Notes

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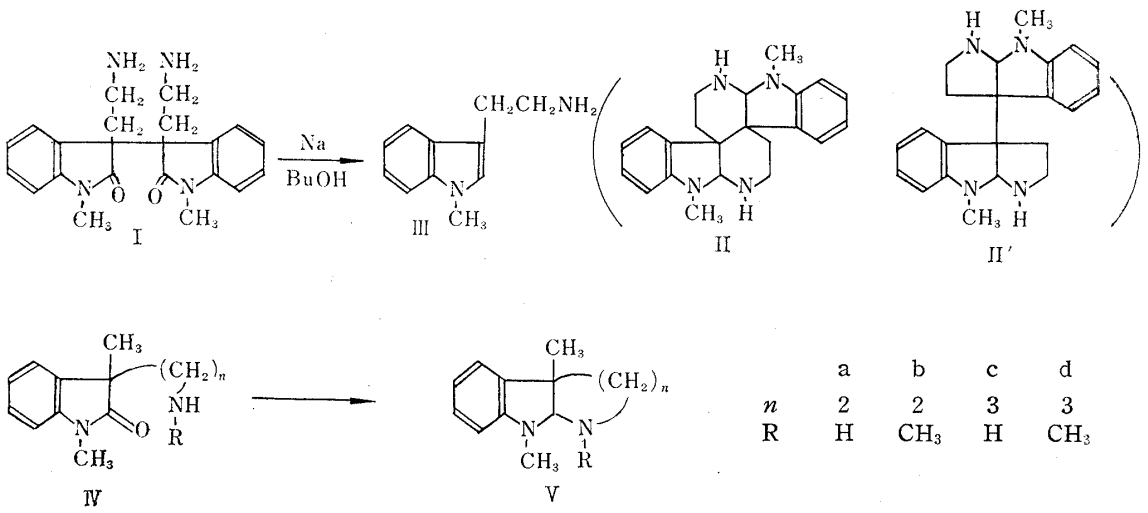
Shun-ichi Yamada, Tohru Hino, and Kiyomi Ogawa : The Reductive Cyclization of 1-Methyl-3-aminoalkyloxindoles with Lithium aluminum Hydride.*1

(*Faculty of Pharmaceutical Sciences, University of Tokyo**2)

In part III of this series one of the present authors (T. H) reported that 1,1′-dimethyl-3,3′-bis(2-aminoethyl)-3,3′-bioxindole (I) did not give the desired cyclized product (II or II′) by the Ladenburg reduction, but gave only 1-methyltryptamine (III) instead. Considering that the reductive cyclization of I to II might be effected by lithium aluminum hydride, the present authors have carried out model experiments with IV and found that under certain working conditions the cyclization products (V) could be produced.



It was P. L. Julian, *et al.*,[1] who first succeeded to cyclize IVa and IVb to Va and Vb by Ladenburg reduction. Several similar cyclizations have been reported since; e. g. by Julian, *et al.*,[2a] Sugasawa, *et al.*[2b] and others[2c]. In our knowledge no agent other than metallic sodium-alcohol, which was used solely in the above-mentioned experiments, has been found in the literature for the same purpose.

When IVa, prepared from 1,3-dimethyloxindole by the Julian's method[1], was treated with lithium aluminum hydride (1.35 moles) in boiling ether for 10 hours, Va was obtained in 60% yield after chromatographic purification. Vb was also obtained in 66% yield by the lithium aluminum hydride (1.0 mole) reduction of IVb. Va and Vb thus obtained are identical with the samples obtained by the Ladenburg reduction[1] of IVa and IVb. The ultraviolet spectra of Va and Vb showed hypsochromic shift in acidic media, which was characteristic feature of Ph-N-C-N.[3]

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*1 "The Synthetic Approaches to the Calycanthaceae alkaloids. IV." Part III : This Bulletin, **9**, 988 (1961).

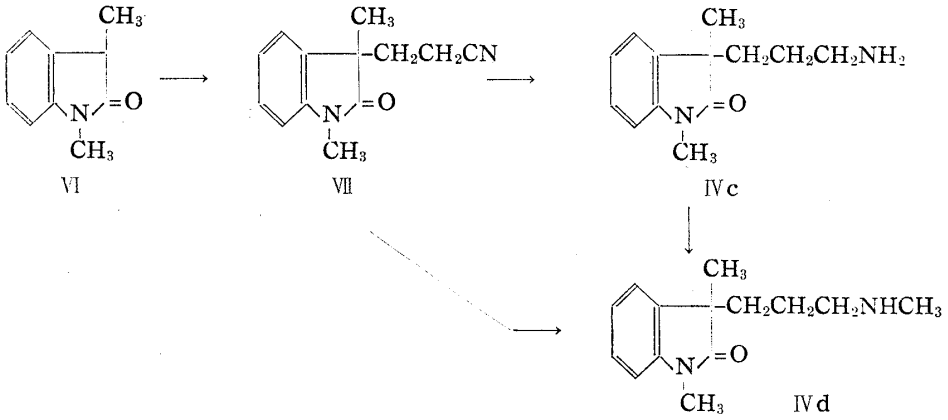
*2 Hongo, Tokyo (山田俊一, 日野 亨, 小川清美).

1) P. L. Julian, *et al.* : J. Am. Chem. Soc., **56**. 1797 (1934); **57**, 539 (1935).

2) *a*) *Idem* : *Ibid.*, **57**, 563 (1935); 755 (1935). *b*) S. Sugasawa, M. Murayama : This Bulletin, **6**, 194, 200 (1958). *c*) N. A. Preobrazhenskii, *et al.* : Zhur. Obshchei. Khim., **23**, 2027 (1953).

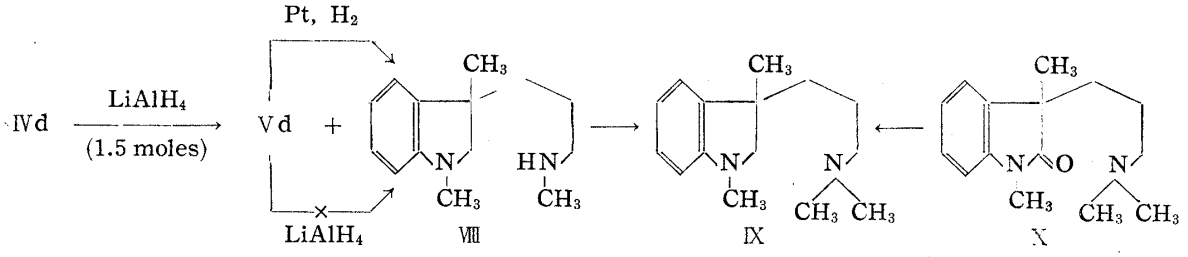
3) H. F. Hodson, G. F. Smith : J. Chem. Soc., **1957**, 1877.

This cyclization method was now extended to include IVc and IVd, prepared from 1,3-dimethyloxindole (VI), to test the feasibility of yielding the corresponding six membered ring compounds (Vc and Vd). Thus VI was cyanoethylated to afford VII by the Horning's procedure[4], which was hydrogenated in methanol saturated with ammonia with Raney nickel to give IVc, b.p_4 180~181°. IVd was obtained by N-methylation of IVc *via* Schiff's base,[1] or by direct hydrogenation of VII in methanol saturated with methylamine with Raney nickel.[2b]



Lithium aluminum hydride reduction of IVc and IVd in boiling ether, as in the cases of IVa and IVb, gave Vc and Vd respectively, which were identified with the samples obtained by the Ladenburg reduction of IVc and IVd.

When IVd was, however, treated with 1.5 moles of lithium aluminum hydride in boiling ether for 10 hours, an indoline derivative (VIII) was obtained besides Vd by alumina chromatography. VIII was also obtained by the catalytic reduction of Vd as was reported by Julian[1], in the cases of Va and Vb, but lithium aluminum hydride reduction of Vd gave only starting material even in boiling dioxane. To prove the structure of VIII this was N-methylated to afford IX, which was identical with the sample obtained by lithium aluminum hydride reduction of X derived from IVd.



Ultraviolet sepctra of Vc and Vd showed similar hypsochromic shift in acidic media as in the cases of Va and Vb.

Experimental*3

Deoxynoreserolin (Va), $LiAlH_4$ reduction of IVa——To a boiling ethereal solution of IVa (1.5 g.) was added dropwise a $LiAlH_4$ (0.37 g., 1.35 mol. equiv.) suspension in dehyd. Et_2O with stirring during 30 min., and the mixture was refluxed for further 10 hr. On cooling excess $LiAlH_4$ and the complexes were decomposed by H_2O (0.4 cc.), 15% NaOH (0.4 cc.) and H_2O (1.1 cc.). The precipitated inorganic salts were filtered and the Et_2O filtrate was extracted with dil. HCl. The acidic aq. solution was basi-

*3 All melting points are not corrected. Ultraviolet spectra were taken by Carry Model 11 spectrophotometer and infrared spectra were taken by Koken DS-301 spectro-photometer.

4) E.C. Horning, *et al.*: J. Am. Chem. Soc., **72**, 3534 (1950).

fied with NaOH solution, and separated oil was extracted with benzene and Et_2O after salting out with NaCl. The benzene-Et_2O solution was washed with sat. NaCl solution and dried. The solvents were evaporated *in vacuo* to leave a brown oil (1.36 g.) which was purified on Al_2O_3 column. Va (0.85 g. 60 %) was obtained as a pale brown oil from the effluent with benzene and $CHCl_3$ mixture. UV and IR spectra were identical with those of Va which was obtained by the Ladenburg reduction and purified through Al_2O_3 column. UV $\lambda_{max}^{EtOH(J.P.)}$ mμ (log ε): 253 (4.00), 305 (3.41); $\lambda_{max}^{EtOH-HCl}$ mμ (log ε): 246 (4.07), 298 (3.45).

The picrate, m.p. 159° (reported[1] m.p. 158~159°) was identical with Va-picrate obtained by the Ladenburg reduction on admixture.

Small amount (0.1 g.) of the starting material was recovered from the effluent with EtOH and identified as picrate.

Deoxyeseroline (Vb)——IVb (1.5 g.) was treated with $LiAlH_4$ (0.27 g., 1 mol. equiv.) in Et_2O as descrived above to afford a crude oil (1.27 g.), which was dissolved in benzene and purified through Al_2O_3 chromatography to give Vb as a colorless oil, yield 930 mg., 66 %.

IR spectra of the oil was identical with that of Vb obtained by the Ladenburg method. UV λ_{max}^{EtOH} mμ (log ε): 251 (4.05), 303 (3.47); $\lambda_{max}^{EtOH-HCl}$ mμ (log ε): 243 (4.06), 295 (3.46).

Picrate, m.p. 180° (reported[1] m.p. 179~180°), showed no depression on admixture with the sample obtained by the Ladenburg method.

3-(2-Cyanoethyl)-1,3-dimethyloxindole (VII)——To an ice-cooled solution of 1,3-dimethyloxindole (41 g.) and 10% Triton B (9.5 g.) in dioxane (800 cc.) was added dropwise acrylonitrile (13.5 g.) in dioxane (60 cc.) under vigorous stirring. After stirring for 4 hr. at room temperature the mixture was neutralized with a few drops of conc. HCl, and evaporated *in vacuo*. The residue was extracted with benzene, and the benzene solution was washed successively with dil. NaOH, H_2O, dil. HCl and H_2O, and dried. Benzene was evaporated and the residue was distilled *in vacuo* to give a colorless oil, $b.p_7$ 190~193°, which soon solidified. It was recrystallized from EtOH to afford colorless prisms (48.7 g., 90 %), *Anal.* Calcd. for $C_{13}H_{14}ON_2$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.22; H, 6.59; N, 12.67. IR: ν_{max}^{capil} 2220 cm^{-1} (C≡N).

3-(3-Aminopropyl)-1,3-dimethyloxindole (IVc)——VII (16.0 g.) was hydrogenated over Raney-Ni (alloy 10 g.) in MeOH (240 cc.) saturated with NH_3 at 110° under 120 atm. of hydrogen. IVc was obtained as a colorless oil (13.0g., 81 %), $b.p_4$ 180~181°, as usual.

Picrate: Yellow pillars, m.p. 127~128° (from EtOH). *Anal.* Calcd. for $C_{13}H_{18}ON_2 \cdot C_6H_3ON_3$: C, 51.0; H, 4.73; N, 15.11. Found: C, 51.3; H, 4.71; N, 15.61.

3-(3-Methylaminopropyl)-1,3-dimethyloxindole (IVd)——a) From IVc: IVc (20.0 g.) was mixed with benzaldehyde (10.5 g.) at room temperature. After an exothermal reaction had subsided, the mixture was kept for 1 hr. at room temperature and the separated water was evaporated *in vacuo*. The residue was triturated with petr. ether to give a solid, which was recrystallized from petr. ether-Et_2O to afford pure Schiff's base (27.7 g., 99 %), m.p. 94~95°. *Anal.* Calcd. for $C_{20}H_{22}ON_2$: C, 78.23; H, 7.24; N, 9.14. Found: C, 78.23; H, 7.49; N, 9.02.

The Schiff's base (28.0 g.) was heated with MeI (13.0 g.) in a sealed tube at 100° for 1 hr. On cooling a red viscous oil formed was taken up in hot EtOH, evaporated *in vacuo* and the residue was treated with dil. HCl, separating benzaldehyde, which was removed with benzene. The acidic aqueous layer was basified with NaOH solution and the separated oil was extracted with benzene. The benzene solution was washed with sat. NaCl, and dried. Benzene was evaporated *in vacuo* and the residue was distilled to afford a colorless oil, $b.p_4$ 157° (17.0 g., 80 %).

Picrate: Yellow prisms, m.p. 183~184° (from EtOH). *Anal.* Calcd. for $C_{14}H_{20}ON_2 \cdot C_6H_3O_7N_3$: C, 52.06; H, 5.02; N, 15.18. Found: C, 52.19; H, 4.62; N, 15.15.

b) From VII: VII (9.5 g.) was hydrogenated as above in MeOH saturated with $MeNH_2$ to afford IVd (6.8 g.) $b.p_4$ 157°, which was identified with the sample obtained above through IR spectra, and picrates of m.p. 183~184°, which was not depressed on admixture.

4a,9-Dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indole (Vc), Reductive Cyclization of IVc——IVc (1.5 g.) was cyclized with $LiAlH_4$ (0.35 g., 1.35 mol. equiv.) in Et_2O as in the case of IVa to afford an oil (1.25 g.), which was chromatographed over Al_2O_3. Crude Vc (0.67 g., 48 %) was obtained from the effluent with benzene as a pale yellow oil which soon solidified. It was recrystallized from petr. ether to afford colorless pillars, m.p. 53~53.5°. *Anal.* Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 76.95; H, 8.20; N, 13.72.

IR: ν_{max}^{KBr} 3333 cm^{-1} (NH). UV λ_{max}^{EtOH} mμ (log ε): 251 (4.00), 296 (3.49). $\lambda_{max}^{EtOH-HCl}$ mμ (lon ε): 245 (4.03); 294 (3.44).

Picrate: Yellow pillars, m.p. 152° (from EtOH). *Anal.* Calcd. for $C_{13}H_{18}N_2 \cdot C_6H_3O_7N_3$: C, 52.90; H, 4.91; N, 16.24. Found: C, 53.13; H, 4.67; N, 16.04.

The same Vc was obtained in 30 % yield by the Ladenburg reduction of IVc, carried out by essentially the same procedure as that of IVa reported by Julian.[1] The both samples were found identical by mixed melting point test and IR spectra.

1,4a,9-Trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-pyrido[2,3-*b*]indole (Vd)——IVd (1.5 g.) was treated with

$LiAlH_4$ (0.25 g., 1 mol. equiv.) in dehyd. Et_2O as in the case of IVa to give a pale brown syrup (1.27 g.) which was chromatographed over Al_2O_3. Crude Vd (0.84 g., 60 %) was obtained from the effluent with benzene as a pale yellow oil, which soon solidified. It was recrystallized from petr. ether to afford colorless pillars, m.p. 40~40.5°. *Anal.* Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 8.71; N, 12.95. Found : C, 77.58; H, 8.71; N, 12.96. UV λ_{max}^{EtOH} mμ (log ε) : 251 (4.01), 297 (3.49). $\lambda_{max}^{EtOH-HCl}$ mμ (log ε) : 247 (4.01), 294 (3.43). Picrate : Yellow plates, m.p. 148° (from EtOH). *Anal.* Calcd. for $C_{14}H_{20}N_2 \cdot C_6H_3O_7N_3$: C, 53.94; H, 5.20; N, 15.72. Found : C, 53.74; H, 5.00; N, 15.71.

The same Vd was obtained by the Ladenbung reduction in 60 % yield, and was identified with the sample obtained above by mixed melting test, IR and UV spectra. Only the starting material was recovered when Vd was treated with $LiAlH_4$ in boiling Et_2O or boiling dioxane.

3-(3-Methylaminopropyl)-1,3-dimethylindoline (VIII)——a) Vd (1.0 g.) was hydrogenated in glacial AcOH (30 cc.) with PtO_2 (140 mg.) at room temperature and atmospheric pressure. After cessation of H_2 uptake, catalyst was removed and the filtrate was evaporatated *in vacuo*. The residue was taken up in dil. HCl, and extracted with benzene. The acidic aqueous layer was basified with NaOH solution and separated oil was extracted with benzene. The benzene solution was washed with sat. NaCl solution and dried. The solvent was evaporated *in vacuo* and the residue was distilled to afford a colorless oil (750 mg., 74 %), b.p_4 150~160°. UV λ_{max}^{EtOH} mμ (log ε) : 253 (3.83), 298 (3.27). IR : λ_{max}^{capil} 3350 cm^{-1} (NH).

Picrate : Yellow plates, m.p. 146~147° (from benzene). *Anal.* Calcd. for $C_{14}H_{22}N_2 \cdot 2C_6H_3O_7N_3$: C, 46.16; H, 4.17; N, 16.56. Found : C, 46.82; H, 4.20; N, 16.87.

b) As a by-product of $LiAlH_4$ reduction of IVd : When IVd (1.5 g.) was treated with $LiAlH_4$ (0.37 g., 1.5 mol. equiv.) in boiling Et_2O for 10 hr. as in the case of IVa, a pale yellow oil VIII (340 mg.) was obtained from the effluent with $CHCl_3$ in a chromatographic purification of the crude products. The oil showed identical IR spectrum with the sample obtained above and both picrates melted at 146~147° alone or admixed. From the effluent with benzene Vd (260 mg.), m.p. 39~40°, was obtained.

When IVd (1.5 g.) was, however, treated with $LiAlH_4$ (1.5 mol. equiv.) in boiling ether for 5 hr. instead of 10 hr., besides recovering IVd (340 mg.) only Vd (670 mg., 40 %), but none of VIII was obtained.

3-(3-Dimethylaminopropyl)-1,3-dimethylindoline (IX)——a) From IVd *via* X : The mixture of IVd (1.5 g.), 30% formaline (1.0 g.) and 80% HCOOH (0.9 g.) was heated at 130° (bath temperature) for 6 hr. On cooling excess of the reagents was removed *in vacuo* and the residue was taken up in dil. HCl solution. After shaken with benzene the acidic solution was basified with NaOH solution, and separated oil was extracted with Et_2O. The solvent was evaporated after drying to afford 3-(3-dimethylaminopropyl)-1,3-dimethyloxindole (X) as a pale brown oil (1.38 g.).

Picrate of X : Yellow plates, m.p. 135~136° (from MeOH). *Anal.* Calcd. for $C_{15}H_{22}N_2O \cdot C_6H_3O_7N_3$: C, 53.05; H, 5.30; N, 14.73. Found : C, 53.34; H, 5.13; N, 14.35.

This oxindole (950 mg.) was reduced with $LiAlH_4$ (380 mg.) in boiling Et_2O for 6 hr. to afford IX as a colorless oil, b.p_7 160° (yield 770 mg.). Neither NH nor C=O band was observed in its IR spectrum. UV λ_{max}^{EtOH} mμ (log ε) : 252 (3.95), 297 (3.38).

Picrate : Yellow plates, m.p. 150~150.5° (from MeOH). *Anal.* Calcd. for $C_{15}H_{24}N_2 \cdot C_6H_3O_7N_3$: C, 46.93; H, 4.38; N, 16.23. Found : C, 46.76; H, 4.04; N, 16.16.

b) From VIII *via* N-formate : The mixture of VIII (0.2 g.) and methyl formate (4 cc.) was kept at room temperature for 36 hr., then refluxed for 3 hr. On cooling excess of methyl formate was evaporated *in vacuo* and the residue was dissolved in benzene. The benznen solution was washed with sat. NaCl solution and dried. The solvent was removed *in vacuo* and the residue was distilled to afford the N-formyl derivative, as a colorless oil (150 mg.), b.$p_{0.2}$ 180~190°. IR : $\nu_{C=O}^{capil}$ 1668 cm^{-1}.

The formate (130 mg.) was reduced with $LiAlH_4$ (200 mg., excess) in boiling Et_2O for 8 hr. After usual work up IX was obtained as a colorless oil, b.p_6 155~160°.

Picrate : Yellow plates, m.p. 150~150.5° (from MeOH). The IR spectrum of the free base was identical with that of the sample obtained above, and the picrate showed no depression of melting point on admixture with the sample obtained above under a).

The authors express their deep gratitude to Prof. Emeritus S. Sugasawa for his encouragement throughout this work. Thanks are also due to Miss M. Ninomiya and Mrs. E. Tanaka for infrared spectral data, and to the members of the Analysis Center of this Faculty for microanalytical data.

Summary

Lithium aluminum hydride also was found to be effective as the Ladenburg method for the reductive cyclization of 3-(2-aminoethyl)-, 3-(3-aminopropyl)-1,3-dimethyl oxindole (IVa and IVc) and their N-methyl derivatives (IVb, IVd) to pyrrolo (and pyrido) [2,3-*b*]

indole derivatives (Va–Vd). With a little excess of lithium aluminum hydride IVd gave a indoline derivative (VIII) together with the cyclized base (Vd) though the latter of which could not be cleaved by lithium aluminum hydride even under more strenuous condition.

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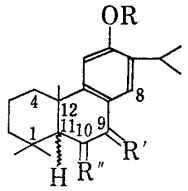
Yoshikazu Kondo,*1 Tsuneo Ikenoue,*2 and Tsunematsu Takemoto*1 : Structure of Xanthoperol.

(*Institute of Pharmacy, School of Medicine, Tohoku University,*1 Chemical Research Institute of Non-Aqueous Solutions, Tohoku University*2*)

Xanthoperol is a phenolic diterpene which was isolated from *Juniperum communis* L. by Bredenberg, *et al.*[1]

Recently, Bredenberg and Shoolery[2] measured the nuclear magnetic resonance spectrum (NMR) of xanthoperol and recognized the fact that V was more compromising than the previously suggested structure.[3] Further on A/B ring juncture, possibility of *cis* was noted. However, since they employed the external referene and did not correct the effect of diamagnetic bulk susceptibility, methyl signal was appeared in the low field.



I : R=H; R′=R″=H$_2$, 11α
II : R=Ac; R′=R″=H$_2$, 11α
III : R=H; R′=O; R″=H$_2$, 11α
IV : R=Ac; R′=O; R″=H$_2$, 11α
V : R=H; R′=R″=O, 11β
VI : R=Ac; R′=R″=O, 11β

Ferruginol (I), sugiol (III) and xanthoperol which were isolated from the wood resin of *Cryptomeria japonica* D. Don[4] were kindly supplied by professor T. Kondo and they were converted to ferruginol acetate (II), sugiol acetate (IV) and xanthoperol acetate (VI) respectively. By the comparison of their NMR, authors observed the significant difference in methyl signal of xanthoperol acetate from those of two others.

The NMR of II, IV and VI measured in chloroform solution are shown in Figs. 1, 2 and 3.

In Fig. 1, the signal appeared in 9.04 (τ') corresponds to six protons and was assigned to *gem*-methyl (e) and angular methyl groups; signals 8.83 (τ') and 8.70 (τ'), in the observation of slow seep, both split into doublet so they must belong to isopropyl group; and signal 8.78 (τ') will be assigned to *gem*-methyl group (a).

In Fig. 2, *gem*-methyl (e) and angular methyl groups are appeared separately in 9.01 (τ') and 9.07 (τ'). And C_8 in ring protons shifts to 2.04 (τ') by the effect of paramagnetic shielding of carbonyl group.

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*1 Kitayomban-cho, Sendai (近藤嘉和, 竹本常松).
*2 Katahira-cho, Sendai (池上恒男).

1) J.B. Bredenberg, J. Gripenberg : Acta Chem. Scand., **10**, 1511 (1956).
2) J.B. Bredenberg, J. N. Shoolery : *Ibid.*, **14**, 556 (1960).
3) J.B. Bredenberg : *Ibid.*, **11**, 927 (1957).
4) T. Kondo, H. Imamura, M. Suda : Yakugaku Zasshi, **79**, 1298 (1959).