[Chem. Pharm. Bull. 16(2) 257—261 (1968)]

UDC 547.94.04 : 542.943

Phenol Oxidation of Isoquinoline Alkaloids. II.[1] Oxidative Coupling of *dl*-N-Methylisosalsoline

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(Received April 4, 1967)

Oxidative coupling of *dl*-N-methylisosalsoline (III) with potassium ferricyanide was carried out, and the structures of the products were determined.

It was found that III gives rise both to biphenyl derivatives (VI, VII) and diphenyl ether derivative (IV), and a steric participation of 1-substituent of 2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline derivative in the product development in the phenol oxidation reactions was observed.

In the preceding paper,[1] the authors reported that the oxidative coupling of corypalline (2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline) (I) and its metho-salt results in the exclusive formation of biphenyl derivatives (II and its diquaternary salt), and alternatively expected diphenyl ether derivatives are not obtainable.

On the other hand, it was reported[3,4] that the phenol oxidations of lophocerine (1-isobutylcorypalline) and of *dl*-magnocuracine iodide (1-(4-hydroxybenzyl)corypalline methiodide) gave diphenyl ether derivatives with intermolecular dehydrogenation of starting materials. Apparently, the presence or absence of these substituents at 1-position of corypalline skeleton seem to affect the development of the products in oxidative coupling reactions.

In this paper, the authors report on the potassium ferricyanide oxidation of *dl*-N-methylisosalsoline (*dl*-1-methylcorypalline) (III), which was undertaken to survey the steric participation of the substituents in the phenol oxidation of isoquinoline alkaloids.

dl-N-Methylisosalsoline[5] (III) was treated with potassium ferricyanide in an ammonium acetate-sulfuric acid solution and the products were isolated and purified by extraction, chromatography, and preparative thin-layer chromatography methods as described in detail in the experimental section, and finally, though in low yields, a crystalline, non-phenolic fraction and two amorphous phenolic fractions (Base A and B) were obtained. The fractions were thin-layer chromatographically pure, as they gave single spots on the chromatogram.

One of the phenolic fractions, Base A showed in the nuclear magnetic resonance (NMR) spectrum (Fig. 1) three singlets in aromatic proton region at 3.33, 3.48, and 3.68τ each corresponding to one proton, and two singlets at 6.08, and 6.15τ (2×3H, methoxyls). The signals for N-methyls and C-methyls appeared at 7.62τ (overlapped singlets, 2×3H), and at 8.63—8.90τ (four doublets, partly overlapped), respectively. Relative intensity of C-methyl singnals corresponded to six protons.

From the nuclear magnetic resonance (NMR) data, Base A was assumed to be a diphenyl ether derivative represented by formula IV. The appearance of C-methyl singnals in four doublets ($J=6.5$ cps) was to be understood as Base A consisted of diastereoisomers with the common planar structural formula (IV).

1) Part I: *Chem. Pharm. Bull.* (Tokyo), **16**, 251 (1968).
2) Location: *Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto.*
3) J.M. Bobbitt, R.E. Ebermann, and M. Schubert, *Tetrahedron Letters*, **1963**, 575.
4) B. Franck and G. Blaschke, *Ann.*, **668**, 145 (1963); B. Franck, G. Blaschke, and K. Lewejohann, *ibid.*, **685**, 207 (1965).
5) I.T. Strukov and O.A. Kolganova, *Z. Obshch. Khim.*, **29**, 3831 (1959).

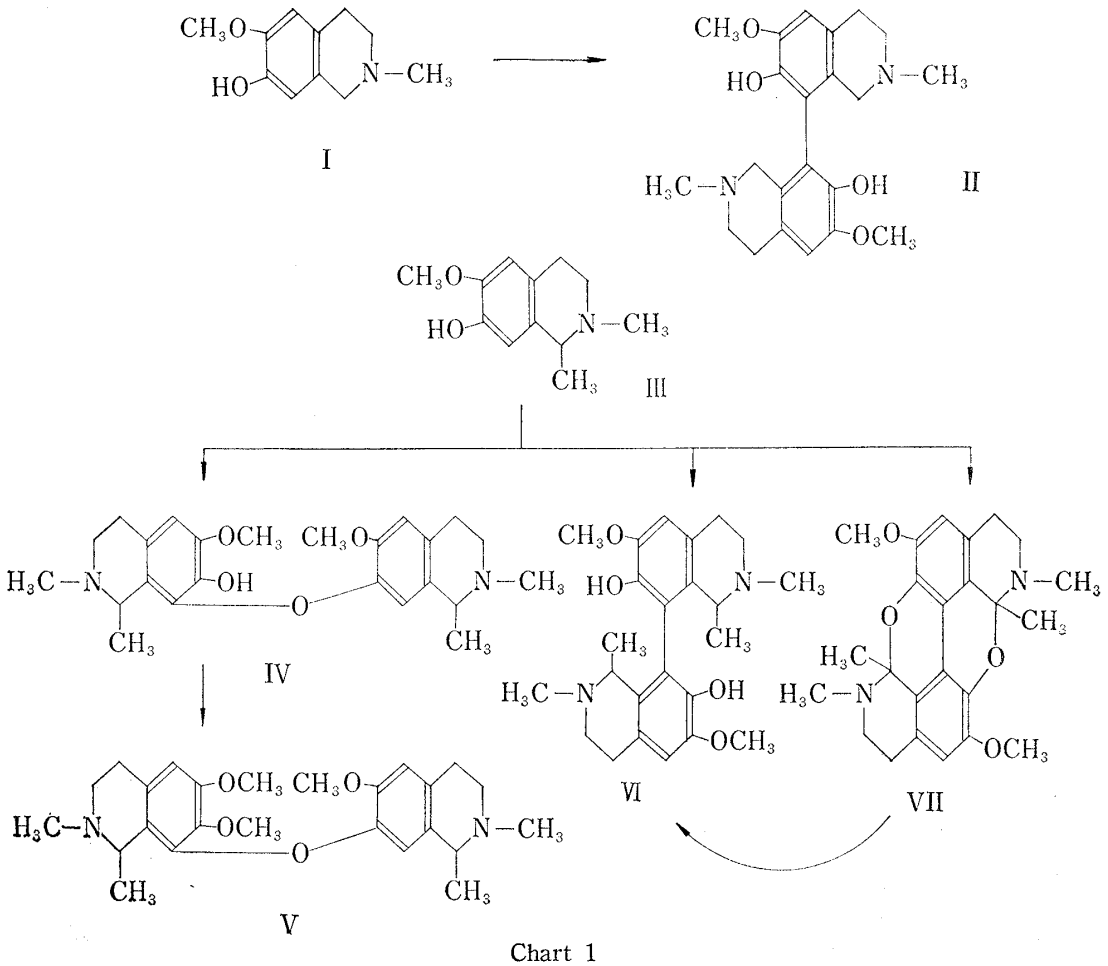

Chart 1

Methylation of Base A with diazomethane gave a non-phenolic base (V), which on mass spectrometry gave its molecular ion peak at *m/e* 426 and a fragmentation pattern similar to those reported[6] for the bisbenzylisoquinoline alkaloids with diphenyl ether linkage between two isoquinoline moieties.

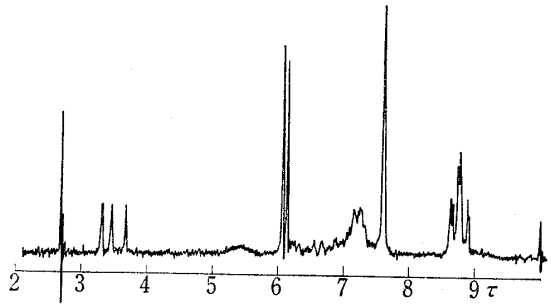

Fig. 1. NMR Spectrum of IV in $CDCl_3$

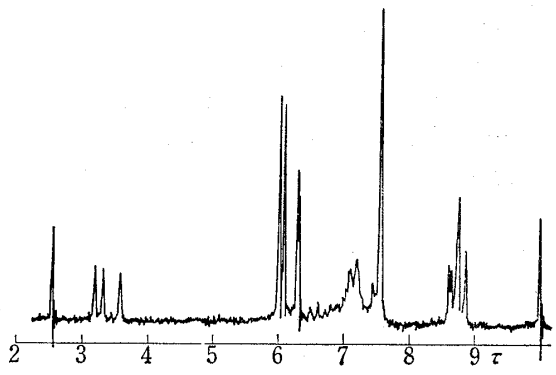

Fig. 2. NMR Spectrum of V in $CDCl_3$

NMR spectrum of V (Fig. 2) showed signals for newly introduced methoxyl group (3H) at 6.35 and 6.38τ, and the relative intensity of the signals of each functional group region agreed with the formula V. The appearance of signals for the newly introduced methoxyl

6) M. Tomita, T. Kikuchi, K. Fujitani, A. Kato, H. Furukawa, Y. Aoyagi, M. Kitano, and T. Ibuka, *Tetrahedron Letters*, **1966**, 857.

in two singlets with almost equal intensity substantiates the character of V, consisting of almost equal amounts of two diastereoisomeric compounds. The up-field shift of the new methoxyl signal explains that the methoxyl group occupies *ortho*-position with respect to the diphenyl ether bond.[7]

On the basis of above spectrometric data, and from the reaction mechanism, the structure of Base A was unequivocally assigned as IV, and its O-methyl ether should be represented by formula V.

Base B, having smaller *Rf* on thin-layer chromatography than IV, presented in its NMR spectrum (Fig. 3) aromatic proton signal at 3.33τ and O-methyl signal at 6.10τ, N-methyl at 7.57—7.68τ, and C-methyl at 8.90—9.05τ. The relative intensities of signals for arom. H, O-methyl, N-methyl, and C-methyl were found to be 1:3:3:3. These findings suggested that Base B was a biphenyl derivative with highly symmetrical structure. Considering the fact that 8,8'-bicorypallyl (II) was formed by the oxidation of corypalline (I), the structure of Base B should be drawn as VI, 8,8'-bi-N-methylisosalsolyl.

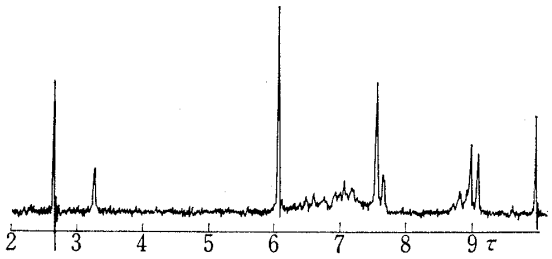

Fig. 3. NMR Spectrum of VI in $CDCl_3$

Signals for N-methyl and C-methyl appeared in somewhat different patterns depending on the isolation and purification procedures of the reaction product. However, in every case, C-methyl signals appeared consistently in two doublets (J=6.5 cps) at 8.88 and 9.05τ, and N-methyl signals in overlapped singlets at 7.57 and two singlets at 7.67 and 7.68τ. Furthermore, it was observed that the intensity of C-methyl signals at 9.05τ corresponded to that of N-methyl at 7.57τ, and the intensity of C-methyl doublet at 8.88τ corresponded to that of N-methyl signals of two singlets. The whole relative intensities for aromatic protons, O-methyls, N-methyls, and C-methyls were not affected by the isolation and purification procedures, and were consistently 1:3:3:3.

The above NMR data gave evidences that Base B consisted of stereoisomers having the common two dimensional structural formula VI.

Among the products isolated, non-phenolic crystalline base (VII) showed molecular ion peak at *m/e* 408 on mass spectrum, and four singlet peaks at 3.37, 6.15, 7.23, and 8.43τ at NMR measurement. The relative intensity was found to be 1:3:3:3.

The spectral data of the non-phenolic base (VII) suggested that it would be a symmetric dimer. The non-phenolic character and the appearance of NMR signal for C-methyls as singlet might suggest that it was produced by further intramolecular dehydrogenation of VI, and would have the structure VII. The UV spectral behavior of the base supported the structure VII, as it presented a spectrum similar to that of a 3,4-dihydroisoquinolinium upon addition of perchloric acid.

The structure VII for the crystalline base was confirmed by the treatment of the base with hydrochloric acid followed by sodium borohydride reduction, which gave Base B (VI) in fairly good yield.

Consequently, dimeric character of VI was to be additionally confirmed by the mass spectral data of VII.

The structures of the products were thus established, and it was made clear that N-methylisosalsoline (III) gave rise both to biphenyl (VI) and diphenyl ether (IV) derivatives when submitted to the phenol oxidation.

Considering the results obtained by the present authors together with those reported in the literature,[3,4] it could be concluded that, in the phenol oxidation of corypalline type

7) W.D. Chandler, W. MacFarlane Smith, and R.Y. Moir, *Can. J. Chem.*, **42**, 2549 (1964).

isoquinoline alkaloids, the size or bulkiness of substituent at 1-position would define an important factor affecting the product development.

Experimental[8]

***dl*-1,2-Dimethyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (*dl*-N-Methylisosalsoline) (III)**[5]——The title compound (III) was prepared by a standard Bischler–Napieralski method. N-(β-3-Methoxy-4-acetoxyphenethyl)acetamide[9] was refluxed with $POCl_3$ in toluene for 2.5 hr to give directly 1-methyl-6-methoxy-7-hydroxy-3,4-dihydroisoquinoline[9] (yield: 80%), which in turn was reduced with $NaBH_4$ in MeOH into 1-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (*dl*-isolsalsoline)[10] (yield: almost quantitative). *dl*-Isosalsoline was N-methylated with formalin-$NaBH_4$ to yield III quantitatively.

Oxidative Coupling of *dl*-N-Methylisosalsoline (III) (Formation of the Diphenyl Ether (IV) and the Biphenyl Derivatives (VI, VII))——i) To a solution of 3 g of $K_3Fe(CN)_6$ in 110 ml of 8% $AcONH_4$, was added dropwise with stirring at room temperature a solution of 1 g of III in 5 ml of 1N H_2SO_4 and 40 ml of 8% $AcONH_4$. Stirring was continued for 1 hr at room temperature, then the reaction mixture was made alkaline with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was shaken with dil. HCl, and the acidic aqueous layer was made alkaline with NaOH and washed with ether. Caustic alkaline solution was made ammonical alkaline with the addition of NH_4Cl, and extracted with ether, then with $CHCl_3$. The extracts were worked up in usual manner, and 130 mg of crude base mixture was obtained from the ether extarct, and 690 mg from the $CHCl_3$ extract.

The fraction extracted first with ether gave three spots on TLC,[11] and the spot with the largest *Rf* corresponded to that of the starting material (III). The products (Base A and B) were submitted to preparative TLC[11] after the removal of the unchanged starting material by alumina column chromatography[12] with a gradient elution system (from benzene to benzene–$CHCl_3$). Base A (12 mg) which had larger *Rf* on TLC was isolated by the preparative TLC, but Base B resisted the purification process. NMR spectrum of Base A (IV) was shown in Fig. 1.

The TLC of the $CHCl_3$ extract showed that it contained Base A and B, but the separation of Base A and B over alumina column with benzene–$CHCl_3$ failed. Base B (VI) was isolated by an extraction method taking advantage of the difference of distribution coefficients of Base A and B in ether/water system. The base mixture was taken into dil. HCl and then made alkaline with NH_4OH, and extracted eight times with each 30 ml of ether. These eight fractions of ether extract were not combined, but shaken with water under counter-current distribution principle with TLC control. Base B was obtained from the fractions less soluble in ether. NMR spectrum of Base B was shown in Fig. 3.

ii) $K_3Fe(CN)_6$ (9 g) was dissolved in 300 ml of 8% $AcONH_4$, and a solution of 3 g of III in 15 ml of 1N H_2SO_4 and 150 ml of 8% $AcONH_4$ was added thereto in portions with stirring. The mixture (pH: 6.55) was stirred for additional 1 hr at room temperature, then made alkline with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was shaken with dil. HCl and the acidic layer was again made alkaline with NH_4OH. The liberated bases were extracted under counter-current distribution principle with eight portions of ether (each 50 ml) was described in procedure i). The first five fractions of ether extract showed on TLC that they contained the unchanged material (III), Base A, Base B, and another base which had the largest *Rf*. The remaining three fractions gave solely Base B (158 mg). NMR spectrum agreed with the formula VI.

The mixture of bases was chromatographed over alumina[12] with a gradient elution system (benzene–$CHCl_3$), and separated into 45 mg of crystalline base, mp 200—205°, 116 mg of Base A (IV), and the starting material (III).

The crystalline base (VII) was practically insoluble in alkali, and presented no absorption attributable to carbonyl, imino, and hydroxyl functions in IR ($CHCl_3$) spectrum. Mass spectrum gave its molecular ion peak at *m/e* 408. NMR τ: 3.37 (s. 2H); 6.15 (s. 6H); 7.23 (s. 6H); 8.43 (s. 6H). UV λ_{max}^{EtOH} mμ (log ε): 228 (4.32), 277 (4.01), 286.5 (4.11), 319 (3.83), 333 (3.95). UV $\lambda_{max}^{EtOH\text{-}HClO_4}$ mμ: 245, 305 (shoulder), 331.

Methylation of IV into V——IV (100 mg) was dissolved in a small amount of ether, and methylated with excess CH_2N_2–ether, to give 70 mg of V as viscous oil, bp 140—150° (2×10^{-5} mmHg). *Anal.* Calcd. for

8) Mp was determined on a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were taken on a Varian A-60 spectrometer at 60 Mc in $CDCl_3$ with TMS as an internal reference. Mass spectra were measured on a Hitachi RMU-6D machine.

9) T. Kametani, S. Takano, and E. Karibe, *Yakugaku Zasshi*, **83**, 1035 (1963).

10) E. Späth, A. Orekhov, and F. Kuffner, *Ber.*, **67**, 1214 (1934).

11) Thin-layer chromatography: Aluminium oxide acc. to Stahl (E. Merck), $CHCl_3$–acetone (1:1), spots were detected with iodine vapor and Dragendorff's reagent.

12) Aluminium oxide standardized acc. to Brockmann.

$C_{25}H_{34}O_4N_2$: C, 70.39; H, 8.03. Found: C, 70.18; H, 8.31. Mass spectrum. *m/e*: 426 (M^+), 411 (M–15) (base peak), 381, 349, 198, 175. NMR: Fig. 2.

Conversion of VII into VI——The crystalline non-phenolic base (VII) (30 mg) was dissolved in 15 ml of EtOH, and stirred with 1 ml of conc. HCl at room temperature for 30 min. The solvent and excess HCl were removed by evaporation *in vacuo*, and the residue was dissolved in 30 ml of EtOH. $NaBH_4$ (500 mg) was added in portions to the EtOH solution, and stirred for 30 min, then the solvent was evaporated off *in vacuo*. The residue was treated in usual manner, and phenolic base was extracted with ether, then with $CHCl_3$. Ether extract gave 11mg of crude oil, while $CHCl_3$ extract gave 6 mg. The base extracted with ether showed on TLC a spot corresponding to VI, but was not thin-layer chromatographically pure. The $CHCl_3$ extract behaved identically with VI on TLC, and gave a superimposable IR ($CHCl_3$) spectrum. NMR spectrum also agreed with the formula VI (Fig. 3).

Acknowledgement The authors wish to acknowledge Dr. T. Shingu for taking NMR spectra, Dr. T. Ibuka for mass measurements. They are also indebted to the members of Microanalytical Center of this University for elemental analysis.