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Phenol Oxidation of Isoquinoline Alkaloids. I. Oxidative Coupling of Corypalline and Its Metho-Salt[1]

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Ferricyanide oxidation of corypalline (I) and its methosalt (V) yielded solely biphenyl derivatives (II and IX), and alternatively expected diphenyl ethers (IV and XII) were not obtained. The result constitutes an information in discussing steric effects of the substituents on the oxidative coupling reactions.

The significance of the phenoxyl radical coupling in the biogenetic sequences from benzylisoquinoline to morphine, proaporphine, aporphine, and bisbenzylisoquinoline alkaloids has long been recognized,[3] and some of the pathways were established with biosynthetic tracer experiments.[3,4]

In parallel with the biogenesis, there exists a recent trend to find new and non-enzymatic synthetic routes to natural alkaloids and related compounds from phenolic bases by oxidative coupling utilizing one electron transfer oxidants.[3,5-12]

In this paper, the authors report on the potassium ferricyanide oxidation of corypalline (I) and its metho-salt, which was undertaken as one of the preliminary experiments of the biogenetic type synthesis of bisbenzylisoquinoline (biscoclaurine) alkaloids.

Corypalline (2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline) (I) was treated with potassium ferricyanide in aqueous media as described in the experimental section.

A phenolic product was isolated in 28% yield from the starting material, when corypalline (I) was treated with potassium ferricyanide in faintly acidic medium (pH: 6.55). The product showed single spot on thin-layer chromatography (TLC), and melted at 229°, and was easily discriminated from the starting material, corypalline.

The molecular formula $C_{22}H_{28}O_4N_2$ was assinged for the product on the basis of elemental analysis and mass spectrometry (*m/e* 384, M^+; *m/e* 192, M^{++}), and it was suggested that the compound was dimeric and afforded by the intermolecular dehydrogenation of corypalline (I). The nuclear magnetic resonance (NMR) spectrum (Fig 1) of the compound presented all the methylimino, methoxyl, and aromatic proton signals as overlapped singlets respectively and positively suggested the symmetry of the molecule. Relative intensities of the signals

1) This work was presented at the 15th Annual Meeting of the Kinki Branch, the Pharmaceutical Society of Japan, Nov. 20, 1965, Kobe, Abstracts of Papers, p. 26.
2) Location: *Yoshida-Shimoadachi-cho, Sakyo-ku, Kyoto.*
3) D.H.R. Barton, "The Chemistry of Natural Products, 3" (Special Lectures, International Symposium, Kyoto, 1964), p. 35. Butterworth (London), 1964, and the literatures cited therein.
4) D.H.R. Barton, G.W. Kirby, and A. Wiechers, *Chem. Comm.*, **1966**, 266; *J. Chem. Soc.* (C), **1966**, 2313.
5) B. Franck, *Angew. Chem.*, **75**, 957 (1963), and the literatures cited therein.
6) B. Franck and G. Blaschke, *Ann.*, **668**, 145 (1963).
7) B. Franck, G. Blaschke, and K. Lewejohann, *Ann.*, **685**, 207 (1965).
8) A.R. Battersby and T.H. Brown, *Proc. Chem. Soc.*, **1964**, 85.
9) J.M. Bobbitt, R. Ebermann, and M. Schubert, *Tetrahedron Letters*, **1963**, 575.
10) S.M. Albonico, A.M. Kuck, and V. Deulofeu, *Ann.*, **685**, 200 (1965).
11) A.H. Jackson and J.A. Martin, *J. Chem. Soc.*, (C), **1966**, 2061; 2222; M. Shamma and W.A. Slusarchyk, *Chem. Comm.*, **1965**, 528.
12) I. Baxter, L.T. Allan, and G.A. Swan, *J. Chem. Soc.*, **1965**, 3645.

are well in accordance with the formula II. Thus, the dehydrogenation product was proved to be a biphenyl derivative, not an alternatively expected diphenyl ether (IV). Considering the structure of radicals produced during the reaction, and from the mechanism of radical pairing in the phenol oxidation,[13] the position of the newly formed biphenyl linkage was assumed to be between 8- and 8'-positions of the isoquinoline moiety, *i.e.*, *ortho* to 7- and 7'-hydroxyl groups.

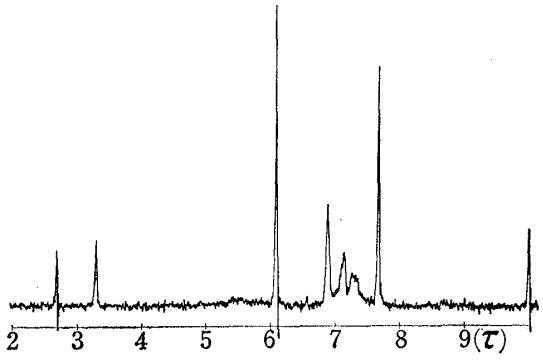

Fig. 1.

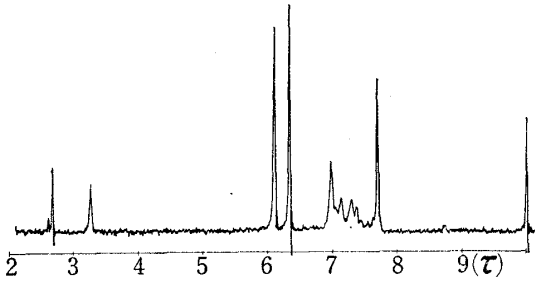

Fig. 2.

Further, the phenolic base (II) was methylated with diazomethane, and a non-phenolic base was obtained. The NMR spectrum of the methylated base (III) (Fig. 2) showed that the signals for the newly introduced methoxyl groups appear also as overlapped singlets corresponding to two methoxyl groups at higher field than initially observed methoxyl gignals by 0.25 ppm. The appearance of this new methoxyl signals at higher field well explains that the biphenyl bond was initially formed at the *ortho* position with respect to the phenolic hydroxyl groups. The diamagnetic ring current of the each phenyl group causes this up-field shift of the *ortho*-methoxyls.[14]

Although II and III have no absorption attributable to the biphenyl conjugation in their UV spectra, this is understandable by the hindered co-planarity of their biphenyl system as they have 2,2',6,6'-tetrasubstituted biphenyl structure.

From the data stated above, the structure of II and III were assinged as 8,8'-bicorypallyl (II) and its dimethyl ether (III), respectively.

Potassium ferricyanide oxidation of corypalline (I) in alkaline medium (pH: 13.00) gave the same product (II), and no substantial difference depending on the reaction conditions was noticed.

Oxidation of quaternary metho-salt was effected with N-methylcorypallinium iodide (V), which was prepared by the treatment of I with methyl iodide. The methiodide (V) was dissolved in sodium carbonate and treated with potassium ferricyanide (pH: 9.5).

The reaction product was treated in a usual manner, and a quaternary picrate was obtained after purification through base reineckate.

NMR spectrum of the quaternary ammonium chloride (VIII), derived from the picrate (IX) showed different signal pattern in the aromatic proton region from that of the starting material (V). Further, the relative intensities of the signals of aromatic protons (singlet), methoxyl (singlet), and methylimino (singlet) groups, and the pattern of the spectrum suggested the symmetry of the molecule as with the spectrum of 8,8'-bicorypallyl (II).

Thus, the quaternary chloride obtained was assumed to be a dimeric N,N'-dimethyl-8,8'-bicorypallinium dichloride (VIII).

13) T.J. Stone and W.A. Waters, *J. Chem. Soc.*, **1964**, 213; F.R. Hewgill, T.J. Stone, and W.A. Waters, *J. Chem. Soc.*, **1964**, 408.

14) Y. Naya and M. Kotake, *Nippon Kagaku Zasshi*, **86**, 313 (1965).

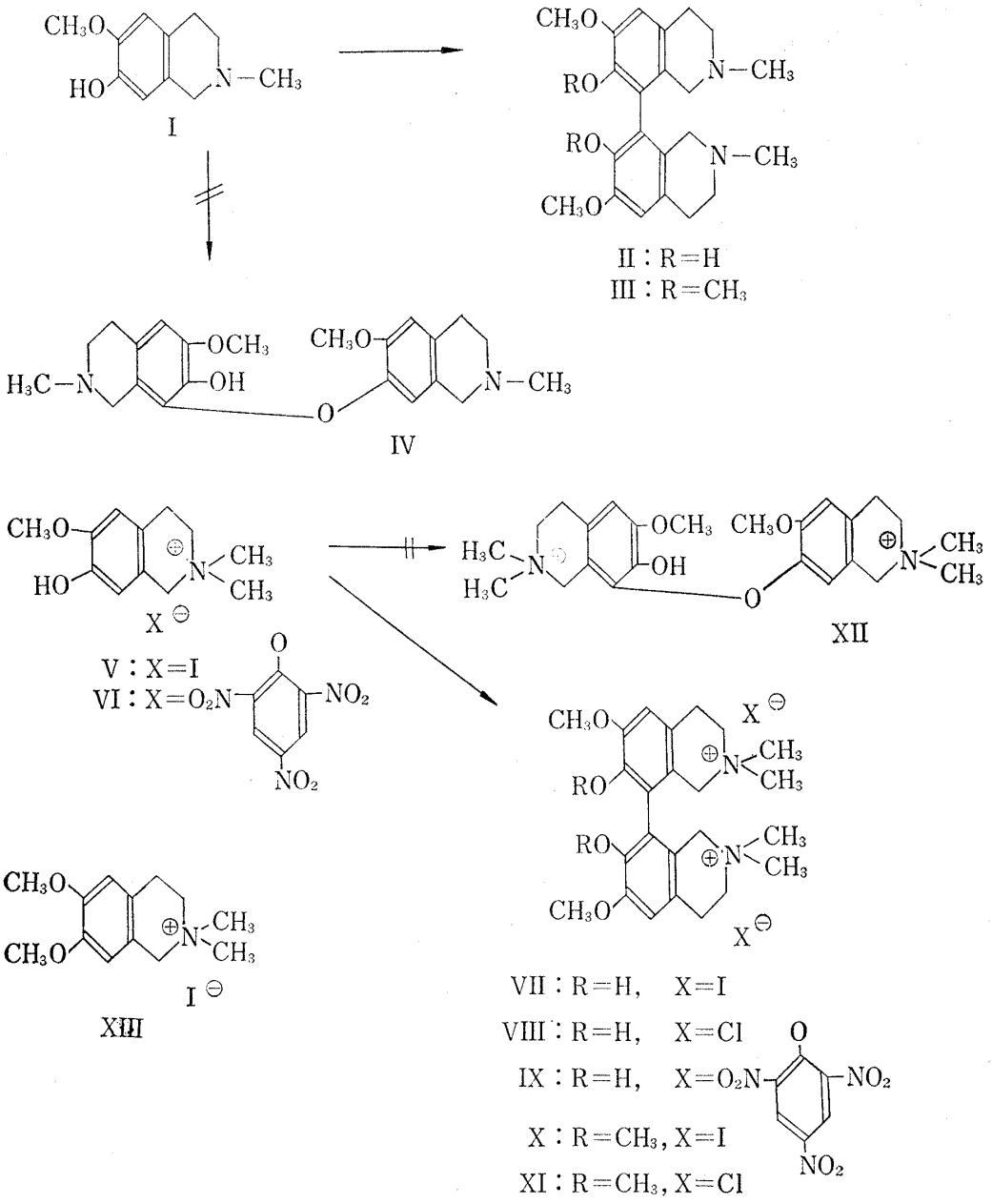

Chart 1

Confirmation of the structure VIII was given by the comparison of the quaternary iodide (VII) with 8,8′-bicorypallyl dimethiodide, prepared from 8,8′-bicorypallyl (II), by mixed melting point determination, IR spectra and paper chromatography, as they were identical.

Further, O-methylation of the quaternary base afforded a nonphenolic iodide (X), and the NMR spectrum of the corresponding chloride (XI) in deuterium oxide was found to be consistent with the structure XI upon comparison with the spectrum of O-methylcorypalline methiodide (XIII).

An attempt was made to give a synthetic proof for the biphenyl structure of the products, and an Ullmann biaryl synthesis was projected with 8-bromo-O-methylcorypalline. The reaction in the presence of copper powder with cupric oxide was carried out, but the product was solely O-methylcorypalline, produced by debromination of the starting material, and the course of the reaction was found to be quite similar as in the case of the Ullmann condensa-

15) M. Tomita and H. Watanabe, *Yakugaku Zasshi*, **58**, 783 (1938).

tion[15] between 8–bromo–O–methylcorypalline and corypalline, and the expected product (III) was not obtained.

Summarizing the results, the ferricyanide oxidation of corypalline (I) and its metho–salt (V), yielded the biphenyl derivatives linked at the *ortho* positions with respcet to the isoquinolinol hydroxyl of the starting materials, and the diphenyl ether derivatives (IV and XII), alternatively anticipated from the reaction mechanism, could not be detected. The biphenyl derivatives were given in an almost equal yield both from the tertiary nitrogen compound (I) and from the quaternary ammonium salt (V).

Lophocerine[9] and its metho–salt,[7] and *dl*–magnocurarine,[6] which bear isobutyl and 4–hydroxybenzyl groups at 1–position of corypalline skeleton respectively, have been reported to give exclusively diphenyl ether derivatives upon phenol oxidation. Exclusive formation of biphenyl linkage with corypalline and its quaternary derivative, seem to constitute an interesting information in discussing steric effects of the substituents on the phenol oxidative coupling reactions.[16]

Experimental[17]

2-Methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (corypalline) (I)——The title compound (I) was prepared by a method essentially the same as described by Tomita, and Watanabe.[15] Modifications adopted were as follows: 3–Methoxy–4–benzyloxyphenethylamine was prepared by $LiAlH_4$ reduction[18] of 3–methoxy–4–benzyloxy–β–nitrostyrene, and 6–methoxy–7–benzyloxy–3,4–dihydroisoquinoline methiodide was reduced with $NaBH_4$ into 2–methyl–6–methoxy–7–benzyloxy–1,2,3,4–tetrahydroisoquinoline (O–benzylcorypalline), and the latter was hydrogenolytically debenzylated.

i) O–Benzylcorypalline: To a solution of 6–methoxy–7–benzyloxy–3,4–dihydroisoquinoline methiodide (8 g) in 200 ml of MeOH, $NaBH_4$ (6 g) was added in small portions at room temperature, with stirring. Stirring was continued for additional 30 min, and the solvent was evaporated off *in vacuo*. To the residue was added 2% NaOH aq. and extracted with ether. Ethereal layer was washed with water, dried over anhyd. K_2CO_3, and the solvent was evaporated to give crude crystalline mass. Recrystallization from *n*–hexane gave 5.1 g of colorless prisms, mp 102—103°. *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47. Found: C, 76.48; H, 7.57.

ii) Hydrogenolysis of O–benzylcorypalline: O–Benzylcorypalline (7.5 g) in EtOH (240 ml) was submitted to catalytic hydrogenation with Pd–C catalyst (prepared from 40 ml of 1% $PdCl_2$ solution and 4 g of active charcoal (Darco G 60)) under atmospheric pressure, at room temperature. After consumption of hydrogen ceased, the catalyst was filtered off, and the filtrate was treated in ususal manner to give phenolic product. Corypalline (I) was obtained as colorless pillars, melting at 165—166° (lit.[15] mp 167°). UV λ_{max}^{EtOH} 287 mμ.

Potassium Ferricyanide Oxidation of Corypalline (I) (Formation of 8,8′-Bicorypallyl (II))——i) A solution of 500 mg of I in 2.5 ml of 1N H_2SO_4 was added to a solution of 1.5 g of $K_3Fe(CN)_6$ in 75 ml of 8% NH_4OAc, and the mixture (pH: 6.55) was kept standing at 3—5° for 18 hr. The reaction mixture was made alkaline with NH_4OH, and extracted with $CHCl_3$. The extract was shaken with 5% NaOH, and the alkaline layer was made ammoniacal alkaline with the addition of NH_4Cl, and extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3, and the solvent was removed to give crude phenolic product (II) (Yield: 141 mg). Recrystallization from MeOH gave colorless cubes, mp 227°. The base gave single spot on TLC,[19] and showed a lower *Rf* value than I. *Anal.* Calcd. for $C_{22}H_{28}O_4N_2$ (8,8′–bicorypallyl): C, 68.72; H, 7.34. Found: C, 68.43; H, 7.53. IR($CHCl_3$) cm^{-1}: ν_{OH} 3510. NMR ($CDCl_3$) τ: 3.32 (2H, arom. H), 6.10 (6H, $2\times OCH_3$) 7.68 (6H, $2\times NCH_3$). Mass spectrum: *m/e* 384 (M^+), 369 (M–15), 341 (M–43), 326, 310, 192 (M^{++}), 191. UV λ_{max}^{EtOH} mμ: 289.

16) During the preparation of the present paper, there appeared a short communication reporting on the electrolytic and photochemical oxidation of corypalline (I) (J.M. Bobbitt, J.T. Stock, A. Marchand, and K.H. Weisgraber, *Chem. Ind.* (London), **1966**, 2117). The major product was reported to be the same compound (II) as obtaiend by the present authors with ferricyanide.

17) Melting points were determined on a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were taken on a Varian A–60 recording spectrometer in $CDCl_3$ with TMS as an internal standard or in D_2O with TMS as external standard. Chemical shifts are presented in τ values. Mass spectra were measured on a Hitachi RMU–6D machine.

18) F.A. Ramirez and A. Burger, *J. Am. Chem. Soc.*, 72, 2781 (1950); M. Erne and F.A. Ramirez, *Helv. Chim. Acta*, 33, 912 (1950).

19) Aluminium oxide G acc. to Stahl, solvent: $CHCl_3$–acetone (1:1). detected by Dragendorff's reagent.

ii) A solution of 500 mg of corypalline (I) in 50 ml of 2N NaOH was added with stirring to a solution of 1.5 g of $K_3Fe(CN)_6$ in 40 ml of water, and the resulted mixture (pH: 13.00) was kept at 3—5° for 20 hr. The reaction mixture was washed with $CHCl_3$ and made ammoniacal alkaline with the addition of NH_4Cl, then extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3, and the solvent was evaporated to give crude product (330 mg), which showed on TLC[19] a spot for the unchanged starting material (I) as well as a spot corresponding to 8,8′-bicorypallyl (II). The density of the unchanged material corresponded to *ca.* one third of the crude product. The product was purified by fractional recrystallization from $CHCl_3$ and from MeOH, and finally 45 mg of colorless cubes, mp 229° was obtained. This was identified as 8,8′-bicorypallyl (II) by IR ($CHCl_3$), NMR ($CDCl_3$), and TLC comparisons and mixed melting point determination with the sample obtained in i) above.

O,O′-Dimethyl-8,8′-bicorypallyl (III)——A methanolic solution of 60 mg of II was added to excess CH_2N_2–ether and left standing overnight at room temperature. Excess reagent and solvent were evaporated, and the residue was dissolved in 5%, HCl, and washed with ether. Acidic layer was basified with 5% NaOH, then extracted with ether. Ethereal solution was dried over anhyd. K_2CO_3, and the solvent was removed. Colorless cubes, mp 145° (16 mg) was obtained. NMR ($CDCl_3$) τ: 3.28 (2H, arom. H), 6.12, 6.35 (2×6H, $4\times OCH_3$), 7.70 (6H, $2\times NCH_3$). UV λ_{max}^{EtOH} mμ: 286.

N-Methylcorypallinium Iodide (V)——To a solution of 6.1 g of corypalline (I) in 200 ml of MeOH, was added 20 g of MeI, and the mixture as refluxed over a water bath for 1.5 hr. Solvent and excess reagent were removed by evaporation, and the crystalline residue was recrystallized from MeOH. Colorless pillars, mp 228—230°, (6.5 g) were obtained. *Anal.* Calcd. for $C_{12}H_{18}O_2NI$: C, 42.76; H, 5.36. Found: C, 42.48; H, 5.66. IR (Nujol) cm^{-1}: ν_{OH} 3350. NMR (D_2O) τ: 2.85, 3.11 (s. 2×1H, arom. H), 5.90 (s. 3H, OCH_3) 6.57 (s. 6H, $>N^+(CH_3)_2$).

N-Methylcorypallinium Picrate (VI)——To an aqueous solution of 150 mg of the iodide (V), was added a saturated aqueous solution of 105 mg of sodium picrate, and the picrate (VI) was recrystallized from acetone. Yellow needles, mp 168—169°. *Anal.* Calcd. for $C_{12}H_{18}O_2N\cdot C_6H_2O_7N_3$: C, 49.54; H, 4.62. Found: C, 49.83; H, 4.86.

Potassium Ferricyanide Oxidation of N-Methylcorypallinium Iodide (V) (Formation of N,N′-Dimethyl-8,8′-bicorypallinium)——One gram of V was dissolved in 40 ml of water, and an aq. $K_3Fe(CN)_6$ (1 g in 20 ml of water) was added dropwise to this solution, and then 80 ml of 0.08N Na_2CO_3 was added; during the additions the temperature was kept below 20°. The reaction mixture (pH: 9.5) was left standing at 3—5° for 20 hr, and acidified with 10% HCl until the reaction of the solution was faintly acidic, then warm (60°) aqueous ammonium reineckate was added to precipitate the base reineckate. Purple colored precipitate was collected by filtration, and dried. The reineckate thus obtained (1.8 g) was dissolved in acetone, filtered, and hot saturated aq. Ag_2SO_4 solution was added to the filtrate, and while warm, aq. $BaCl_2$ was added. Ag–reineckate and $BaSO_4$ were filtered off, and the filtrate was condensed under reduced pressure. Aqueous sodium picrate was added to the concentrate, and the picrate (IX) was collected by filtration, and recrystallized from aqueous acetone. Yellow microcrystalline (690 mg), mp 271—272° (decomp.), was obtained. The picrate showed single spot on TLC[20]. *Anal.* Calcd. for $C_{24}H_{34}O_4N_2\cdot C_{12}H_4O_{14}N_6$: C, 49.65; H, 4.39. Found: C, 49.66; H, 4.62.

N,N′-Dimethyl-8,8′-bicorypallinium Dichloride (VIII)——Dipicrate (IX) (100 mg) was dissolved in aqueous acetone, and 15 ml of 1% HCl was added. Picric acid was washed off with ether, and the aqueous layer was evaporated *in vacuo* to dryness. HCl was removed by repeated addition of water followed by evaporation *in vacuo*, and 70 mg of colorless crystalline residue was obtained. NMR (D_2O) τ: 2.50 (s. 2H, arom. H), 5.64 (6H, $2\times OCH_3$), 6.47 (12H, $2\times>N^+(CH_3)_2$).

N,N′-Dimethyl-8,8′-bicorypallinium Diiodide (VII)——i) A mixture of 50 mg of 8,8′-bicorypallyl (II), 0.5 ml of MeI, and 10 ml of MeOH, was refluxed over a water bath for 1 hr. Evaporation of the solvent gave crude quaternary iodide (VII). Recrystallization from MeOH gave 60 mg of colorless microprisms, mp 238—240° (decomp.). *Anal.* Calcd. for $C_{24}H_{34}O_4N_2I_2\cdot4H_2O$: C, 38.93; H, 5.71; N, 3.78. Found: C, 38.72; H, 5.88; N, 3.76. UV λ_{max}^{EtOH} mμ: 290. PPC[21] *Rf* 0.09.

ii) To a concentrated aq. solution of VIII (70 mg), conc. aq. KI solution was added, and the iodide (VII) crystallized out. This was recrystallized from MeOH, and colorless microprisms (40 mg), mp 238—240° (decomp.) were obtained. PPC,[21] *Rf* 0.09. This was identified as VII by comparisons (IR (Nujol, KBr), PPC,[21] mixed mp) with the methiodide (VII) obtained by the procedure i) described above.

N,N′,O,O′-Tetramethyl-8,8′-bicorypallinium Diiodide (X)——Dipicrate (IX) (200 mg) was dissolved in a small volume of aq. acetone, and treated with 1% HCl, and the picric acid liberated was washed off with ether. Acidic aqueous layer was condensed to dryness *in vacuo*, and the residue (111 mg) was dissolved in 5 ml of MeOH. To the methanolic solution, 10 ml of 0.5N KOH–MeOH and 4 ml of MeI were added, and the

20) Silica Gel G acc. to Stahl, solvent: MeOH–acetone–2N HCl–AcOH (14:3:6:3), detected by Dragendorff's reagent.

21) Paper chromatography: Toyo Roshi No. 50, solvent: *n*–BuOH–AcOH–H_2O (63:10:27), developed by ascending method and detected by Dragendorff's reagent.

mixture was refluxed over a water bath for 2 hr, then the solvent was evaporated to dryness. The methylating procedure was repeated twice to complete the reaction. Residual crystalline iodide was washed with $CHCl_3$ and a small volume of water, and recrystallized from MeOH to give 80 mg of orange yellow needles, mp 285° (decomp.). PPC[21] *Rf* 0.19. *Anal.* Calcd. for $C_{26}H_{38}O_4N_2 \cdot 5H_2O$: C, 39.70; H, 6.15. Found: C, 39.67; H, 6.21. UV λ_{max}^{EtOH} mμ: 287.

N,N′,O,O′-Tetramethyl-8,8′-bicorypallinium Dichloride (XI)——A methanolic solution of 40 mg of diiodide (X) was shaken with wet AgCl freshly prepared from $AgNO_3$ and HCl. Insoluble material was filtered off, and the solvent was evaporated *in vacuo* to dryness, and the crystalline residue (XI) was obtained. NMR (D_2O) τ; 2.36 (s. 2H, arom. H), 5.58, 5.93 (s. 2×6H, 4×OCH_3), 6.41, 6.44 (s. 2×6H, 2×$>N^+(CH_3)_2$).

O,N-Dimethylcorypallinium Iodide (XIII)——A solution of 100 mg of V in 3 ml of MeOH, was refluxed with 2 ml of 0.5N KOH–MeOH and 3 ml of MeI for 2 hr over a water bath. MeOH and excess MeI were removed by evaporation, and the residue was taken into $CHCl_3$, filtered and condensed to dryness. Recrystallization of the residue from MeOH gave 60 mg of colorless microcrystalline, mp 242—243°. *Anal.* Calcd. for $C_{13}H_{20}O_2NI$: C, 44.70; H, 5.77. Found: C, 44.73: H, 6.04. NMR (D_2O) τ: 2.63, 2.78 (s. 2×1H, arom. H), 5.73, 5.75 (s. 2×3H, 2×OCH_3), 6.36 (s. 6H, $>N^+(CH_3)_2$).

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