[5] product which had been obtained by another synthetic method. Formylation of **XI** was accomplished by VILSMEYER-HAACK's method[6] with phosphoroxychloride and dimethylformamide. Cleavage of methoxy group of **XII** with aluminum chloride in refluxing xylene gave **XIII**. Potassium nitrosodisulfonate oxidation of **XIII** gave orthoquinone (**XIV**). Thiele acetoxylation of **XIV** gave triacetate **XV** using acetic anhydride and boron-fluoride. Hydrolysis of **XV** in dil. NaOH followed by air oxidation gave **XVI**, which was methylated with diazomethane to give the para-quinone (**XVII**). REMERS *et al.*[3d], reported that hydrolysis of triacetoxy compound was unsuccessful when position 6 of 1-H-pyrrolo (1,2a) indole was hydrogen. But in our experience, hydrolysis was successful and the *p*-quinone was identified as **XVIII** by elemental analysis, nmr spectrum and infrared spectrum. Reduction of **XVIII** with $NaBH_4$ followed by oxidation with $FeCl_3$ gave **XIX**.

Our quinone **XIX** (m.p. 199~201°C) was different in melting point than REMER'S[3e]

Chart 3.



product (m.p. 164~165°C) which was obtained by another synthetic method. Our quinone was identified by elemental analysis and infrared spectrum and nmr spectrum.

Another synthetic method for *p*-quinone (**XIX**) was also examined as shown in Chart 3. Nitration of **XII** with quantitative fuming nitric acid in acetic acid gave a mixture of two mononitro compounds, (**XX** and **XXI**). One was identified as the 4-nitro compound (**XX**) by its nmr spectrum, which showed two doublets, typical of ortho aromatic protons. (The other was an isomer of **XXI**, but location of nitro group could not be determined by nmr spectrum, which showed two aromatic protons as singlet).

Reduction of **XX** with iron powder in acetic acid followed by oxidation with potassium nitrosodisulfonate produced *p*-quinone (**XVIII**), which was identical with the substance prepared from the orthoquinone.

When catalytic reduction was performed with Pd-C, four *p*-quinones were formed by thin-layer chromatography. After purification with silica gel chromatography, four crystalline compounds were obtained.

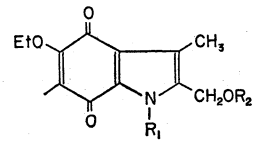
The one was 3-methyl *p*-quinone (**XXII**), the second was 3-formyl *p*-quinone (**XVIII**), the third was methyl ether of **XIX** and the fourth was 3-hydroxymethyl *p*-quinone **XIX**, identified by nmr spectrum.

Acyloxy derivatives of **VIII** or **XIX** were prepared by acylchloride and pyridine or acylanhydride and pyridine. Phenylcarbonate or ethyl carbonate of **VIII** or **XIX** was prepared by chlorophenylcarbonate or chloroethylcarbonate in pyridine. Ammonolysis of phenylcarbonate gave the carbamoyl derivatives.

III. Antibacterial Activities

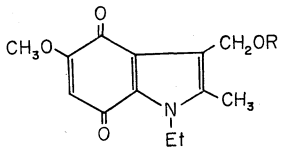
The derivatives prepared as described above were subjected to antibacterial testing with the results shown in Tables 1 and 2. Derivatives of 3-hydroxymethylindolequinone (4,7) showed marked activity against Gram-positive organisms but no activity against Gram-negative organisms. On the other hand, derivatives of 2-hydroxymethylindolequinone (4,7) showed no activity against Gram-positive or negative bacteria. These results indicated that the protonation of methylene in 3-position of

Table 1. Antibacterial activities of 2-hydroxymethylindolequinone (4, 7) derivatives



No.	R_1	R_2	M.I.C. in mcg/ml				
			Gram-positive bacteria			Gram-negative bacteria	
			B. subtilis ATCC 6633	*S. aureus* 209P	*S. lutea* PCI 1001	*E. coli* K-12	*E. coli* B(H)
1	H	H	>100	25	>100	25	25
2	H	$COCH_3$	>100	>100	>100	>100	>100
3	H	$COCH{=}CHCH_3$	>100	>100	>100	>100	>100
4	H	COC_6H_5	>100	>100	>100	>100	>100
5	H	$COCH_2Cl$	>100	>100	>100	>100	>100
6	H	$COCH_2Br$	>100	>100	>100	>100	>100
7	H	$COCHCl_2$	>100	>100	>100	>100	>100
8	H	$COOC_6H_5$	>100	>100	>100	>100	>100

Table 2. Antibacterial activities of 3-hydroxymethyl-indolequinone (4, 7) derivatives



R	M.I.C. in mcg/ml					
	Gram-positive bacteria				Gram-negative bacteria	
	S. lutea PCI 1001	*S. aureus* 209P	*B. sutilis* ATCC 6633	*S. aureus* K (resistant)	*E. coli* B(H)	*P. aeruginosa*
H	>100	>100	>100	>100	>100	>100
$COCH_3$	0.766	0.192	0.192	0.192	12.25	> 50
COC_2H_5	2.5	1	1	0.5	25	>100
CO-*n*-C_3H_7	1.531	0.192	0.192	0.766	25	> 50
$COCH{=}CHCH_3$	1.531	0.766	0.766	0.766	25	> 50
COC_6H_5	1.531	1.531	0.766	0.766	> 50	> 50
$COCH_2Cl$	2.5	10	10	1	10	> 50
$COCHCl_2$	50	50	50	50	> 50	> 50
$COCH_2Br$	3.063	3.063	1.531	1.531	> 50	> 50
COOEt	50	50	50	50	> 50	> 50
$COOC_6H_5$	0.766	1.531	0.766	50	25	> 50
$CONH_2$	1.531	0.191	0.093	0.383	6.125	> 50
$CONHCH_3$	1.531	0.383	0.766	3.063	12.25	> 50

indole is necessary for antibacterial activity, but that similar reactivity at the 2-position does not yield activity.

Experimental

Ethyl-5-ethoxy-3-methyl-4-nitro-indole-2-carboxylate (**Va**) To a solution of 5 g of ethyl-5-ethoxyindole-2-carboxylate (**IVa**) in a mixture of 50 ml of acetic acid and 50 ml of acetic anhydride was added 1 ml of fuming nitric acid. After two hours at room

temperature water was added slowly and the precipitate was collected. Recrystallization from ethanol gave 4.5 g (76.3 %) of **Va** m.p. 177~178°C. nmr: τ 2.6, 2.95 two doublets (ortho aromatic protons); 5.65, 5.80 two quartets ($-CH_2-$); 7.57 singlet (3-methyl); 8.62, 8.66 two triplets (CH_3-). Anal. Calcd. for $C_{14}H_{16}N_2O_5$ (292.28): C 57.53, H 5.52, N 9.59. Found: C 57.41, H 5.42, N 9.62.

5-Ethoxy-2-hydroxymethyl-3-methyl-4-nitroindole (**VIa**) To a mechanically stirred solution of 4 g of **Va** in anhydrous tetrahydrafuran was added a suspension of 600 mg of $LiAlH_4$ in anhydrous ether during about 1 hour at room temperature. After extraction with organic solvent and drying with anhydrous Na_2SO_4, the solution was evaporated. Recrystallization from dil. ethanol gave 3.3 g (96.4 %) of yellow crystals (m.p. 184~185°C). Anal. Calcd. for $C_{12}H_{14}N_2O_4$ (250.25): C 57.79, H 5.64, N 11.20. Found: C 57.74, H 5.69, N 10.86.

5-Ethoxy-2-hydroxymethyl-3-methylindolequinone (4,7) (**VIIIa**) A solution of 3 g of **VIa** in 100 ml of methanol was treated with hydrogen with 600 mg of 5 % Pd-C at room temperature and atmospheric pressure. After absorption of quantitative hydrogen, catalyst was filtered off and filtrate was oxidized with a solution of 8 g of potassium nitrosodisulfonate in 200 ml of water and 200 ml of 1/6 M KH_2PO_4 under the mechanical stirring. After 1 hour, it was extracted with organic solvent and dried. After the evaporation precipitate was recrystallized from ethanol to give 1.5 g (50.7 %) of reddish orange needles. m.p. 213°C, IR, 3300 cm^{-1} ($-CH_2OH$), 3200 (=NH), 1675, 1635 (=CO). Anal. Calcd. for $C_{12}H_{13}NO_4$ (235.23): C 61.27, H 5.57, N 5.96. Found: C 61.34, H 5.60, N 5.76.

Ethyl-5-ethoxy-1,3-dimethylindole-2-carboxylate (**IVb**) Methylation of **IVa** with dimethylsulfate in acetone and potassium hydroxide solution gave **IVb**, pale yellow needles. m.p. 68~68.5°C. Anal. Calcd. for $C_{15}H_{19}NO_3$ (261.31): C 68.94, H 7.33, N 5.36. Found: C 69.28, H 7.83, N 5.50.

Ethyl-5-ethoxy-1,3-dimethyl-4-nitroindole-2-carboxylate (**Vb**) 693 mg of fuming nitric acid was added to a solution of 2.61 g of **IVb** in 30 ml of acetic acid. After 2 hours water was added to this solution and resulting precipitate was filtered and recrystallized from ethanol to give 1.7 g (55.5 %) of yellow crystals. m.p. 82~85°C. nmr: τ 2.68, 2.97 two doublets (ortho aromatic protons), 5.85, 5.92 two quartets ($-CH_2-$), 6.10 ($N-CH_3$), 7.62 ($C-3-CH_3$) 8.53, 8.62 two triplets (CH_3-). Anal. Calcd. for $C_{15}H_{18}N_2O_5$ (306.31): C 58.81, H 5.92, N 9.15. Found: C 59.28, H 6.12, N 9.18.

5-Ethoxy-2-hydroxymethyl-1,3-dimethyl-4-nitroindole (**VIb**) Selective reduction of **Vb** with $LiAlH_4$ according to the procedure of **VIa** gave 76.2 % of yellow needles (m.p. 142~143°C after two recrystallization from ethanol). Anal. Calcd. for $C_{13}H_{16}N_2O_4$ (264.27): C 59.08, H 6.10, N 10.60. Found: C 59.12, H 6.07, N 10.10.

5-Ethoxy-2-hydroxymethyl-1,3-dimethyl-indolequinone (4,7) (**VIIIb**) Catalytic reduction of **VIb** followed by oxidation with potassium nitrosodisulfate according to procedure of **VIIIa** gave 55.2 % of reddish orange needles after recrystallization from ethanol. m.p. 184.5~185.5°C. IR 3300 cm^{-1} ($-CH_2OH$), 1680, 1630 (=CO). Anal. Calcd. for $C_{13}H_{15}NO_4$ (249.26): C 62.64, H 6.07, N 5.62. Found: C 62.51, H 6.05, N 5.71.

Synthesis of 1-Ethyl-3-hydroxymethyl-5-methoxy-2-methylindolequinone (4,7) **XIX**

XIX were prepared by the method of ALLEN.[3c] Physicochemical data were shown as follows:

1-Ethyl-5-hydroxy-2-methylindole (**X**) Yield; 98.4 %, m.p. 114~115°C as white needles from cyclohexane.

1-Ethyl-5-methoxy-2-methylindole (**XI**) Yield 71.8 %, b.p.$_{21}$ 185~190°C. m.p. 21°C as white needles.

1-Ethyl-3-formyl-5-methoxy-2-methylindole (**XII**) Yield 86.7 %, m.p. 95~96°C as white crystals from ethanol. Anal. Calcd. for $C_{13}H_{15}NO_2$ (217.26): C 71.86, H 6.96, N 6.45. Found: C 71.78, H 7.01, N 6.69.

1-Ethyl-3-formyl-5-hydroxy-2-methylindole (**XIII**) Yield 72.5 %, m.p. 207~212°C as white needles from ethanol. Anal. Calcd. for $C_{12}H_{13}NO_2$ (203.23): C 70.91, H 6.45, N 6.89. Found: C 71.3, H 6.90, N 6.75.

1-Ethyl-3-formyl-2-methyl-indolequinone (4,5) (**XIV**) Yield 85 %, m.p. 198~201°C as black needles from ethanol. IR 1670, 1665, 1650 cm^{-1} (=CO, -CHO). Anal. Calcd. for $C_{12}H_{11}NO_3$ (217.22): C 66.35, H 5.10, N 6.45. Found: C 66.82, H 5.19, N 6.31.

4,5,7-Triacetoxy-1-ethyl-3-formyl-2-methylindole (**XV**) Yield 76.5 %, m.p. 192~194°C as white needles from ethanol. IR 1770 cm^{-1} (CH_3CO-), 1660 (-CHO). Anal. Calcd. for $C_{18}H_{19}NO_7$ (361.34): C 59.83, H 5.30, N 3.88. Found: C 60.06, H 5.20, N 3.99. Acetyl value 36.0 % (Calcd. 35.74 %)

1-Ethyl-3-formyl-5-methoxy-2-methylindolequinone (4,7) (**XVIII**) Yield 48 %, m.p. 207~208°C as orange needles from ethanol. nmr: τ 4.30 (C-6-hydrogen, singlet), 5.55 ($-CH_2-$, quartet), 6.15 ($O-CH_3$, singlet), 7.37 ($C-2-CH_3$), 8.63 (CH_3-, triplet), −0.26 (formyl). IR 1680, 1665 cm^{-1} (=O), 1640 (-CHO). Anal. Calcd. for $C_{13}H_{13}NO_4$ (247.24): C 63.15, H 5.30, N 5.67. Found: C 62.89, H 5.39, N 5.17.

1-Ethyl-3-hydroxymethyl-5-methoxy-2-methylindolequinone (4,7) (**XIX**) Yield 63 %, m.p. 199~201°C as reddish orange needles from ethanol. IR 3420 cm^{-1} ($-CH_2OH$) 1670, 1635 (=CO). Anal. Calcd. for $C_{13}H_{15}NO_4$ (249.26): C 62.64, H 6.07, N 5.62. Found: C 63.02, H 6.35, N 5.66.

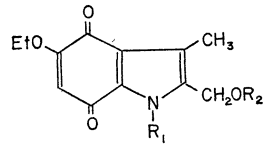
1-Ethyl-3-formyl-5-methoxy-2-methyl-4-nitroindole (**XX**) To a solution of 1 g of 1-ethyl-3-formyl-5-methoxy-2-methylindole (**XII**) in 20 ml of acetic acid was added 0.3 ml of fuming nitric acid. After 1 hour at room temperature water was added slowly and resulting precipitate was collected to give 1 g of a mixture of mononitro compounds, **XX** and **XXI**. After purification from silica gel chromatography, two crystals were obtained. The one was main product of 4-nitro compound **XX**. m.p. 179°C nmr: τ 0.05 (3-formyl singlet), 2.69, 3.07 (ortho aromatic protons, two doublets), 5.86 ($1-CH_2-$, quartet), 6.11 ($5-CH_3O$, singlet), 7.31 ($2-CH_3$, singlet), 8.62 ($1-CH_2-$, triplet). The other was **XXI**, isomer of **XX**, m.p. 189°C yellow prisms. nmr: τ 0.10 (3-formyl, singlet), 2.14, 2.16 (2 aromatic protons, 2 singlet), 5.87 ($1-CH_2-$, quartet), 6.06 ($5-CH_3O$, singlet), 7.31 ($2-CH_3$, singlet), 8.59 ($1-CH_3-$, triplet).

Indolequinone (4,7) from **XX**. Method A: A stirred solution of 1 g of a mixture of mononitrocompounds **XX** and **XXI** in 100 ml of glacial acetic acid and 10 ml of water was heated to steam bath temperature and treated with 2 g of iron powder over 90 minutes. Additional 10 ml of water was added after 45 minutes. After cooling large volume of water was added and this solution was extracted with $CHCl_3$. Evaporation of the dried organic solution gave mono amino compounds which were used for subsequent oxidation without purification. A solution of above 4-amino compound in 150 ml of acetone was added to a stirred solution of 2 g of potassium nitrosodisulfonate in 100 ml of water and 50 ml of 1/6 M KH_2PO_4.

Resulting reddish solution was stirred for 2 hours, then crude product was extracted with $CHCl_3$ and chromatographed on silica gel. The main fraction of orange band was recrystallized from ethanol to give 400 mg of orange needles, which was identical with the substance prepared from orthoquinone by melting point, elemental analysis, infrared and nmr spectra.

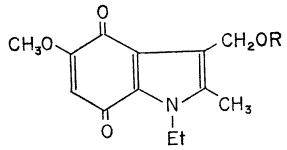
Method B: A solution of 1 g of **XX** in 150 ml of methanol was treated with hydrogen with 200 mg of Pd-C at room temperature and atmospheric pressure. After an absorption of quantitative hydrogen, catalyst was filtered off and filtrate was oxidized with a solution of 4 g of potassium nitrosodisulfonate in 300 ml of water and 150 ml of 1/6 M KH_2PO_4 under mechanical stirring. After 2 hours resulting orange solution was extracted with $CHCl_3$ and chromatographed on silica gel. From the first eluate main product of reddish needles was obtained after recrystallization from acetone - petroleum ether. m.p. 184~186°C. nmr: τ 4.42 (6-H, singlet), 5.65 ($1-CH_2-$, quartet), 6.21 ($5-CH_3O$,

Table 3. The derivatives of 2-hydroxymethyl indolequinone



R_1	R_2	m.p. (°C)	Formula	Carbon %		Hydrogen %		Nitrogen %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
H	$COCH_3$	182~184	$C_{14}H_{15}NO_5$	60.64	60.34	5.47	5.71	5.05	5.20
H	$COCH=CHCH_3$	not clear	$C_{16}H_{17}NO_5$	63.36	63.51	5.65	5.40	4.62	4.32
H	COC_6H_5	〃	$C_{19}H_{17}NO_5$	67.25	67.56	5.05	4.96	4.13	4.08
H	$COCH_2Cl$	〃	$C_{14}H_{14}NO_5Cl$	53.94	53.84	4.53	4.38	4.49	4.64
H	$COCHCl_2$	〃	$C_{14}H_{13}NO_5Cl_2$	48.57	48.23	3.79	3.85	4.05	3.98
H	$COCH_2Br$	〃	$C_{14}H_{14}NO_5Br$	47.21	46.87	3.96	4.12	3.93	4.07
H	$COOC_6H_5$	193~195	$C_{19}H_{17}NO_6$	64.22	64.13	4.82	4.48	3.97	3.74
CH_3	$COCH_3$	167~170	$C_{15}H_{17}NO_5$	61.83	61.95	5.89	5.99	4.81	4.56
CH_3	$COCH_2Cl$	122~125	$C_{15}H_{16}NO_5Cl$	55.49	55.06	4.93	4.89	4.28	4.80
CH_3	$COCHCl_2$	152.5~153.5	$C_{15}H_{15}NO_5Cl_2$	50.20	50.51	4.18	4.33	3.87	4.16

Table 4. The derivatives of 3-hydroxymethyl indolequinone (4, 7)



R	m.p. (°C)	Formula	Carbon %		Hydrogen %		Nitrogen %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
$COCH_3$	175~180	$C_{15}H_{17}NO_5$	61.85	62.18	5.88	5.93	4.81	4.65
COC_2H_5	120~122	$C_{16}H_{19}NO_5$	62.94	63.11	6.27	6.97	4.59	4.84
$CO\text{-}nC_3H_7$	74~ 76	$C_{17}H_{21}NO_5$	63.93	63.70	6.63	6.98	4.39	4.29
$COCH=CHCH_3$	110~113	$C_{17}H_{19}NO_5$	62.94	62.53	6.27	6.58	4.59	4.71
COC_6H_5	145~146	$C_{20}H_{19}NO_5$	67.98	67.02	5.42	5.11	3.96	4.07
$COCH_2Cl$	149~152	$C_{15}H_{16}NO_5Cl$	55.49	55.86	4.93	4.77	4.28	4.20
$COCHCl_2$	162~165	$C_{15}H_{15}NO_5Cl_2$	50.20	50.13	4.18	4.11	3.87	3.78
$COCH_2Br$	114~118	$C_{15}H_{16}NO_5Br$	48.66	48.98	4.36	4.03	3.78	3.50
$COOC_2H_5$	123~124	$C_{16}H_{19}NO_6$	59.80	59.83	5.96	5.74	4.36	4.62
$COOC_6H_5$	73~ 84	$C_{20}H_{19}NO_6$	65.03	65.21	5.19	4.88	3.79	3.22
$CONH_2$	225~228	$C_{14}H_{16}N_2O_5$	57.53	57.36	5.52	6.08	9.59	9.08
$CONHCH_3$	204~207	$C_{15}H_{18}N_2O_5$	58.81	58.68	5.92	5.94	9.15	8.70

singlet), 7.77, 7.82 (1-CH_3, 2-CH_3, two singlets), 8.70 (1-CH_3-, triplet). Identified as 1-ethyl-5-methoxy-2,3-dimethylindolequinone **XXII**.

The second eluate was identical with 1-ethyl-3-formyl-5-methoxy-2-methylindolequinone (4,7) **XVIII**. The third fraction was determined as 1-ethyl-5-methoxy-3-methoxymethyl-2-methylindolequinone (4,7) **XXIII**, orange needles after recrystallization from acetone - petroleum ether. m.p. 170~180°C. nmr: τ 4.20 (6-H, singlet), 5.18 (3-CH_2-O, singlet), 5.42 (1-CH_2-, quartet), 6.01, 6.40 (5-CH_3O, 3-OCH_3, two singlets), 7.54 (2-CH_3, singlet), 8.50 (1-CH_3, triplet).

The fourth fraction was identical with 1-ethyl-3-hydroxymethyl-5-methoxy-2-methylindolequinone (4,7) **XIX**.

Derivatives of **VIIIa, VIIIb,** or **XIX** Acyl, alkylcarbonate and carbamate derivatives of **VIIIa, VIIIb** or **XIX** were prepared by usual methods.

The derivatives of the above quinone studied in this work are listed in Tables 3 and 4.

Infrared spectra were measured in potassium bromide disk by a JASCO spectrophotometer. Elemental analysis were carried out by Yanagimoto elemental analyzer. Nuclear magnetic resonance spectra were measured in deuterio chloroform by a Varian Spectrophotometer.

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