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Studies on Tetrahydroisoquinolines. I. Formation and Acid-Catalyzed Rearrangement of 10-Acetoxy-6-methoxy-2-methyl-7-oxo-$\Delta^{5,6,8,9}$-hexahydroisoquinolines[1]

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Treatment of 7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (IXa—d) with lead tetraacetate was found to give the corresponding *p*-quinol acetates (XIa—d) irrespective of the absence or the presence of substituent at 1-position.

Reaction of XIa—d under Thiele condition (Ac_2O–conc. H_2SO_4) afforded the corresponding 4,7-diacetates (XIIIa—d), in which one of newly introduced acetoxy groups was not at 5- but 4-position. 4-Hydroxy compound (XV) was also synthesized by application of Pomeranz–Fritsh type reaction to N-formyl-N-veratrylglycine (XIX).

The present rearrangement was infered to proceed through *p*-quinone methide (XXV-II) as an intermediate.

Lead tetraacetate, $Pb(OAc)_4$,[3] one of the most versatile oxidants, has been well known to oxidize phenol,[4] such as 2,4,6-trimethylphenol[5] (I) or 7-hydroxytetraline[6,7] (II), giving the corresponding *ortho* or *para*-quinol acetate [(III), (IV) or (V)]. Among others, oxidation of phenol ether, such as anisole,[8] or of aromatic compound with side chain, such as toluene[9]

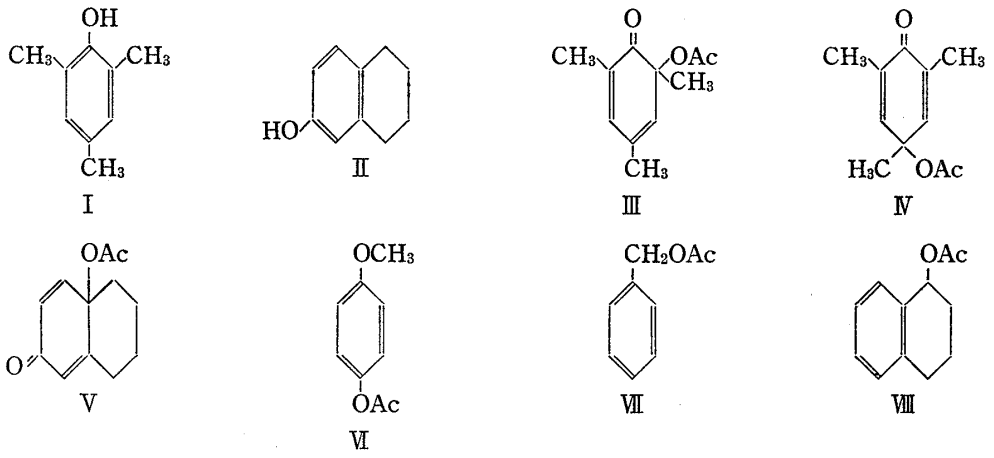


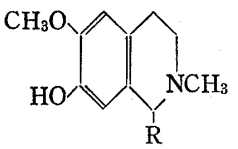
Chart 1

1) The preliminary communication of this work appeared in B. Umezawa, O. Hoshino, and Y. Terayama, *Chem. Pharm. Bull.* (Tokyo), **16**, 180 (1968).
2) Location: *12, Ichigayafunagawara-machi, Shinjuku-ku, Tokyo, 162, Japan*; Present address: *a) The Lion Dentifrice Co., Ltd., 1, Honjo, Sumida-ku; b) Tobishi Pharmaceutical Co., Ltd., Ohta-ku.*
3) R. Criege, "Oxidation in Organic Chemistry," Part A, ed. by K.B. Wiberg, Academic Press, New York, 1965, p. 277.
4) F.D. London, "Progress in Organic Chemistry," Vol. 5, ed. by J.W. Cook and W. Carruthers, Butterworths, 1961, p. 51.
5) F. Wessely and F. Sinwel, *Monotsch.*, **81**, 1055 (1950).
6) S. Goodwin and B. Witkop, *J. Am. Chem. Soc.*, **79**, 179 (1957).
7) E. Hecker, *Chem. Ber.*, **92**, 1386 (1959).
8) G.W.K. Cavill and D.H. Solomon, *J. Chem. Soc.*, **1955**, 1404.
9) G.W.K. Cavill and D.H. Solomon, *J. Chem. Soc.*, **1954**, 3943.

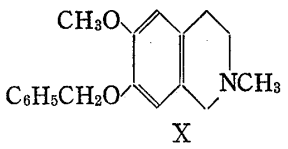
or tetraline[10] gives rise to the corresponding acetate [(VI), (VII) or (VIII)] and nitrogen heterocyclic compound is frequently dehydrogenated with $Pb(OAc)_4$.

However, few examples of similar reaction on nitrogen heterocyclic compound having phenolic hydroxy group were encountered so far. Therefore, its chemical behavior toward the oxidant attracted our attention and the reaction of hydroxy-tetrahydroisoquinoline with $Pb(OAc)_4$ was undertaken.

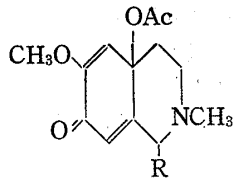
7-Hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[11] (corypalline) (IXa) was chosen as starting material. IXa was synthesized by the following improved method. Namely, a solution of formate[11] of 4-benzyloxy-3-methoxy-phenethylamine and 35% formalin in acetic acid (AcOH) was refluxed for 2 hr and usual work-up of the reaction mixture gave O-benzylcorypalline[12] (X), mp 103—105° in 76% yield. Debenzylation of X with 20% HCl afforded IXa, mp 167—167.5°, in 70% yield.



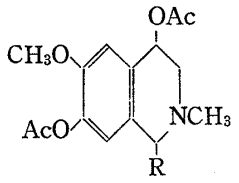
IXa : R=H
IXb : R=CH_3
IXc : R=C_6H_5
IXd : R=$CH_2C_6H_5$



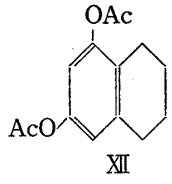
X



XIa : R=H
XIb : R=CH_3
XIc : R=C_6H_5
XId : R=$CH_2C_6H_5$



XIIIa : R=H
XIIIb : R=CH_3
XIIIc : R=C_6H_5
XIIId : R=$CH_2C_6H_5$



XII

Chart 2

A solution of IXa and $Pb(OAc)_4$ in AcOH was stirred for 2.15 hr at room temperature. Usual treatment of the reaction mixture followed by chromatography (silicic acid, Mallinckrodt) led to colorless prisms of XIa, mp 118—120°, in 20% yield. Nuclear magnetic resonance (NMR) spectrum of XIa showed three proton singlets at τ 7.92, 7.60 and 6.28 for acetoxy, N-methyl and methoxy groups, a two proton AB quartet (J=15 Hz) at τ 7.03 and 6.67 for C-1 hydrogens and each one proton singlet at τ 4.10 and 3.73 for two olefinic hydrogens. Its infrared (IR) spectrum ($CHCl_3$) indicated absorption bands due to acetoxy group at 1745 cm^{-1} and due to dienone group at 1675, 1655 and 1630 cm^{-1}.

These spectral data and elemental analysis supported that structure of XIa was 10-acetoxy-6-methoxy-2-methyl-7-oxo-$\Delta^{5,6,8,9}$-hexahydroisoquinoline (p-quinol acetate). Thus the result pointed out that $Pb(OAc)_4$ oxidation of IXa gave p-quinol acetate with nitrogen atom and that oxidation of benzylic site or nitrogen atom did not occur. Similarly, reaction of IXa with $Pb(OAc)_4$ in anhydrous ethanol (at room temperature) or anhydrous benzene (at reflux) gave XIa in 13 or 15% yield, respectively.

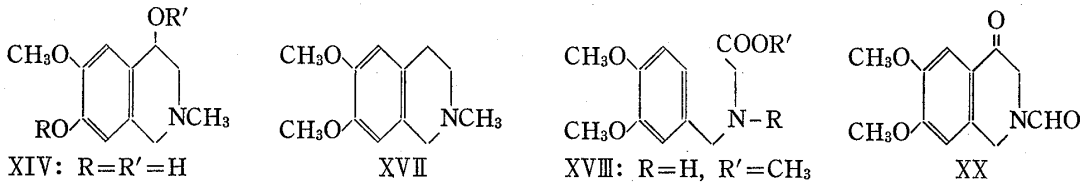
10) R. Criegee, *Ann.*, **481**, 263 (1930).
11) M. Tomita and H. Watanabe, *Yakugaku Zasshi*, **58**, 783 (1938).
12) M. Tomita, K. Fujitani, Y. Masaki and K. -H. Lee, *Chem. Pharm. Bull.* (Tokyo), **16**, 251 (1968).

In general, treatment of quinol acetates under Thiele condition (Ac_2O–conc.H_2SO_4) has been known to afford the products resembling dienone–phenol type rearrangement ones. For example, V is rearranged to 5,7-diacetoxytetraline (XII).[6]

Therefore, in order to obtain further evidence on structure of XIa and a compound in which acetoxy group was introduced into aromatic ring in IXa, a solution of XIa in Ac_2O containing conc. H_2SO_4 (two or more equivalnts) was stirred for 2.25 hr at room temperature. Usual treatment of the reaction mixture accompanied by chromatography yielded colorless prisms of XIIIa, mp 82—84°, in 47% yield. Its NMR spectrum showed four three proton singlets at τ 7.85, 7.69, 7.54 and 6.21 for two acetoxy, N-methyl and methoxy groups, a two proton octet (J=12.5 Hz, J=3 Hz) at τ 7.30 and 7.03 for C-3 hydrogens, a two proton AB quartet (J=15 Hz) at τ 6.71 and 6.22 for C-1 hydrogens, a one proton triplet (J=3 Hz) at τ 4.06 for C-4 hydrogen and each one proton singlet at τ 3.24 and 3.06 for C-8 and C-5 hydrogen and the IR spectrum (KBr) displayed absorption bands due to aromatic and aliphatic acetoxy group at 1765 and 1730 cm^{-1}, respectively.

This spectral data clearly supported structure of XIa being 4,7-diacetoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, in which one of newly introduced acetoxy groups was not at 5- but 4-position. Surprisingly, this was quite different from that[6] in the case of V.

Furthermore, it was proved by the following two ways that a newly introduced acetoxy group was at 4-position. Firstly, hydrolysis of XIIIa in 5% aqueous potassium hydroxide solution led to colorless prisms of the corresponding 4,7-dihydroxy compound (XIV), mp 153—155° (decomp.), in 55% yield. Methylation of XIV with diazomethane resulted in colorless prisms of XV, mp 127—128°, in 32% yield, whose structure was confirmed to be 6,7-dimethoxy-4-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline by means of its NMR spectrum showing three three proton singlets at τ 7.63, 6.12 and 6.10 for N-methyl and two methoxy groups, a two proton octet (J=12.5 Hz, J=2.5 Hz) at τ 7.51 and 7.03 for C-3 hydrogens, a two proton AB quartet (J=15 Hz) at τ 6.27 and 6.58 for C-1 hydrogens, a one proton triplet (J=2.5 Hz) at τ 5.46 for C-4 hydrogen and each one proton singlet at τ 3.56 and 3.07 for C-8 and C-5 hydrogen and its IR spectrum (KBr) displaying absorption band due to hydroxy group at 3500 cm^{-1}. Acetylation of XIV or XV with Ac_2O in pyridine furnished XIIIa, mp 81—84° or colorless prisms of XVI, mp 90—91.5°. Structure of XVI was confirmed to be 4-acetoxy-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline by inspection of its NMR spectrum depicting three three proton singlets at 7.88, 7.52 and 6.15 for acetoxy, N-methyl and methoxy groups, a two proton octet (J=12.5 Hz, J=2.5 Hz) for C-3 hydrogens, a two proton AB quartet (J=15 Hz) at τ 6.72 and 6.15 for C-1 hydrogens, a one proton triplet (J=2.5 Hz) at 4.05 for C-4 hydrogen and each one proton singlet at τ 3.43 and 3.15 for C-8 and C-5 hydrogen and by means of IR spectrum (KBr) showing absorption band due to acetoxy group at 1725 cm^{-1}.



XIV: R=R'=H
XV : R=CH_3, R'=H
XVI: R=CH_3, R'=Ac

XVII

XVIII: R=H, R'=CH_3
XIX: R=CHO, R'=H

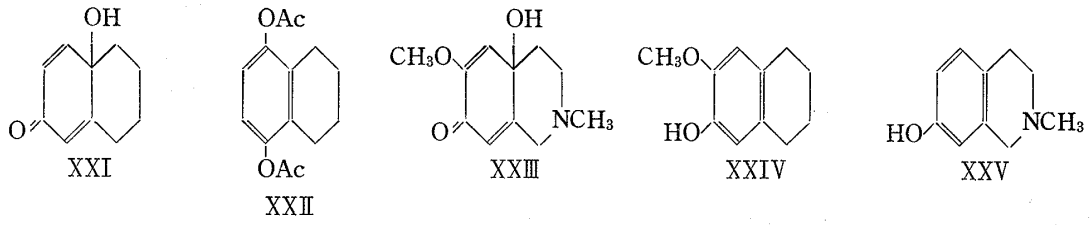
XX

Chart 3

Moreover, catalytic hydrogenation (10% Pd-C, AcOH, conc. H_2SO_4) of XIIIa gave IXa and treatment of XIIIa with lithium aluminum hydride ($LiAlH_4$) followed by methylation

(CH_2N_2) led to XV and 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[13] (XVII) in approximately 1:1 ratio. Formation of XVII besides XV in the case of the latter would take place by replacement of acetoxy group at 4-position with hydride ion.

Secondly, validity of structure of XIIIa was secured by an alternate synthesis of XV, to which Pomeranz–Fritsch type reaction of N-veratrylglycine derivative was applied. Heating of a mixture of veratraldehyde,[14] methyl glycinate hydrochloride[15] and potassium carbonate in anhydrous benzene gave the corresponding Schiff base, sodium borohydride reduction of which led to methyl N-veratrylglycinate (XVIII) (oxalate, mp 200—201°). N-



XXI XXII XXIII XXIV XXV

Chart 4

Formylation and successive hydrolysis of XVIII resulted in N-formyl-N-veratrylglycine (XIX), mp 193—196°, in 55% yield (based on XVIII). Cyclization of XIX with polyphosphoric acid[16] at 74—78° afforded N-formyl-6,7-dimethoxy-4-oxo-1,2,3,4-tetrahydroisoquinoline (XX) as an oil (oxime, mp 178—179°), in 26% yield together with undetermined yellow crystals, mp 287—289° (decomp.). Subsequent $LiAlH_4$ reduction of XX in anhydrous ether and anhydrous tetrahydrofuran gave rise to XV, which was identical with a product obtained from XIIIa by comparison of IR spectrum and retention time (14.45 min; column temperature, 150°) of gaschromatography and by mixed fusion.

Thus, one of acetoxy groups in XIIIa was confirmed to be at 4-position and acid-catalyzed treatment of XIa was found to furnish a different rearranged product (XIIIa) from that[6] in the case of *p*-quinol acetate (V).

On the basis of the result, analogous treatment of 1-substituted hydroxy-tetrahydroisoquinolines with $Pb(OAc)_4$ followed by acid (Ac_2O–conc.H_2SO_4) treatment was undertaken. 1-Methyl-,[17] 1-phenyl-[18] or 1-benzyl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[19] [(IXb), (IXc) or (IXd)] was oxidized with $Pb(OAc)_4$ to afford a diastereoisomeric

Table I. Reaction Time, Yield, Melting Point and Elemental Analysis of XI

Compound	Reaction time (hr)	mp (°C)	Yield (%)	Formula	Analaysis (%) Calcd. C	H	N	Found C	H	N
XIa	1.5	118—120	20	$C_{13}H_{17}O_4N$	62.14	6.82	5.57	62.34	6.94	5.63
XIb	4.5	81—84.5	18	$C_{14}H_{19}O_4N$	63.38	7.22	5.28	63.24	7.30	5.22
XIc	2.5	145	27	$C_{19}H_{21}O_4N$	69.70	6.47	4.28	69.43	6.45	4.35
XId	2.75	149—151	14	$C_{20}H_{23}O_4N$	70.36	6.79	4.10	70.33	6.93	3.98

13) M. Tomita and T. Kitamura, *Yakugaku Zasshi*, **79**, 997 (1959).
14) J.S. Buck, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, N. Y., 1966, p. 619.
15) J.P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley and Sons, Inc., New York, 1961, p. 926.
16) *cf.* F.D. Popp and W.E. McEwen, *Chem. Revs.*, **58**, 312 (1958).
17) I.T. Strukor, *Zh. Obshch. Khim.*, **31**, 2709 (1961) [*Chem. Abst.*, **56**, 11567 f (1962)].
18) T. Kametani, M. Shio and K. Fukumoto, *Yakugaku Zasshi*, **85**, 960 (1965).
19) T. Kametani, K. Wakisaka and K. Fukumoto, *Yakugaku Zasshi*, **85**, 956 (1965).

mixture of the corresponding *p*-quinol acetate [(XIb), (XIc) or (XId)] in 18, 27 or 14% yield, respectively. Each structure was determined by means of each NMR, IR spectrum and elemental analysis. Furthermore, reaction of IXb, IXc or XId under the same condition as noted in the case of XIa led to only a diastereoisomeric mixture of the corresponding 4,7-diacetate [(XIIIb), (XIIIc) or (XIIId)] in 16, 34 or 43% yield, respectively. Characterization of each structure was performed by means of spectral data as well as elemental analysis. These results were shown in Table I and II.

TABLE II. Reaction Time, Yield, Melting Point and Elemental Analysis of XIII

Compound	Reaction time (hr)	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIIIa	2.25	82—84	47	$C_{15}H_{19}O_5N$	61.42	6.53	4.78	62.28	6.61	4.68
XIIIb	1.0	72—82	16	$C_{16}H_{21}O_5N$	62.52	6.88	4.56	62.83	7.01	4.35
XIIIc	1.5	125—128	34	$C_{21}H_{23}O_5N$	68.28	6.28	3.79	68.20	6.40	3.83
XIIId	2.5	153—157	43	$C_{32}H_{33}O_{10}N_5 \cdot H_2O$[a]	57.65	5.25	10.51	57.74	5.08	10.36

a) picrolonate

Thus, the reaction with $Pb(OAc)_4$ was proved to afford *p*-quinol acetate derivative (XIa—d), acid-catalyzed reaction of which furnished a novel rearranged product, 4,7-diacetoxy compound. (XIIIa—d), irrespective of the absence or the presence of 1-substituent.

In general, it has been known[20] that while acid-catalyzed treatment of quinols results in alkyl migration, acid-catalyzed treatment of quinol acetates results in acetoxy migration. For example, while rearrangement of XXI furnishes XXII,[21] rearragement of V leads to XII.[6]

With this in mind, treatment of *p*-quinol (XXIII), mp 153.5—155° (prepared by hydrolysis of XIa), under the same condition as noted above was carried out to yield only XIIIa in 55% yield. Thus, rearrangement of XIa or XXIII was found to take place in acetoxy migration, direction of which was quite different from that[6] in V. Such a remarkable difference was considered to be attributable to the presence of 6-methoxy group and/or nitrogen atom in IXa, when compared with V. In order to solve the problem, $Pb(OAc)_4$ oxidation of 7-hydroxy-6-methoxy-tetraline[22] (XXIV) or 7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline[23] (XXV) was carried out to be unsuccessful. Accordingly, this result supported that the presence of both 6-methoxy group and nitrogen atom was probably necessary requirement as for formation of *p*-quinol acetate. In addition, the finding that 5,7-diacetoxy compound (XXVI) could not be formed would be due to electron-donating effect of 6-methoxy group, though influence of nitrogen atom could not be excluded at this stage.

Finally, the reaction pathway on the present rearrangement would be visualized in Chart 5. Namely, detouch of acetic acid would result in an intermediate (*p*-quinone methide[24] (XXVII), which was immediately transformed to XIII by attack of acetoxyl anion on 4-positon. As to the pathway on formation of *p*-quinone methide (XXVII), the following two

20) B. Miller, "Mechanisms of Molecular Migrations," Vol. 1, ed. by B.S. Thyagarajan, Interscience Publishers, 1968, pp. 291—302.
21) Y. Asahina and T. Momose, *Ber.*, **71**, 1421 (1938).
22) T. Momose and S. Goya, *Chem. Pharm. Bull.* (Tokyo), **7**, 849 (1959).
23) T. Tomioka, T. Nakamura and Y. Hoshide, *Bull. Chem. Soc. Japan*, **36**, 441 (1963).
24) *cf* A.B. Turner, *Quart. Rev.*, **18**, 347 (1964).

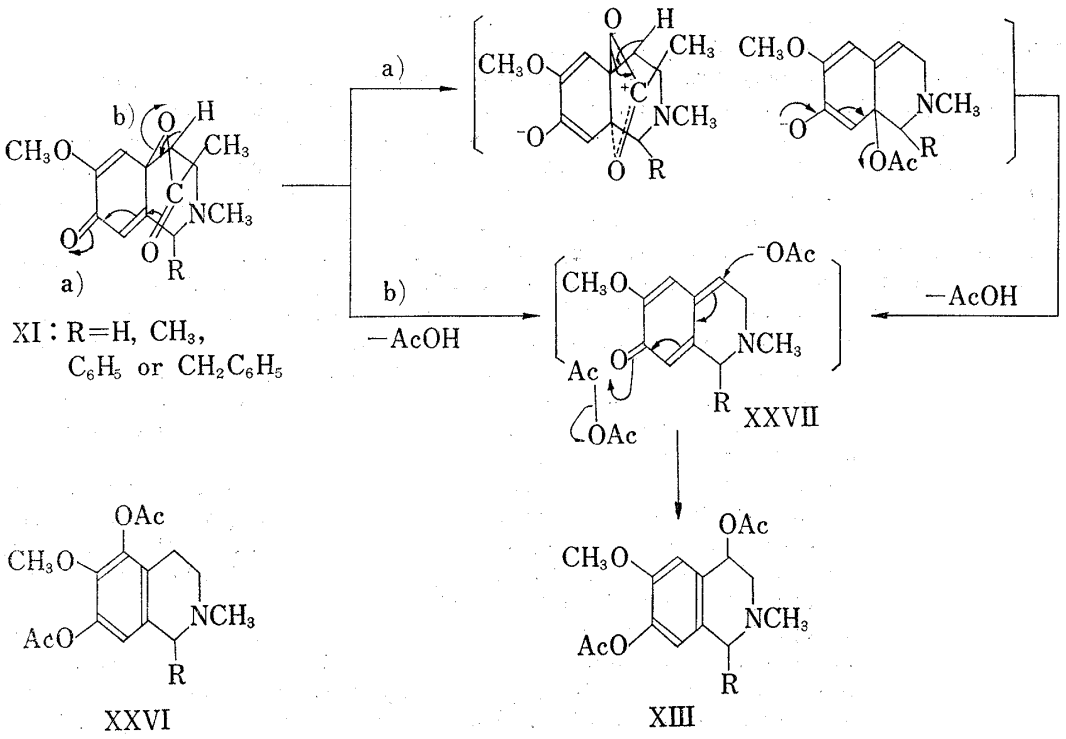


Chart 5

route a) and b) would be preferable. While cyclic migration[25,26] of 10-acetoxy group to 9-position followed by elimination of acetic acid would preceed to afford XXVII in the route a), the same intermediate would be originated by direct elimination of acetic acid in the route b). Considering the fact that XXIII reacted with Ac_2O and conc. H_2SO_4 to give XIa, however, the latter would be favored.

Experimental[27]

7-Hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (Corypalline) (IXa)——A solution of formate[11] of 4-benzyloxy-3-methoxyphenethylamine (177 g) and 35% formalin (177 ml) in AcOH (1000 ml) was gently refluxed for 2 hr. An oily residue obtained on removal of the solvent under reduced pressure was basified with 10% NaOH and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ layer afforded an oil (212 g), which was extracted with hot *n*-hexane. The *n*-hexane extract was condensed to a small volume. When the solution was allowed to stand at room temperature, a solid (X), mp 91—94°, (125 g, 76%) was obtained. Recrystallization gave colorless prisms of X, mp 103—105° (lit.[12] mp 102—103°) *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.04; H, 7.41; N, 4.89.

A solution of X (34.8 g) in 20% HCl was heated for 0.5 hr and after cooling, the solution was washed with ether. This treatment was repeated and the total reaction time was 1.5 hr. To a residue obtained on removal of the solvent under reduced pressure, H_2O (100 ml) was added and then NH_3 gas was indtroduced into the whole under ice-cooling. A crystalline mass was precipitated. After the solution became comple-

25) The reaction mechanism[6] on formation of XII from V is explained by cyclic migration acetoxy group.

26) The authors are grateful to Dr. T. Onaka, ITSUU Laboratory, Tokyo, for his valuable discussion on the reaction pathway.

27) All melting points were uncorrected and measured on a Yanagimoto micro melting point measuring apparatus. NMR spectra were taken with a Japan Electron Optics Labs. Model JNR-4H-100 spectrometer in $CDCl_3$ solution (5—10%) by using $(CH_3)_4Si$ as internal standard. Following abbreviations were used: s: singlet; bs: broad singlet; d: doublet; t: triplet; dt: defused triplet; AB q: AB quartet; m: multiplet. IR spectra were run on a Hitachi infrared spectrometer Model EPI-S_2. Gas chromatography was carried out with a Shimadzu gas chromatograph GC-lC equipped with hydrogen flame ionization detector by using 5% SE-30 on Shimalite W (80—100 mesh) as stationary phase. Unless otherwise noted, column chromatography was performed over silicic acid (Mallinckrodt), the organic phase was dried over $MgSO_4$ and recrystallization was carried out from *n*-hexane.

tely basic, the precipitate was collected and dried. Recrystallization from MeOH gave colorless prisms of IX, mp 167—167.5° (lit.[11] mp 167°) (16 g, 70%).

1-Benzyl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (IXd)——A solution of O-benzyl-IXd (800 mg) (prepared according to the method[19] of T. Kametani, *et al.*) and conc. HCl (20 ml) in EtOH (20 ml) was refluxed for 3.5 hr. To a residue obtained on removal of the solvent under reduced pressure, H_2O was added and the solution washed with ether. The solution was basified with NH_3 gas and the product was taken up in ether. Usual work-up of the ether layer gave an oil (527 mg), whose treatment with ether afforded a solid (IXd), mp 86—88.5° (468 mg, 77%). Recrystallization from C_6H_6–*n*-hexane furnished colorless prisms of IXd, mp 88.5—89.5° (lit.[19] mp 130—131°). *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.43; H, 7.26; N, 4.94. NMR τ: 7.52 (3H, s, NCH_3), 6.24 (1H, t, $J=5$ Hz, $>C\underline{H}$-$CH_2C_6H_5$), 6.13 (3H, s, OCH_3), 3.58, 3.42 (each 1H, s, aromatic ring proton), 2.85—2.65 (5H, m, $CH_2C_6\underline{H}_5$).

General Procedure for Reaction of IX with $Pb(OAc)_4$——To a solution of IX in AcOH, $Pb(OAc)_4$ was added in one portion and the whole was stirred at roomt emperature. To the reaction mixture, H_2O was added and the solution was carefully basified with $NaHCO_3$ (powder). The product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried. Removal of the solvent under reduced pressure below 30° gave an oil, which was chromatographed.

(1) XIa: IXa (200 mg), $Pb(OAc)_4$ (680 mg) and AcOH (5 ml) were used. Chromatography of an oil (213 mg) over Al_2O_3 (neutral, Woelm) gave a solid (85 mg), mp 114—117° (from an eluate with $CHCl_3$), which was recrystallized to colorless prisms of XIa, mp 118—120° (72 mg, 20%). NMR τ: 7.92 (3H, s, OAc), 7.60 (3H, s, NCH_3), 7.03, 6.67 (2H, AB q, $J=15$ Hz, C-1 H_2), 6.28 (3H, s, OCH_3), 4.10, 3.73 (each 1H, s, olefinic proton). IR ν_{max}^{KBr} cm^{-1}: 1745 (OAc), 1675, 1655, 1630 (dienone).

(2) XIb: IXb[17] (520 mg), $Pb(OAc)_4$ (1.3 g) and AcOH (9 ml). The mixture was stirred for 4.5 hr at room temperature. Chromatography of an oil (675 mg) afforded an oil from an eluate with $CHCl_3$–MeOH (100: 2). Treatment of an oil with petroleum ether (bp 33—35°) yielded a solid, which was recrystallized to colorless prisms of XIb, mp 81—84.5°, (120 mg, 18%). NMR τ: 8.69 (3H, d, $J=6.3$ Hz, $>CH\underline{CH}_3$), 7.91 (3H, s, OAc), 7.68 (3H, s, NCH_3), 6.89 (1H, q, $J=6.3$ Hz, $>C\underline{H}CH_3$), 6.28 (3H, s, OCH_3), 4.14, 3.72 (each IH, s, olefinic proton). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745 (OAc), 1670, 1645, 1630 (dienone).

(3) XIc: IXc[18] (215 mg), $Pb(OAc)_4$ (390 mg) and AcOH (1.7 ml). The reaction mixture was stirred for 2.5 hr. Chromatography of an oil (286 mg) gave a solid (from an eluate with $CHCl_3$), which was recrystallized from CCl_4 to colorless prisms of XIc, mp 145°, (71 mg, 28%). NMR τ: 7.80 (6H, bs, OAc and NCH_3), 6.30 (3H, s, OCH_3), 6.19 (1H, bs, C-1 H_2), 4.55 (1H, d, $J=1.5$ Hz, C-8 H), 4.03 (1H, s, C-5 H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (OAc), 1675, 1655, 1630 (dienone).

(4) XId: IXd[19] (2 g), $Pb(OAc)_4$ (4.8 g) and AcOH (20 ml). The reaction mixture was stirred for 2.75 hr. Chromatography of an oil (1.77 g) was performed. Elution with $CHCl_3$–MeOH (400: 1) gave an oil (530 mg), which was crystallized with *n*-hexane to a solid (XId), mp 141—152°, (330 mg, 14%). Recrystallization from C_6H_6–*n*-hexane afforded colorless prisms of XId, mp 149—151°. NMR τ: 7.92 (3H, s, OAc), 7.78 (3H, s, NCH_3), 7.02 (2H, d, $J=7.5$ Hz, $>CHC\underline{H}_2C_6H_5$), 6.28 (3H, s, OCH_3), 6.06 (1H, t, $J=7.5$ Hz, C-1 H), 4.11, 3.70 (each 1H, s, olefinic proton), 2.70 (5H, s, $CH_2C_6\underline{H}_5$). IR ν_{max}^{KBr} cm^{-1}: 1740 (OAc), 1663, 1640, 1623 (dienone).

General Procedure for Reaction of XI with Ac_2O-conc. H_2SO_4——To an ice-cooled, stirred solution of XI in Ac_2O, a solution of Ac_2O snd conc. H_2SO_4 was added dropwise. During this time, the reaction mixture displayed dark brown color disappearing immediately. The whole was carefully poured onto crashed ice and excess Ac_2O was washed with ether. The aqueous solution was cautiously basified with $NaHCO_3$ (powder) and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried. Removal of the solvent under reduced pressure below 30° gave an oil, chromatography of which was undertaken.

(1) XIIIa: XIa (275 mg), Ac_2O (4 ml) and conc. H_2SO_4 (0.3 ml)–Ac_2O (1 ml) were used. Chromatography of an oil (227 mg) gave an oil (200 mg) from an eluate with $CHCl_3$–MeOH (100: 1). It was crystallized with *n*-hexane to a solid (XIIIa), mp 76—78°, (145 mg, 48%), whose recrystallization afforded colorless prisms of XIIIa, mp 82—84°. NMR τ : 7.85, 7.69 (each 3H, s, OAa×2), 7.54 (3H,s, NCH_3), 7.30, 7.03 (2H, octet, $J=12.5$ Hz, $J=3$ Hz, C-3 H_2), 6.71, 6.22 (2H, AB q, $J=15$ Hz, C-1 H_2), 6.21 (3H, s, OCH_3), 4.06 (1H, t, $J=3$ Hz, C-4 H), 3.24, 3.06 (each 1H, s, C-8 and C-5 H). IR ν_{max}^{KBr} cm^{-1}: 1765 (arom, OAc), 1730 (aliph. OAc), 1615 (C=C).

(2) XIIIb: XIb (790 mg), Ac_2O (8 ml) and conc. H_2SO_4 (0.85 ml) –Ac_2O (2 ml) were used. Chromatography of an oil (578 mg) gave a solid (281 mg) from an eluate with $CHCl_3$–MeOH (100: 1). Recrystallization afforded colorless prisms of XIb, mp 72—82°, (148 mg, 16%). NMR τ: 8.76, 8.56 [3H, d, $J=7.5$ Hz, $>CHC\underline{H}_3$(1: 3)], 7.87, 7.70 (each 3H, s, OAc×2), 7.52 (3H, s, NCH_3), 6.67, 6.62 [1H, q, $J=7.5$ Hz, $>C\underline{H}$-CH_3 (1: 3)], 6.21 (3H, s, OCH_3), 4.09 (1H, t, $J=3$ Hz, C-4 H), 3.19, 3.12, 3.07 [2H, each s, aromatic proton (1: 4: 3)]. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (arom. OAc), 1730 (aliph. OAc), 1620 (C=C).

(3) XIIIc: XIc (300 mg), Ac_2O (1 ml) and conc. H_2SO_4 (0.26 ml)–Ac_2O (0.33 ml) were used. Chromatography of an oil (231 mg) gave a solid (155 mg) from an eluate with $CHCl_3$–MeOH (100: 1). Recrystallization from C_6H_6–*n*-hexane to colorless prisms of XIIIc, mp 125—128, (139 mg, 42%). NMR τ: 7.80 (6H, s, OAc and NCH_3), 7.17, 6.71 (2H, octet, $J=12.5$ Hz, $J=3$ Hz, C-3 H_2), 6.17 (3H, s, OCH_3), 5.90 (1H, s, C-1 H), 4.00 (1H, dt, C-4 H), 3.65, 2.99 (each 1H, s, aromatic proton), 2.65 (5H, s, $>CHC_6\underline{H}_5$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (arom. OAc), 1730 (aliph. OAc), 1620 (C=C).

(4) XIIId: XId (330 mg), Ac_2O (6 ml) and conc. H_2SO_4 (1 ml)–Ac_2O (1.5 ml) were used. Chromatography of an oil (221 mg) gave an oil (XIIId) (160 mg, 43%); picrolonate, mp 153—157°. Free base; NMR τ: 7.89, 7.75 (each 3H, s, OAc×2), 7.46, 7.38 [3H, each s, NCH_3 (1:3)], 6.25, 6.05 [1H, each t, J=6.3 Hz, >CHCH$_2$ C_6H_5 (1:3)], 4.14, 4.02 [1H, dt and t (J=6.3 Hz), C-4 H (3:1)], 3.67, 3.50 [1H, s, aromatic proton (3:1)], 3.08 (1H, s, aromatic proton), 2.95—2.82, 2.82—2.65 [5H, each m, $CH_2C_6H_5$ (1:3)]. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (arom. OAc), 1723 (aliph. OAc), 1620 (C=C).

4,7-Dihydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (XIV)——A mixture of XIIIa (130 mg) in 5% KOH (10 ml) was stirred for 0.75 hr at room temperature. During this time the starting material was completely dissolved. The solution was acidified with 10% HCl under ice-cooling and carefully basified with K_2CO_3 (powder). The product was taken up in $CHCl_3$. The $CHCl_3$ extract was dried. Removal of the solvent afforded a solid (XIV) [65 mg, 70%, mp 150—155° (decomp.)], recrystallization of which from $CHCl_3$–*n*-hexane furnished colorless prisms of XIV, mp 153—155° (decomp.). *Anal.* Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.17; H, 7.31; N, 6.50. IR ν_{max}^{KBr} cm^{-1}: 3350, 3050 (OH), 1615 (C=C).

Methylation of XIV——A solution of XIV (70 mg) and CH_2N_2 in MeOH (4 ml) was allowed to stand for 15 hr at 0—5° and then for 27 hr at room temperature. Removal of the solvent gave an oil (76 mg) which was chromatographed over Al_2O_3 (neutral, Woelm). Elution with C_6H_6–$CHCl_3$ (10:1) gave a solid (XV), mp 115—120° (32 mg, 42%), whose recrystallization from C_6H_6–*n*-hexane afforded colorless prisms of XV, mp 127—128°. *Anal.* Calcd. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.30; H, 7.83; N, 5.96. NMR τ: 7.63 (3H, s, NCH_3), 7.51, 7.03 (2H, octet, J=12.5 Hz, J=2.5 Hz, C-3 H_2), 6.87, 6.58 (2H, AB q, J=15 Hz, C-1 H_2), 6.12, 6.10 (each 3H, s, OCH_3×2), 5.46 (1H, t, J=2.5 Hz, C-4 H), 3.56, 3.07 (each 1H, s, C-8 and C-5 H). IR ν_{max}^{KBr} cm^{-1}: 3150 (OH), 1605 (C=C).

Acetylation of XIV——A solution of XIV (15 mg) and Ac_2O (0.05 ml) in pyridine (0.3 ml) was kept for 4.5 hr at room temperature. To a residue obtained on removal of the solvent under reduced pressure, H_2O was added and the solution was basified with $NaHCO_3$ (powder). The product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried. Removal of the solvent gave an oil which was crystallized with *n*-hexane to a solid (XIIIa), mp 80—83°, (10 mg, 48%), whose recrystallization afforded colorless prisms of XIIIa, mp 81—84°. This was identical with a sample (mp 82—84°) obtained from XIa in all respects.

Acetylation of XV——A solution of XV (69 mg) and Ac_2O (0.2 ml) in pyridine (1 ml) was kept for 12 hr at room temperature. The same treatment as noted in the case of XV gave an oil (58 mg), which was crystallized with *n*-hexane to a solid (XVII), mp 86—89°, (49 mg, 69%), whose recrystallization yielded colorless prisms of XVII, mp 90—91.5°. *Anal.* Calcd. for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.30; H, 7.24; N, 5.40. NMR τ: 7.88 (3H, s, OAc), 7.52 (3H, s, NCH_3), 7.35, 7.00 (2H, octet, J=12.5 Hz, J=2.5 Hz, C-3 H_2), 6.72, 6.15 (2H, AB q, J=15 Hz, C-1 H_2), 6.13 (6H, s, OCH_3×2), 4.05 (1H, t, J=2.5 Hz, C-4 H), 3.43, 3.15 (each 1H, s, C-8 and C-5 H). IR ν_{max}^{KBr} cm^{-1}: 1725 (OAc), 1620 (C=C).

Catalytic Hydrogenation of XIIIa——A solution of XIIIa (40 mg) and conc. H_2SO_4 (0.05 ml) in AcOH (5 ml) was shaken with 10% Pd-C (20 mg) in H_2 atmosphere for 20 hr under heating by IR lamp. After filtration of catalyst the solvent was removed under reduced pressure. H_2O was added to a residue and the solution was basified with K_2CO_3 (powder). The product was taken up in $CHCl_3$–iso-PrOH (5:1) and dried over K_2CO_3. Removal of the solvent gave IXa, mp 155—167°, (24 mg, 91%), which was recrystallized from iso-PrOH to colorless prisms of IXa, mp 166—169°. This was identical with an authentic specimen (lit.[11] mp 167°) by mixed fusion.

$LiAlH_4$ Reduction of XIIIa——A mixture of XIIIa (100 mg) and $LiAlH_4$ (50 mg) in anhydrous ether (20 ml)–anhydrous THF (10 ml) was stirred for 3 hr at room temperature. To the reaction mixture, crashed ice was carefully added and the solution was acidified with 20% HCl. The organic layer was separated and the acidic solution was basified with K_2CO_3 (powder). The product was taken up in $CHCl_3$. The $CHCl_3$ layer was washed with brine and dried over K_2CO_3. Removal of the solvent afforded an oil (60 mg), treatment of which with CH_2N_2 in MeOH (2 ml) (at 0—5° for 50 hr) gave an oil (58 mg). Chromatographic purification [elution with $CHCl_3$–MeOH (100:1)] gave an oily crystals (XVII) (16 mg, 23%), which was identical with an authentic specimen (lit.[13] mp 81—82°) by comparison of IR spectrum ($CHCl_3$). Elution with $CHCl_3$–MeOH (100:2) gave a solid (XIV), mp 115—120°, (16 mg, 21%), which was recrystallized from C_6H_6–*n*-hexane to colorless prisms of XV, mp 124—126°. This was identical with a product (mp 127—128°) obtained from XIV by comparison of IR spectrum and by mixed fusion.

Methyl N-Veratrylglycinate (XVIII)——A mixture of veratraldehyde[14] (2.4 g), mehtyl glycinate·HCl[15] (4.0 g) and K_2CO_3 (5.0 g) in anhydrous C_6H_6 (60 ml) was stirred for 10 hr under reflux. After filtration of the precipitate, removal of the solvent under reduced pressure gave an oil (3.7 g) of Schiff base. To an ice-cooled, stirred solution of Schiff base (3.7 g) obtained above in MeOH (60 ml), $NaBH_4$ (0.6 g) was added and the whole was kept for 1 hr at room temperature and refluxed gently for additional 1 hr. To a residue obtained on removal of the solvent under reduced pressure, H_2O was added and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ layer gave an oil (XVIII) (3 g, 63%) (overall yield based on veratraldehyde): oxalate, mp 200—201° (MeOH). *Anal.* Calcd. for $C_{14}H_{19}O_8N$: C, 51.06; H, 5.82; N, 4.26. Found; C, 51.30; H, 5.85; N, 4.63. IR ν_{max}^{KBr} cm^{-1}: 1755 ($COOCH_3$), 1610 1595 (C=C). Free base; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 ($COOCH_3$), 1610, 1595 (C=C).

N-Formyl-N-veratrylglycine (XIX)——XVIII (0.97 g) [prepared from its oxalate (1.8 g) was heated with 95% HCOOH (2 ml) for 4 hr at 105—110° (oil-bath) under reduced pressure. After cooling, H_2O was added to the reaction mixture and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with 10% HCl, brine and dried. Removal of the solvent gave an oil (0.86 g), attempted crystallization of which was unsuccessful. A solution of an oil (0.8 g) obtained above in 1% KOH–EtOH (20 ml) was refluxed for 2 hr. To a residue left on removal of the solvent under reduced pressure, H_2O was added and the solution was washed with $CHCl_3$. The aqueous solution was acidified with conc. HCl and the product was taken up in $CHCl_3$. Usual treatment of the $CHCl_3$ layer gave a solid (XIX), mp 184—188°, (421 mg, 55%), which was recrystallized from MeOH to colorless prisms of XIX, mp 193—196°. *Anal.* Calcd. for $C_{12}H_{15}O_5N$: C, 56.91; H, 5.91; N, 5.53. Found: C, 56.91; H, 5.94; N, 5.45. IR ν_{max}^{KBr} cm^{-1}: 1740 (COOH), 1645 (NCHO).

N-Formyl-6,7-dimethoxy-4-oxo-1,2,3,4-tetrahydroisoquinoline (XX)——A mixture of XIX (1 g) and PPA[16] (10 g) [prepared by heating (for 3 hr under stirring at 82—85°) of a mixture of P_2O_5 (6.2 g) and 85% H_3PO_4 (4 ml)] was stirred for 2.5 hr at 74—78°. To the whole, ice water was added and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was washed with 2% NaOH, 2% HCl and brine, and dried. Usual treatment of the $CHCl_3$ layer afforded a solid (618 mg), which was chromatographed over Al_2O_3 (Merck). Elution with C_6H_6 furnished a solid [71 mg, mp 258—265° (decomp.)], which was recrystallized from C_6H_6–$CHCl_3$ to pale yellow prisms; mp 287—289° (decomp.) Its structure was not characterized. Elution with C_6H_6–$CHCl_3$ (50: 1) gave an oil (XX) (238 mg, 26%) [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 [(c=0, shoulder, 1670 (NCHO), 1605 (C=C)]; oxime, mp 178—179° (EtOH). *Anal.* Calcd. for $C_{12}H_{14}O_4N_2 \cdot {}^1/_2H_2O$: C, 55.60; H, 5.41; N, 10.81. Found: C, 55.82; H, 5.64; N, 11.12. IR ν_{max}^{KBr} cm^{-1}: 3230 (OH), 1655 (NCHO), 1625 (C=N), 1600 (C=C).

$LiAlH_4$ Reduction of XX——A mixture of XX (55 mg) and $LiAlH_4$ (50 mg) in anhydrous ether (6 ml)–anhydrous THF (6 ml) was stirred for 4 hr under reflux. To the ice-cooled whole, crashed ice was added and the solution was acidified with 20% HCl. The organic layer was separated and the acidic solution was washed with ether. The aqueous solution was made basic with K_2CO_3 (powder) and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ layer gave an oil (28 mg), which was chromatographed. Elution with $CHCl_3$–MeOH (100: 1) afforded XV, mp 117—125°, (13 mg, 25%), which was recrystallized from C_6H_6–n-hexane to colorless prisms of XV, mp 124—126°. This was identical with a prodcut (mp 127—128°) obtained from XIIIa by comparison of t_R (14.45 min; column temperature, 150°) and IR spectrum, and by mixed fusion.

10-Hydroxy-6-methoxy-2-methyl-7-oxo-$\Delta^{5,6,8,9}$-hexahydroisoquinoline (XXIII)——To an ice-cooled, stirred solution of KOH (300 mg) in MeOH (10 ml), a solution of XIa (672 mg) in MeOH (5 ml) was added and the whole was stirred for 0.5 hr at room temperature. AcOH (500 mg) was added to the reaction mixture. The solution was basified with K_2CO_3 (powder) and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ layer gave an oil (471 mg), which was chromatotgraphed. Elution with $CHCl_3$–MeOH (100: 4)—(100: 5) gave a solid (XXIII), mp 149.5—152°, (97 mg, 17%), which was recrystallized from C_6H_6–n-hexane to colorless prisms of XXIII, mp 153.5—155°. *Anal.* Calcd. for $C_{11}H_{15}O_3N$: C, 63.14; H, 7.21; N, 6.69. Found: C, 63.01; H, 7.13; N, 6.65. NMR τ: 7.53 (3H, s, NCH_3), 6.74 (2H, bs, C-1 H_2), 6.32 (3H, s, OCH_3), 4.23, 3.93 (each 1H, s, C–8 and C–5 H). IR ν_{max}^{KBr} cm^{-1}: 3080 (OH), 1680, 1660, 1630 (dienone).

Reaction of XXIII with Ac_2O-conc. H_2SO_4——To an ice-cooled, stirred solution of XXIII (72 mg) in Ac_2O (3 ml), a solution of conc. H_2SO_4 (500 mg) in Ac_2O (0.1 ml) was added and the agitation was continued for 0.5 hr at room temperature. The same treatment of the reaction mixture as noted in the case of XIa afforded an oil (91 mg), which was crystallized with n-hexane to a solid (XIIIa), mp 80—84°, (56 mg, 55%). Recrystallization furnished colorless prisms of XIIIa, mp 81—82°, which was identical with a product (mp 82—84°) obtained from XIa by comparison of IR spectrum and by mixed fusion.

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