b) Photo-induced: A soln. of **1a** (177 mg) in cyclohexane (150 ml) was bubbled with a stream of oxygen for 8 hr under irradiation with a 100-W high pressure mercury lamp and worked up as usual. **2a** was recrystallized from EtOH; 94 mg.

c) Radical-initiated: A soln. of **1a** (180 mg, 1 mmole) and benzoyl peroxide (23.4 mg, 0.1 mmole) in cyclohexane (50 ml) were bubbled with a stream of oxygen under reflux for 80 min and worked up as usual. **2a** was recrystallized from EtOH; 136 mg.

2-Acetyl-3,3-tetramethylene-3*H*-indole 2b——a) Photo-induced: A soln. of **1b** (100 mg) in cyclohexane (150 ml) was bubbled with a stream of oxygen under irradiation with a 100-W high pressure mercury lamp for 5 hr at room temp. After removal of the solvent *in vacuo* at room temp. the residue was applied to a preparative thin-layer chromatography (TLC) (silica gel), developed with benzene, separated an upper portion of this TLC, eluted with ether. The crude **2b** was obtained on evaporation of the solvent; 41 mg. The UV spectrum was previously described. NMR (CCl_4): 8.20—6.80 δ (m, 4H, aromatic), 2.55 (s, 3H, 2-$COCH_3$), 2.40—1.50 (m, 8H, 3,3-$(CH_2)_4$).

b) Radical-initiated: A soln. of **1b** (13 mg; 6.5×10^{-5} mole) and benzoyl peroxide (7.8 mg; 3.3×10^{-5} mole) in cyclohexane (15 ml) was bubbled with a stream of oxygen under reflux for 1 hr. After removal of the solvent *in vacuo* at room temp. the residue was applied to a silica gel TLC to give 9 mg of crude **2b**.

Attempted Oxygenation of 3,3-Dimethyl-3*H*-indole with Photosensitizer——a) Methylene blue: A soln. of **1a** (5.6 mg; 2.3×10^{-5} mole) and methylene blue (0.75 mg; 2.0×10^{-5} mole) in MeOH (25 ml) saturated with O_2 was irradiated with a 100-W high pressure mercury lamp for 4 hr. No appreciable oxidation took place as measured by UV.

b) Benzophenone: A soln. of **1a** (1.00 mg; 5.7×10^{-6} mole) in cyclohexane (4 ml) saturated with O_2 with or without benzophenone (0.01 mg; 5.2×10^{-8} mole) was irradiated as above for 30 min. In both cases no appreciable reaction took place as measured by UV. Experiment in benzene soln. gave the same result.

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A Further Investigation on Oxidative Coupling of *dl*-2-Methylisosalsoline

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In a previous paper,[2] oxidative coupling of *dl*-2-methylisosalsoline (*dl*-1,2-dimethyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline) (I)[3] with potassium ferricyanide in a mixture of 2.8% ammonia solution and dioxane has shown to give *dl*-1,1′,2,2′-tetramethyl-6,6′-dimethoxy-7,7′-dihydroxy-1,1′,2,2′,3,3′,4,4′-octahydro-8,8′-bisisoquinoline (C–C dehydrodimer) (II)[4,5] and *dl*-1,1′,2,2′-tetramethyl-6,6′-dimethoxy-7′-hydroxy-1,1′,2,2′,3,3′,4,4′-octahydro-7,8′-bisisoquinolyl ether (C–O dehydrodimer) (III)[4,5] in 10.5 and 2.1% yield (as each dihydrochloride), respectively. Compared with the case of corypalline (2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline) (IV), in which 8,8′-bicorypallyl (C–C dehydrodimer) (V)[6–8] is only formed under the similar condition, the above formation of C–O dehydrodimer (III) suggested that this reaction might be largely dependent on both oxidants and solvents

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[1] Location: *12, Ichigayafunagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*

[2] B. Umezawa, O. Hoshino, H. Hara and J. Sakakibara, *Chem. Pharm. Bull.* (*Tokyo*), **16**, 566 (1968).

[3] I.T. Strukov and O.A. Kolganova, *Z. Obshch. Khim.*, **29**, 3831 (1959) [*C.A.*, **54**, 19675h (1960)].

[4] M. Tomita, Y. Masaki and K. Fujitani, *Chem. Pharm. Bull.* (Tokyo), **16**, 257 (1968).

[5] Diasteroisomeric mixture.

[6] J.M. Bobbitt, J.T. Stock, A. Marchand and K.H. Weisgraber, *Chem. Ind.* (London), **1966**, 2127.

[7] M. Tomita, K. Fujitani, Y. Masaki and K.-H. Lee, *Chem. Pharm. Bull.* (Tokyo), **16**, 251 (1968).

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as well as on steric effect of methyl group at 1-position and that possibly proper choice of oxidant and/or solvent would give rise to selective or predominant formation of III. On the other hand, the synthesis of bis-benzylisoquinoline alkaloids having bis-diphenyl ether linkage, *e.g.* limacine (VI)[9] and limacusine (VII),[9] by oxidative coupling would require efficient C-O bond making process as a vital step.

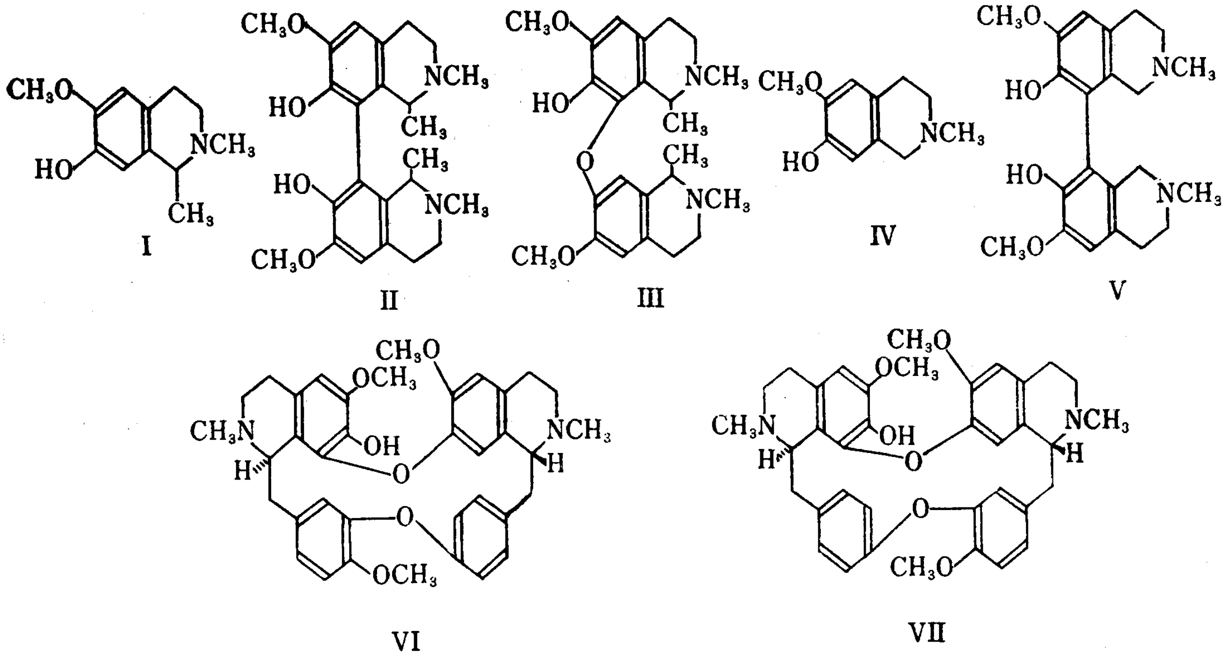

Chart 1

From these consideration, *dl*-2-methylisosalsoline (I) was chosen as a model compound and its oxidative coupling with various oxidants under different conditions was examined. In the present experiment, gas chromatographic determination of the oxidation products (as methyl ethers) in the reaction mixture was performed.

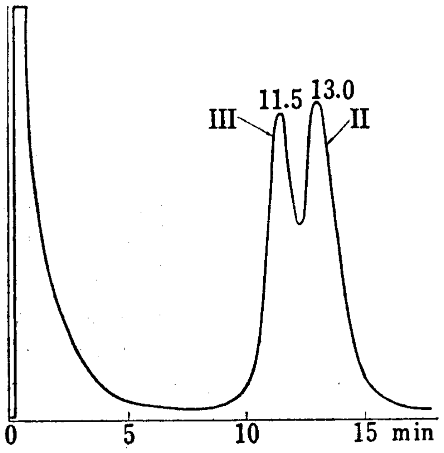

Fig. 1. Gas Chromatogram of standard Samples, II and III (as Methyl Ether)

1.5% OV-17 on Chromosorb W (80—100 mesh); 248°; N_2 flow rate 70 ml/min

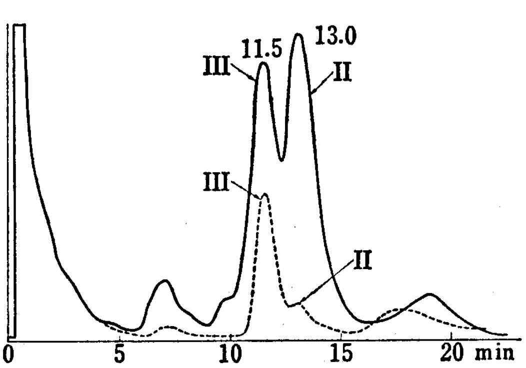

Fig. 2. Gas Chromatogram of the Reaction Mixture obtained by Methylation with Diazomethane

1.5% OV-17 on Chromosorb W (80—100 mesh); 248°; N_2 flow rate 70 ml/min

——: in 1% NH_4OH solution ------: in H_2O solution

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9) M. Tomita, M. Furukawa and K. Fukagawa, *Yakugaku Zasshi*, **87**, 793 (1968).

10) Authors are indebted to Dr. N. Ikekawa, Tokyo Institute of Technology, for supplying silicone polymer OV-17.

Namely, gas chromatographic behavior of standard samples, C–C and C–O dehydrodimer (II and III), was examined using 1.5% OV-17[10] and 1.5% SE-30 column packings. Of these two the former gave the satisfactory results and the gas chromatogram was shown in Fig. 1.

The reaction was carried out with various oxidants under different conditions and the products were characterized by means of gas chromatographic analysis. A typical gas chromatogram of the reaction mixture was shown in Fig. 2. In these attempts, the reaction with potassium ferricyanide in aqueous solutions was successful, while that with other oxidizing reagents (manganese dioxide, lead dioxide, silver oxide and ferric chloride) in organic solvents or aqueous solutions was fruitless. Therefore, potassium ferricyanide (2 molar equivalents) was used as the oxidant and the oxidation in a mixture of different aqueous solutions and dioxane was further performed to give the results shown in Table I.

TABLE I

Condition		Ratios of products[a]	
Solvent[b]	Reaction time (hr)[c]	II	III
1% NH_4OH	6.5	1	0.8
5% aq. NH_4Cl	24.0	1	1.3
20% aq. CH_3COONH_4	27.0	1	1.4
3% aq. CH_3NH_2	22.0	1	1.5
1% aq. $C_2H_5NH_2$	8.0	1	1.1
7% aq. $C_2H_5NH_2$	7.0	1	1.7
0.1% aq. Li_2CO_3	24.0	1	2.2
1% aq. Na_2CO_3	0.5	1	6.3
1% aq. K_2CO_3	0.5	1	4.5
0.08N aq. Na_2CO_3	2.5	1	7.0
H_2O	24.0	1	5.0

a) Values were calculated by the conventional method of multiplying peak height by width at half height.
b) Dioxane was used as co-solvent.
c) The time when spot due to the starting material on TLC disappeared.
d) Dioxane was not empolyed.

From the above observation, the reaction was found to afford both II and III, irrespective of the kind of solvent employed. Additionally speaking, even in aqueous organic amine solutions instead of ammonia solution this reaction could be conducted similarly. In each case, the unknown compound observed was not yet fully investigated.

As stated above, 2 molar equivalents of potassium ferricyanide were employed, however an adequate amount of the oxidant in the reaction like the other ordinary oxidation should be defined. Thereupon, the reaction with varying quantities of the oxidant was carried out in two different solutions (1% aq. sodium carbonate and 1% ammonia solution) and results shown in Table II were obtained.

As a result, it was proved that an appropriate quantity of potassium ferricyanide for the present oxidative coupling was 1 to 2 molar equivalents and that the desired C–O dehydrodimer (III) was predominantly formed in aqueous carbonate rather than in ammonia solution.

With these finding in mind, reactions in 0.08N aq. sodium carbonate solution and in water were preparatively carried out. In each case, the practical silicic acid chromatographic purification of the reaction mixture gave only III (as dihydrochloride) in 13.1% and 9.3% yield, respectively, and II could not be obtained.

In conclusion, it was found that in the present reaction employment of potassium ferricyanide (2 molar equivalents) and aqueous carbonate solutions was the most useful for the preparative formation of the desired C–O dehydrodimer (III).

TABLE II

Condition[a)]		Ratios of products[b)]	
Solvent[c)]	$K_3Fe(CN)_6$ (Molar equivalent)	II	III
1% NH_4OH	0.5	1	0.9
	1	1	1.3
	2	1	0.8
	3	1	0.4
	5	—	—[d)]
1% aq. Na_2CO_3	0.5	1	2
	1	—[e)]	1
	2	1	6.3
	3	1	2.4
	5	—	—[d)]

a) Each reaction was carried out for 3 to 4 hr.
b) Values were obtained by the same method as noted in Table I.
c) Dioxane was employed as co-solvent.
d) Each peak due to II and III could not be detected.
e) Peak due to II could not be observed.

Experimental[11)]

Reactions and Analysis of Products——I (0.1 mmole) was treated with $K_3Fe(CN)_6$ (0.2 mmole) in a mixture of various solvents (4 ml) and dioxane (1.6 ml) under stirring at room temperature. After completion of the reaction the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried (K_2CO_3). Removal of the solvent afforded an oily mass which was methylated with diazomethane in CH_3OH. The reaction mixture obtained was subjected to gas chromatographic determination [U-type glass column, 180 cm × 3 mm i.d., 1.5% OV-17 on chromosorb W (80—100 mesh); column temperature, 248°; N_2 flow rate, 70 ml/min]. Results were given in Table I.

2) I (0.1 mmole) was treated in the same manner as noted above excluding varying amounts of the oxidant and gas chromatographic determination gave results shown in Table II.

***dl*-1,1′,2,2′-Tetramethyl-6,6′-dimethoxy-7′-hydroxy-1,1′,2,2′,3,3′,4,4′-octahydro-7,8′-bisisoquinolyl Ether Dihydrochloride (C-O Dehydrodimer) (III·2HCl)**——1) To a solution of I (500 mg, 2.4 mmole) in dioxane (10 ml), 0.08N aq. Na_2CO_3 solution (100 ml) and $K_3Fe(CN)_6$ (1.65 g, 5.0 mmole) were added and the reaction mixture was stirred at room temperature for 2.5 hr. To the reaction mixture, K_2CO_3 (powder) was added and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried (K_2CO_3). The concentrated solution was treated with dry HCl gas and removal of the solvent gave an amorphous mass (619.3 mg), whose silicic acid chromatographic purification afforded III·2HCl[2)] (75 mg, 13.1%) from eluate [$CHCl_3$–CH_3OH (100:20)].

2) I (500 mg, 2.4 mmole) in dioxane (60 ml) was treated with water (100 ml) and $K_3Fe(CN)_6$ (1.65 g, 5.0 mmole) at room temperature for 41 hr. The same work-up of the reaction mixture as noted in 1) afforded III·2HCl[2)] (53 mg, 9.3%) from eluate [$CHCl_3$:CH_3OH (100:20)].

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[11)] Gas chromatography (GLC) was measured with a Shimadzu gaschromatography GC-1C (hydrogen flame ionization detector). Thin-layer chromatography (TLC) was carried out on silica gel G (Merck), developing solvent [conc. NH_4OH–CH_3OH (1:20)]. Nuclear magnetic resonance (NMR) spectra were taken with a JNR-4H-100 spectrometer in D_2O using DSS as internal standard. The product was identical with an authentic sample by comparison of each TLC, NMR and GLC.