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Studies on Ergot Alkaloids and Related Compounds. XV.[1] Reductions of *cis*- and *trans*-4-Methyl-2-methylen-3-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines and Preparation of *trans-syn*-2,4-Dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo-[*f*]quinoline

Zen-ichi Horii, Takushi Kurihara, and Ichiya Ninomiya[2]

Faculty of Pharmaceutical Sciences, Osaka University[2]

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The behaviors of *cis*- and *trans*-4-methyl-2-methylen-3-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines toward catalytic and chemical reductions were examined and thereby the hitherto unknown *trans-syn*-2,4-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo-[*f*]quinoline was secured.

In the previous paper,[3] three isomers of 2-substituted 4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline, *i.e.*, the *trans-anti* (I), the *cis-anti* (II) and the *cis-syn* (III), have been prepared by reductions of IV, V, VI and VII and their stereochemistries were established.

In the present paper, the behaviors of the *trans*- and *cis*-methylene lactams (VIII) and (IX) toward reduction were examined and the new fourth isomer, *trans-syn*-2,4-dimethyl-1,2,3,4,4a,5,6,10b-octahyrdobenzo[*f*]quinoline (XVI), was prepared.

In order to obtain the fourth diastereomer (XVI), it seemed essential to start with the B/C *trans*-fused compound, such as *trans*-methylene lactam (VIII), which could be subjected to reduction, introducing an axial methyl group. In line with this idea, VIII was reduced with lithium aluminum hydride in an attempt to obtain the non-carbonyl compound(X). The product, however, showed many spots on thin-layer chromatography and we failed to isolate any single product.

Then, we attempted to prepare X through Hofmann degradation of the metho-*p*-toluenesulfonate of *trans-anti*-2-dimethylaminomethyl-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XIII), which was obtained from the 2-hydroxymethyl derivative(XI)[3] by bromination with phosphorus tribromide in benzene,[4] followed by reaction with dimethylamine in a sealed tube. Treatment of the metho-*p*-toluenesulfonate of XIII under the condition of Hofmann degradation reaction, however, gave only the starting material.

Therefore, upon considering difficulties to reduce the carbonyl group first, we next examined the method to saturating a methylene group of VIII to yield *trans-anti*- or *trans-syn*-methyl lactam (XIV or XV) through catalytic means.[5] Catalytic hydrogenation of the *trans*-methylene lactam (VIII) over 10% palladium on carbon in ethanol afforded a mixture of saturated lactams, *i.e.*, *trans-anti*- and *trans-syn*-2,4-dimethyl-3-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (XIV and XV) in the ratio of 8.5:1.5 shown by vapor phase chromatography (vpc), although only XIV could be isolated by elution chromatography over alumina with benzene. Lithium aluminum hydride reduction of XIV gave the known I.

1) Part XIV: *Chem. Pharm. Bull.* (Tokyo), **15**, 1641 (1967).
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4) S. Ohki and K. Yamakawa, *Pharm. Bull.* (Japan), **1**, 260 (1953).
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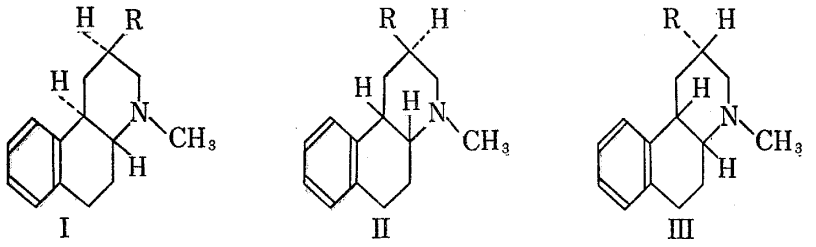
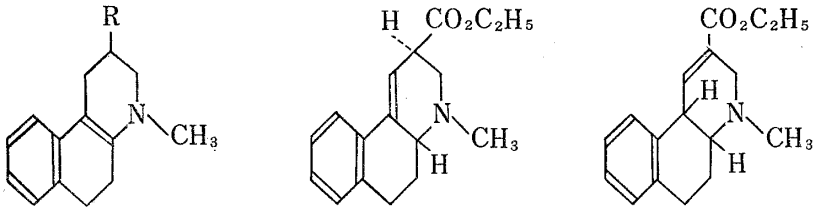


I II III

R in I, II, III=$CO_2C_2H_5$, CO_2H, CH_2OH, CH_3



IV : R=$CO_2C_2H_5$
V : R=CH_3

VI VII

VIII IX

Chart 1

However, when a mixture of XIV and XV was reduced, the hitherto unknown XVI from the former fraction and the known isomer (I) from the latter fraction of the benzene elution over alumina column chromatography of the reaction mixture were obtained.

The structure of XVI was determined by nuclear magnetic resonance spectra. The signal due to C_2-methyl group in I appeared at 9.02 τ as a doublet (J=6.1 cps), whereas in XVI at 8.75 τ as a doublet (J=6.2 cps). The C_2-methyl proton in XVI was expected to be deshielded by 0.27 cps by the nitrogen lone-pair in a *cis*-1:3-diaxial relationship.[6] And this result is consistent with the Moynehan's data[7] which showed the similar deshielding effect on the axial methyl proton by the lone-pair electrons of nitrogen by 0.26 cps relative to the equatorial methyl proton in the two possible *trans*-fused 3-methylquinolizidines.

For the purpose of comparison, the behavior of the *cis*-methylene lactam (IX) toward reduction was also examined. Lithium aluminum hydride reduction of IX followed by catalytic hydrogenation over platinum oxide afforded *cis-anti-* and *cis-syn*-2,4-dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (II) and (III), in the ratio of 2.7:7.3 by vpc. The occurrence of an intermediary 2-methylene structure (XVII), though not isolated, could be readily suggested from the infrared absorptions at 1620 and 895 cm^{-1} in the crude reaction mixture. Catalytic hydrogenation of IX over 10% palladium on carbon in ethanol afforded *cis-syn*-2,4-dimethyl-3-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XVIII) as a sole product. Lithium aluminum hydride reduction of XVIII yielded only III.

6) W.F. Trager, C.M. Lee, and A.H. Beckett, *Tetrahedron*, **23**, 365 (1967).
7) T.M. Moynehan, K. Schofield, R.A.Y. Jones, and A.R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

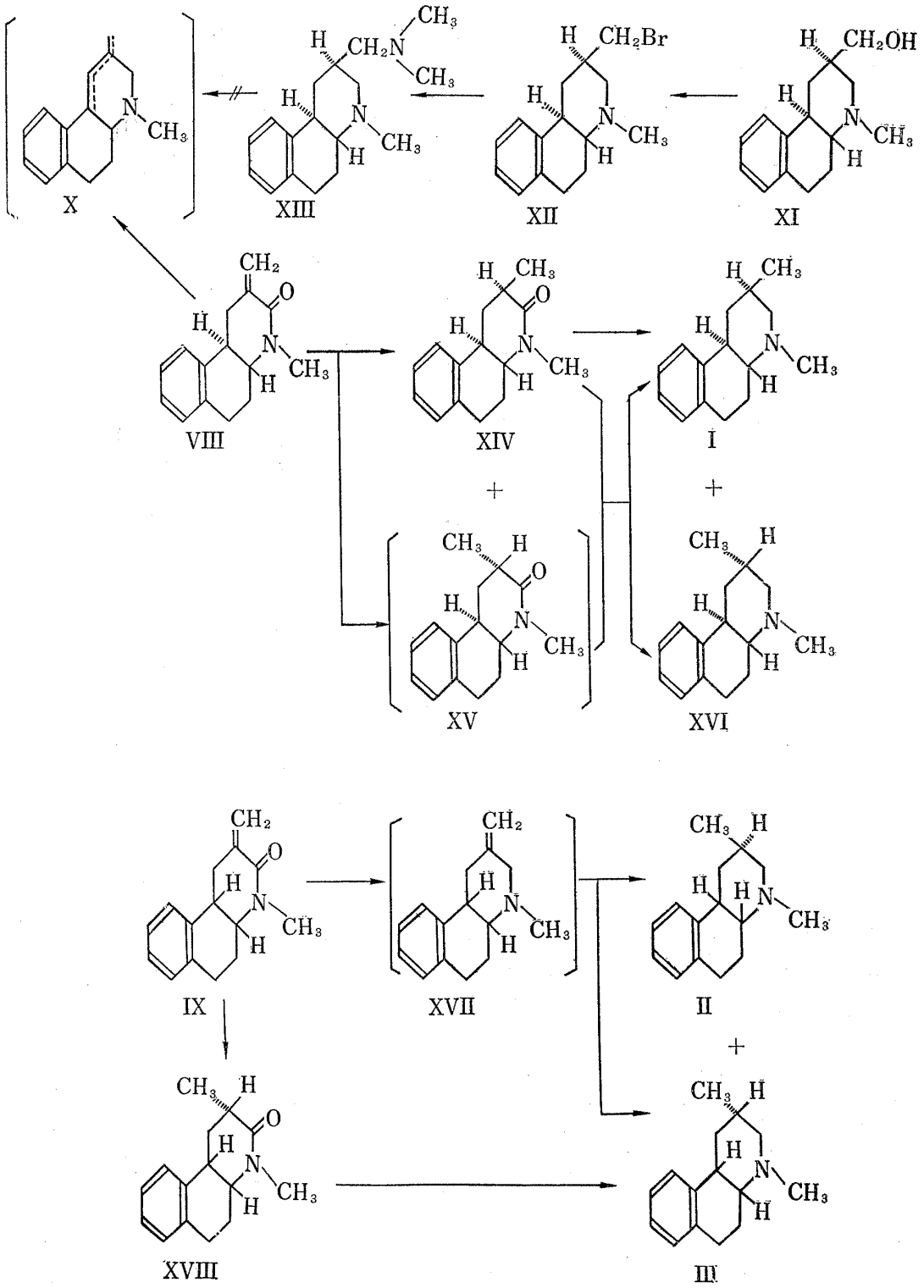


Chart 2

Experimental

***trans-anti*-2-Bromomethyl-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XII)**——To a solution of *trans-anti*-2-hydroxymethyl-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline[3] (XI; 2.17 g) in anhyd. benzene (60 ml) was added phosphorus tribromide (5 ml) in small portions under ice cooling. The mixture was refluxed for 2 hr. The reaction mixture was made alkaline with 10% NaOH solution under ice cooling. The benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residual

oil was distilled *in vacuo* to give a pale yellow oil (1.82 g), bp 180° (0.01 mmHg) (bath temp.), characterized as the perchlorate, which was recrystallized from EtOH–ether as white needles, mp 205—208° (decomp.). *Anal.* Calcd. for $C_{15}H_{21}NBrClO_4$: C, 45.63; H, 5.36; N, 3.55. Found: C, 45.82; H, 5.38; N, 3.45.

***trans-anti*-2-Dimethylaminomethyl-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XIII)**——A mixture of XII (750 mg) and EtOH solution (5 ml) saturated with dimethylamine was placed in a sealed tube and heated in a boiling water bath for 4 hr. The resulting brown solution was evaporated under reduced pressure. The residual oil was distilled *in vacuo* to give a yellow oil (420 mg), bp 160° (0.01 mm Hg) (bath temp.). NMR τ: 7.81 (singlet, 6H, $(CH_3)_2$–N). *Anal.* Calcd. for $C_{17}H_{26}N_2$: C, 79.02; H, 10.14; N, 10.84. Found: C, 78.51; H, 9.97; N, 10.59.

Attempted Hofmann Degradation of XIII——To a solution of *trans-anti*–dimethylamino derivative (XIII; 136 mg) in anhyd. benzene (10 ml) was added one molar equivalent of methyl *p*–toluenesulfonate (98 mg). The mixture was refluxed for 10 min and the crystalline metho–*p*–toluenesulfonate was separated out, collected and dried. This salt was heated at 200° under reduced pressure (0.7 mmHg), but the starting material was recovered unchanged.

Lithium Aluminum Hydride Reduction of *trans*-4-Methyl-2-methylen-3-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (VIII)——To a stirred suspension of $LiAlH_4$ (200 mg) in anhyd. ether (15 ml) was added a solution of VIII (200 mg) in anhyd. ether (10 ml) at room temperature. The mixture was heated under reflux for 4 hr before decomposing the excess $LiAlH_4$ by adding H_2O under ice cooling. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue (165 mg), showing many spots on TLC, was subjected to chromatography over alumina with benzene, but we could not isolate any single product.

Catalytic Hydrogenation of VIII with 10% Palladium on Carbon Catalyst——A solution of the *trans*–methylene lactam (VIII; 500 mg) in EtOH (50 ml) was shaken with hydrogen in the presence of 10% Pd–C (300 mg) at room temperature. After the uptake of one molar equivalent of hydrogen, the catalyst was removed by filtration and the solvent was evaporated, leaving an oil, which showed the presence of two components in the ratio of 8.5:1.5 by vpc. Chromatographical separation over alumina with benzene gave only *trans–anti*–2,4–dimethyl–3–oxo–1,2,3,4,4a,5,6,10b–octahydrobenzo[*f*]quinoline (XIV) (370 mg), mp 73.5—75°, recrystallized from *n*–hexane. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1638 (CO–N). *Anal.* Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.69; H, 8.24; N, 6.04.

Lithium Aluminum Hydride Reduction of a Mixture of XIV and XV to *trans-syn*-2,4-Dimethyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (I) and Its *trans-anti*-Isomer (XVI)——To a stirred suspension of $LiAlH_4$ (400 mg) in anhyd. ether (30 ml) was added a solution of a mixture of XIV and XV (470 mg) in anhyd. ether (20 ml) at room temperature. The mixture was heated under reflux for 4 hr before decomposing the excess $LiAlH_4$ by adding H_2O under ice cooling. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue (385 mg), showing the presence of two components by TLC, was subjected to chromatography over alumina. The first fraction eluted with benzene afforded XVI (65 mg), characterized as a methiodide as colorless needles, mp 244—245°, recrystallized from MeOH–ether. *Anal.* Calcd. for $C_{16}H_{24}NI$: C, 53.78; H, 6.78; N, 3.92. Found: C, 53.32; H, 6.68; N, 3.84. NMR τ: 8.92 (doublet, 3H, J=6.1 cps, CH_3–CH). Further elution with benzene gave I (195 mg) identified with the authentic sample[3] by the comparison of their IR spectra and vpc.

Lithium Aluminum Hydride Reduction followed by Catalytic Hydrogenation of *cis*-4-Methyl-2-methylen-3-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (IX)——To a stirred suspension of $LiAlH_4$ (20 mg) in anhyd. ether (15 ml) was added a solution of IX (30 mg) in anhyd ether (10 ml) at room temperature. The mixture was heated under reflux for 4 hr before decomposing the excess $LiAlH_4$ by adding H_2O under ice cooling. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue (XVII), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1620, 895 ($C{=}CH_2$), without further purification, was hydrogenated in EtOH (10 ml) in the presence of PtO_2 (10 mg) under atmospheric pressure and at room temperature. After the uptake of one molar equivalent of hydrogen, the catalyst was removed by filtration and the solvent was evaporated to give a mixture of II and III in the ratio of 2.7:7.3 by vpc, both identified with the authentic samples[3] by the comparison of their IR and vpc.

***cis-syn*-2,4-Dimethyl-3-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (XVIII)**——The *cis*–methylene lactam (IX; 800 mg) in EtOH (20 ml) was shaken with hydrogen in the presence of 10% Pd–C (500 mg) After the uptake of one molar equivalent of hydrogen, the catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residual oil, which gave a single spot on TLC, gave colorless oil upon distillation, bp190° (0.01 mmHg) (bath temp.). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1642 (CO–N). *Anal.* Calcd. for $C_{15}H_{19}ON$: C, 78.56; 8.35; N, 6.11. Found: C, 77.86; H, 8.26; N, 6.04.

Lithium Aluminum Hydride Reduction of XVIII——To a stirred suspension of $LiAlH_4$ (15 mg) in anhyd. ether (10 ml) was added a solution of XVIII (20 mg) in anhyd. ether (10 ml) at room temperature. The reaction was carried out as described as above to give a single product (8 mg), which was identified as III H, by the comparison with the authentic sample[3] on their IR and vpc.