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Aminoethylation. III.[1] Stereochemical Configuration of 2-Oxo-3-ethoxycarbonyl-*trans*-octahydroindole

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The configuration of C_3-methyl group in each isomer of 2-oxo-3-methyl-*trans*-octahydroindole (VIIa and VIIb) was determined by the evidence of their NMR spectra and the conformational analyses using Dreiding model. Accordingly, the C_3-ethoxycarbonyl group in 2-oxo-3-ethoxycarbonyl-*trans*-octahydroindole (I), which was obtained by the reaction of *meso-cis*-cyclohexenimine and diethyl malonate, was proved to have *cis*-configuration in relation to C_{3a}–H.

The methylation of I and its N-benzylsulfonyl derivative (X) gave Vb, and XI of which C_3–methyl group had *trans*-configuration to C_{3a}–H, respectively. On the other hand, the methylation of 2-oxo-1,3-diethoxycarbonyl-*trans*-octahydroindole (XII) gave also C_3–methyl derivative (XIII), but the configuration of C_3–methyl group of XIII was *cis* to C_{3a}–H.

In the previous paper,[1] we have reported that *meso-cis*-cyclohexenimine or its N-benzylsulfonyl derivative reacted with diethyl malonate to give 2-oxo-3-ethoxycarbonyl-*trans*-octahydroindole (I) or its N-benzylsulfonyl derivative (X). However, the configuration of C_3-ethoxycarbonyl group of I has been remained uncertain. In this paper, its configuration was confirmed by the derivation of ethoxycarbonyl to methyl group.

Reduction of I with $LiAlH_4$ gave 3-hydroxymethyl-*trans*-octahydroindole (II), which was led to 3-iodomethyl-*trans*-octahydroindole·HI (III) by refluxing with hydrogen iodide. Deiodination of III with $LiAlH_4$ afforded 3-methyl-*trans*-octahydroindole (IVa) (picrate; mp 177—178°). Our attention, therefore, turned to the determination of the configuration of C_3-methyl group in IVa.

Methylation of I with CH_3I in diethyl carbonate in the presence of Na catalyst gave 2-oxo-3-methyl-3-ethoxycarbonyl-*trans*-octahydroindole (Vb) (mp 104—105°) in 59.9% yield. Hydrolysis of the ester group of Vb with 5N NaOH afforded carboxylic acid (VIb) [mp 201° (decomp.)]. Decarboxylation of VIb by heating gave 2-oxo-3-methyl-*trans*-octahydroindole (VIIa) (mp 133—134°) in 77.3% yield, which was reduced with $LiAlH_4$ to afford IVa. Accordingly, there is no doubt that each C_3-substituent in VIIa and I has the same configuration. Next, Vb was hydrolyzed in refluxing HCl to give 2-(*trans*-2-aminocyclohexyl)-propionic acid·HCl (VIIIb) [mp 202—203° (decomp.)], which was treated with 15% ethanolic HCl to give ethyl ester·HCl (IXb). The smooth cyclization of the ester (IXb) with NaOH gives lactam (VIIb) (mp 116—118°) in 89.8% yield. Reduction of VIIb with $LiAlH_4$ gave octahydro derivative (IVb) (picrate; mp 161.5—162.5°). Elemental analyses and spectral evidences of VIIa and VIIb demonstrated that they were in the relation of stereo isomer on C_3-methyl groups. The pass way from Vb to VIIa or VIIb is described in detail later.

The relative stability of the isomers (VIIa and VIIb) was examined to confirm their configuration. When VIIa and VIIb were heated in the presence of EtONa in EtOH, respectively, both of them were unchanged. However, on heating them with potassium *t*-butoxide in *t*-BuOH, only VIIb isomerized to VIIa. The rearrangement of VIIb to VIIa was followed

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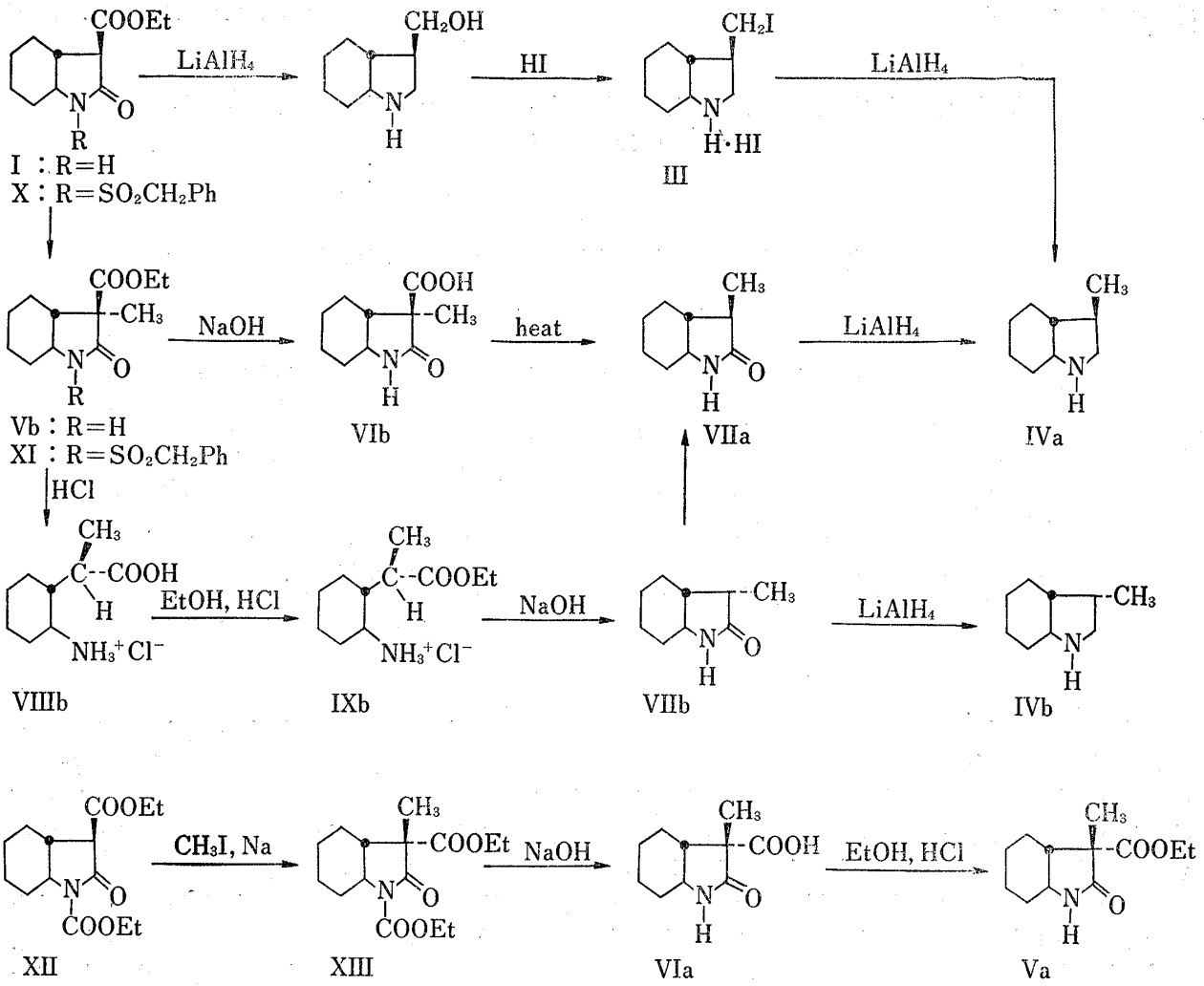
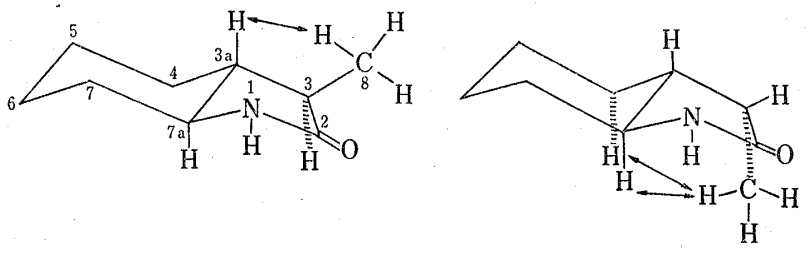


Chart 1

TABLE I. Distance between Two Adjacent Atoms in Dreiding Model

VIIa		VIIb	
C_{3a}-H~C_8-H	2.12 Å	C_4-H~C_8-H	1.74 Å
		C_{7a}-H~C_8-H	2.29 Å



by gas–liquid chromatography (GLC) (Fig. 1). The variation of VIIb to VIIa was 42% at 3 hr, 55% at 5 hr, 73% at 14 hr and 87% at 20 hr, respectively. In the separate experiment, pure VIIa was isolated in 62% yield by heating of VIIb for 14 hr. Evidently the above result shows that VIIa has more stable configuration than that of VIIb.

In the conformational analysis of VIIa and VIIb using Dreiding Model (Table I), when C_3-methyl group situates in *cis* to C_{3a}–H, the shortest distance from the hydrogen of C_3-methyl group to the hydrogen of C_{3a}, which exists in the nearest position from the methyl group, is

2.12Å. On the other hand, when the methyl group situates in *trans*-configuration to C_{3a}–H, the shortest distance from the hydrogen of methyl group to the nearest hydrogen at C_4 is 1.74Å. The Dreiding Model shows that the stable configuration of C_3-methyl group is *cis* in relation to C_{3a}–H. Accordingly, the configuration of the C_3-methyl group in VIIa is *cis* to C_{3a}–H, and that VIIb is *trans*.

Furthermore, this configurational relation between VIIa and VIIb was investigated by nuclear magnetic resonance (NMR) spectrometry. Narayanan[3] found that each chemical shift of C_{11}-methyl groups of α-santonin, β-santonin and their related compounds follows the constant rule in comparison with their NMR spectra. Namely, between pseudo-axial configuration (*trans*-configuration to C_7–H) and pseudo-equatorial configuration (*cis*-configuration to C_7–H) of C_{11}-methyl group, each chemical shift of C_{11}-methyl groups in $CDCl_3$ and in C_6H_6 shows different values. The compounds having pseudo-equatorial methyl group show an upfield shift of 0.23±0.06 ppm in benzene, comparing with that in chloroform, whereas the compounds having pseudo-axial methyl group show a larger upfield shift of 0.46±0.06 ppm under the same condition. With reference to the above data, each chemical shift of methyl groups in the NMR spectra of VIIa and VIIb was examined. As shown in Table II, the difference of the chemical shifts in C_6H_6 and in $CDCl_3$ is 0.02 ppm in case of VIIa, and 0.13 ppm in case of VIIb, respectively. Namely, VIIb shows the larger chemical shift in benzene than that of VIIa. Because of the structural similarity of VIIa and VIIb with santonin, the methyl group of VIIb showing a larger upfield shift should have *trans*-configuration to C_{3a}–H. Accordingly, the methyl group of VIIa shoud have *cis*-configuration to C_{3a}–H. The above result of NMR spectra agrees with the consideration by molecular stereomodel.

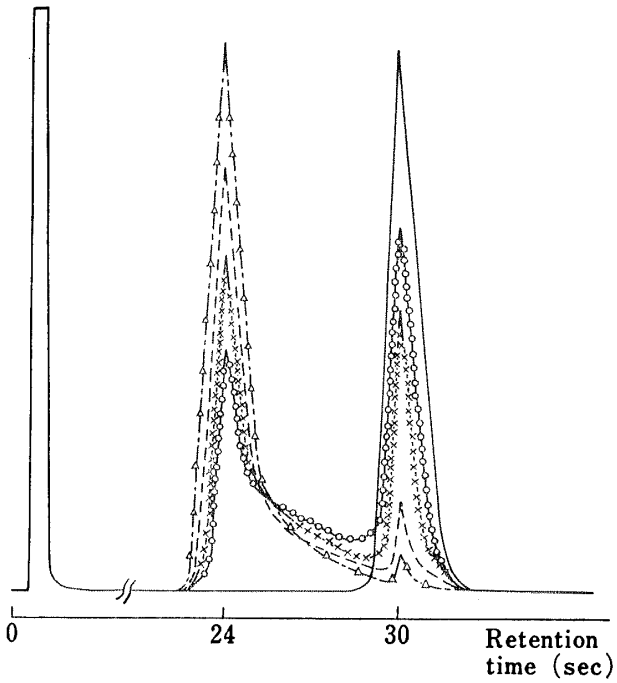


Fig. 1. Gas Chromatographic Changes in the Rearrangement of VIIb to VIIa

column: 15% OV-17 on Shimalite W (80—100 mesh)
temp.: column 160° N_2: 21 ml/sec
injec. 190°
detect. 160°
———: 0 hr, —○—○: 3 hr, —×—×: 5 hr,
– – – – –: 14 hr, —△—△: 20 hr

Table II. Chemical Shift of C_3-Methyl Group in NMR Spectra of VIIa and VIIb

	$\delta(CDCl_3)$ppm	$\delta(C_6H_6)$ppm	δC_6H_6-$\delta CDCl_3$
VIIa	1.15	1.13	+0.02
VIIb	1.07	0.94	+0.13

Since the configuration of C_3-methyl group in VIIa and VIIb were ascertained, the configuration of C_3-methyl group in IVa was also confirmed to have the same configuration as VIIa. When IVa is derived from I, as the configuration of C_3-methyl group remains unchanged, the configuration of C_3-ethoxycarbonyl group to C_{3a}–H in I is assigned to be *cis*.

3) C.R. Narayanan and N.K. Venkatasubramanian, *Tetrahedron Lett.*, **1966**, 5865.

The methylation of I with CH_3I was applied to the derivatives of I such as N-benzylsulfonyl or N-ethoxycarbonyl compound. Reaction of 1-benzylsulfonyl-2-oxo-3-ethoxycarbonyl-*trans*-octahydroindole[1] (X) with CH_3I in diethyl carbonate in the presence of Na gave 3-methyl derivative (XI) (mp 118—119°) in 41.9% yield. Desulfurization of XI with Raney nickel afforded Vb. Accordingly, the configuration of XI is same to that of Vb. Methylation of 2-oxo-1,3-diethoxycarbonyl-*trans*-octahydroindole (XII), which was prepared in a good yield on heating of I in diethyl carbonate in the presence of Na, gave different result with the methylation of I or XI. The reaction proceeded quickly at room temperature to give 3-methyl derivative (XIII) (oil) in 85.1% yield. After hydrolysis of XIII with NaOH, carboxylic acid (VIa) mp 181.5—182° (decomp.), which didn't agree with VIb, was obtained. Furthermore, ethoxycarbonyl compound (Va) (mp 112—114.5°), which was obtained by treatment of VIa with 15% ethanolic HCl, also didn't agree with Vb. As the result of the above experiments, Va and VIa have relation of stereoisomer with Vb and VIb on the C_3-methyl group, respectively.

The above reaction could be accounted for steric effect in the reaction process. The bulky C_3-ethoxycarbonyl group in I and X is favorably located in *cis*-configuration to C_{3a}–H, because of less barrier, so that the attack of methyl group to C_3-carbanion perhaps occurrs from the lower part. Even if a bulky substituent, such as benzylsulfonyl group, was introduced at the ring nitrogen, the configuration of the product in the methylation was not affected, but only the decreased yield was shown. A similar reaction has been shown in the methylation of 3-ethoxycarbonyl-*trans*-octahydrofuran-2-one with CH_3I in aprotic solvent in the presence of Na, and methyl group is introduced into the C_3-position and its configuration is *trans* to C_{3a}–H.[4]

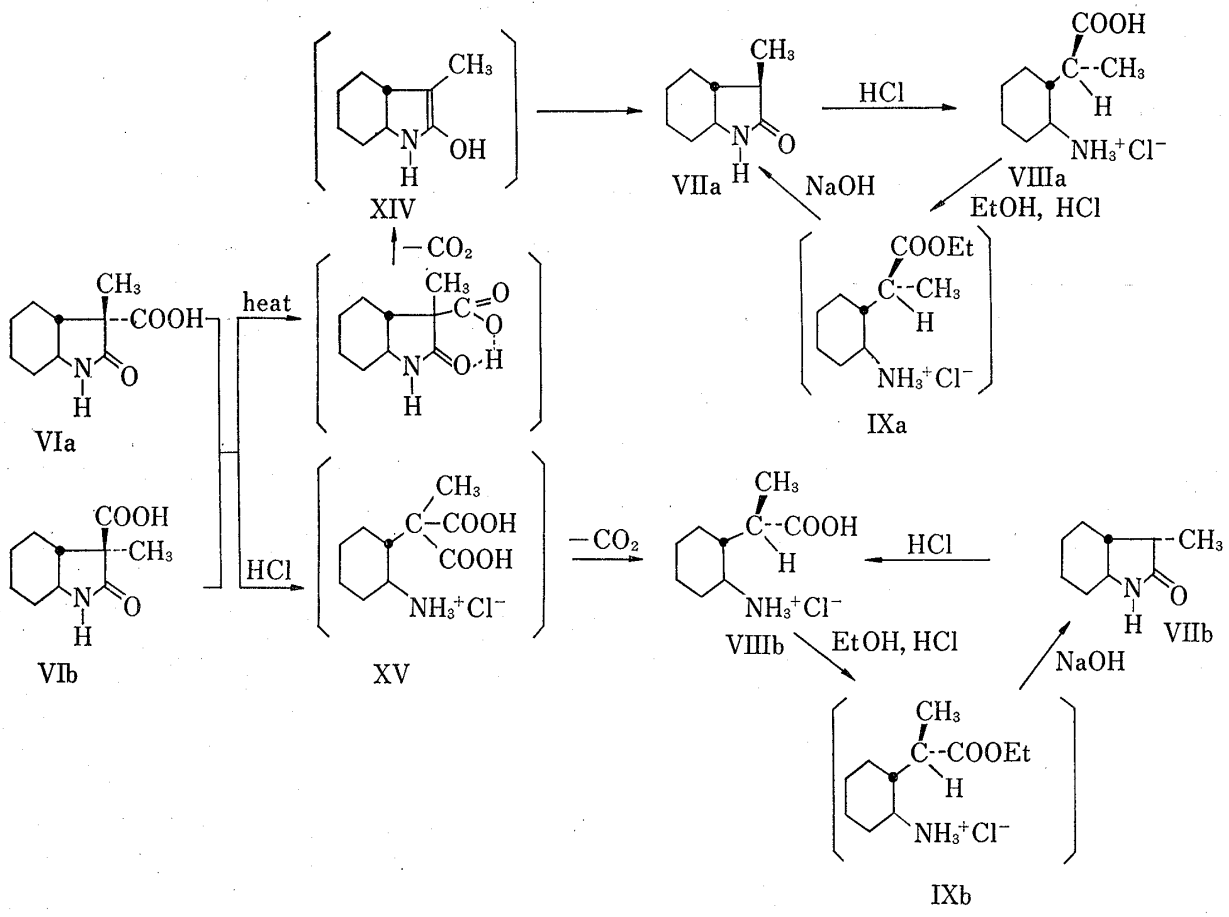
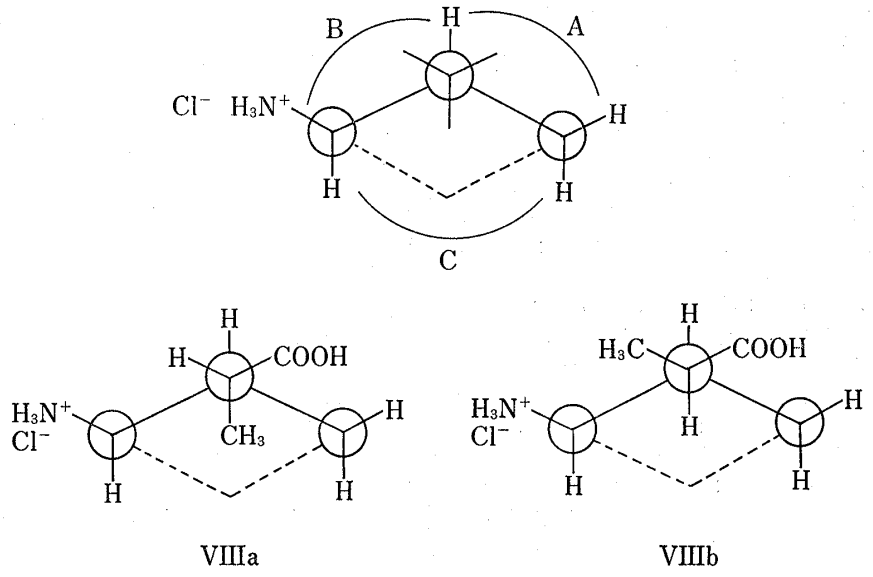


Chart 2

4) R.S. Reeve, B.G. Ramsay, and R.Y. Moir, *Tetrahedron Lett.*, **1973**, 1529.

Interestingly, in case of N-ethoxycarbonyl derivative of I (XII), quite different result was obtained comparing with the case of the methylation of I or X. The methylation of XII proceeded faster and the yield was higher than that of I or X. Moreover, the configuration of the methyl group of the product (XIII) was related to *cis* with C_{3a}–H, suggesting that the introduction of methyl group to XII ocurred from the upper side. At present, it is not apparent how N-ethoxycarbonyl group behaves in the methylation of XII.

We examined why VIb produced simply VIIa by decarboxylation on heating, or produced VIIb by hydrolysis followed ring closure as previously described. Decarboxylation of VIa on heating also produced only VIIa. Namely, both of VIa and VIb formed only VIIa having a stable configuration. This process would be rationalized by the formation of six membered hydrogen bond in both VIa and VIb, and the subsequent formation of an enol intermediate (XIV). In case of hydrolysis of VIa and VIb with HCl, both of them produced VIIIb alone. In this procedure, if it should be assumed that the ring-opening occurred after decarboxylation of VIa or VIb, this assumption was denied by the fact that VIIb was formed from VIIIb *via* IXb. Moreover, evidently VIIIb holds the same configuration as VIIb by the fact that VIIIb is reproduced from VIIb by hydrolysis with HCl. On the other hand, hydrolysis of VIIa with HCl gave VIIIa and the ethyl ester (IXa) of VIIIa reformed VIIa by treatment with alkali. Thus, it was ascertained that in the hydrolysis of VIIa and VIIb with HCl, their configuration didn't change. The mechanism of the above reaction could be explaned as follows. Decarboxylation of VIa or VIb didn't occur before ring opening because of the inhibition of the formation of the hydrogen bond between C_3-carboxy group and lactam carbonyl group by the existence of proton. Accordingly, the ring opening precedes preferably, and then VIIIb having stable configuration may be formed by decarboxylation of the intermediate (XV).



VIIIa VIIIb

Chart 3

Considering the Newman projection (Chart 3) which has the axis formed with the methine carbon of side chain and the C_1 carbon of cyclohexane ring, the area of the least barrier is A, and C area has the biggest barrier. On the other hand, the order of the sizes of the side chain groups follows COOH>CH_3>H. When COOH group situates in A area, CH_3 group in B area, and H in C area, the compound has the most stable conformation in energy, and the compound being in such conformation is VIIIb. After all, it could be regarded that the decarboxylation of the intermediate (XV) gave VIIIb.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were obtained with a JASCO DS-301. The NMR spectra are taken on a JNM C-60H using tetramethylsilane as an internal standard. Mass spectra were obtained on a JMS-01SG mass spectrometer. Gas chromatographic analysis were carried out with a Simazu Gas Chromatograph Model GC-2C with hydrogen flame detector.

3-Hydroxymethyl-*trans*-octahydroindole (II)——To a solution of $LiAlH_4$ (9 g) in dry ether (200 ml) were added slowly I (10 g) under cooling and the mixture was refluxed for 2 hr, cooled, and treated successively with moist ether, water and 10% sodium hydroxide solution. The ethereal layer was then separated. Aqueous layer was extracted with ether. The combined ethereal solution was dried (Na_2SO_4) and evaporated. The residue was crystallized to give II; yield 5.5 g (74.9%). mp 105—109°. Recrystallization from acetone gave colorless needles; mp 111—112°. *Anal.* Calcd. for $C_9H_{17}ON$: C, 69.61; H, 11.04; N, 9.02. Found: C, 69.58; H, 10.98; N, 9.10.

II–HCl: Colorless needles (ether–ethanol); mp 158—159°. *Anal.* Calcd. for $C_9H_{18}ONCl$: C, 56.38; H, 9.46; N, 7.30. Found: C, 56.19; H, 9.30; N, 7.51.

3-Iodomethyl-*trans*-octahydroindole·HI (III)——A mixture of II (1 g) and 57.5% hydroiodic acid was refluxed for 7 hr. The reaction mixture became orange. After cooling, precipitated crystals of III were collected, and washed with water and dried. Orange needles (EtOH); yield 2.41 g (94.9%). mp 227° (decomp.). *Anal.* Calcd. for $C_9H_{17}NI_2$: C, 27.53; H, 4.36; N, 3.56. Found: C, 27.75; H, 4.39; N, 3.84.

3-Methyl-*trans*-octahydroindole (IVa)——To a solution of $LiAlH_4$ (0.27 g) in dry ether (20 ml) was added III (0.5 g) slowly under cooling, and the mixture was refluxed for 2 hr. After cooling, the reaction mixture was treated successively with moist ether, water and 20% sodium hydroxide. The ethereal layer was then separated and the aqueous layer was extracted with ether. The combined ethereal layer was dried (Na_2SO_4), and evaporated to give oily residue (IVa) which was characterised by the preparation of the picrate; yield 0.35 g (74.8%). mp 168—172°. Yellow plates (EtOH); mp 177—178°. *Anal.* Calcd. for $C_{15}H_{20}O_7N_4$: C, 48.88; H, 5.47; N, 15.21. Found: C, 49.12; H, 5.52; N, 14.93.

2-Oxo-3-methyl-3-ethoxycarbonyl-*trans*-octahydroindole (Vb)——To dry sodium ethoxide (Sodium, 0.109 g) was added diethyl carbonate (10 ml) solution of I (1 g), and the resulting ethanol was removed by evaporation *in vacuo* on a water bath. To the solution, methyl iodide (2 g) was added, and stirred for 3 hr at room temp. After addition of water, the diethyl carbonate layer was washed with water, and removed *in vacuo*. Pet. ether was added to the residue and precipitate of Vb was collected and dried, 0.641 g (59.9%), mp 103—103.5°. Colorless needles (pet. ether–ether); mp 104—105°. IR ν_{max}^{KBr} cm^{-1}: 3260, 3144 (NH), 1743 (EtO–C=O), 1684 (>N–C=O). NMR (in $CDCl_3$) δ: 1.28 (3H, s, C_3–CH_3). NMR (in C_6H_6) δ: 1.31 (3H, s, C_3–CH_3). Mass Spectrum *m/e*: 225 (M^+). *Anal.* Calcd. for $C_{12}H_{19}O_3N$: C, 64.24; H, 8.09; N, 6.24. Found: C, 64.14; H, 8.44; N, 6.21.

2-Oxo-3-methyl-3-carboxy-*trans*-octahydroindole (VIb)——A mixture of Vb (0.4 g), ethanol (1 ml) and 5 N NaOH (4 ml) was allowed to stand for 3 hr at room temp. After removal of the solvents *in vacuo*, the residue was dissolved in water and acidified with 20% hydrochloric acid. Appeared crystals of VIb were collected, washed with water and dried, 0.224 g (63.8%), mp 199—200.5° (decomp.). Colorless columns (EtOH), mp 201° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3332 (NH), 2657, 1733 (HO–C=O), 1669 (>N–C=O). NMR (in DMSO-d_6) δ: 1.08 (3H, s, C_3–CH_3). Mass Spectrum *m/e*: 197 (M^+). *Anal.* Calcd. for $C_{10}H_{15}O_3N$: C, 60.87; H, 7.66; N, 7.10. Found: C, 61.04; H, 7.62; N, 6.93.

2-Oxo-3-methyl-*trans*-octahydroindole (VIIa)——Half a gram of VIb was heated at 210° for about 5 min until evolution of CO_2 gas ceased. After cooling, ether (10 ml) was added, and insoluble material was filtered off. The ether was removed to give crystals of VIIa, 0.3 g (77.3%), mp 128—131°. Colorless needles (H_2O), mp 133—134°. IR ν_{max}^{KBr} cm^{-1}: 3228, 3118 (NH), 1688 (>N–C=O). NMR (in $CDCl_3$) δ: 1.15 (3H, d, J=7.5 Hz, C_3–CH_3). NMR (in C_6H_6) δ: 1.13 (3H, d, J=7.5 Hz, C_3–CH_3). Mass Spectrum *m/e*: 153 (M^+). *Anal.* Calcd. for $C_9H_{15}ON$: C, 70.53; H, 9.87; N, 9.14. Found: C, 70.50; H, 9.92; N, 9.17.

2-(*trans*-2-Aminocyclohexyl)-propionic Acid·HCl (VIIIb)——i) A solution of Vb (2 g) in 20% HCl (28 ml) was refluxed for 10 hr. The solvent was evaporated to dryness. To the residue ether was added, and the crystals of VIIIb were collected and dried, 1.8 g (97.8%), mp 192—194° (decomp.). Colorless needles (EtOH–ether), mp 202—203° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3180, 3138 (NH_3^+), 2620, 1717 (HO–C=O). *Anal.* Calcd. for $C_9H_{18}O_2NCl$: C, 52.02; H, 8.73; N, 6.74. Found: C, 51.74; H, 8.71; N, 6.74.

ii) A solution of VIb (0.2 g) in 20% HCl (10 ml) was refluxed for 5 hr. The solvent was evaporated to dryness, and the crystalline residue of VIIIb was washed with ether, filtered and dried, 0.199 g (94.3%), mp 193—196°. Colorless needles (EtOH–ether), mp 202—203° (decomp.).

2-Oxo-3-methyl-*trans*-octahydroindole (VIIb)——A solution of VIIIb (0.2 g) in 15% ethanolic HCl (5 ml) was refluxed for 5 hr at 135—140° on an oil bath. The solvent was evaporated to dryness, and the oily residue was dissolved in water (0.5 ml) and neutralized with 5% NaOH. The separated oil was extracted with three portions (10 ml) of ether, and dried (Na_2SO_4). After removal of the ether, 0.132 g (89.8%) of VIIb was obtained, mp 106—110°. Colorless needles (H_2O), mp 116—118°. IR ν_{max}^{KBr} cm^{-1}: 3205 (NH), 1681 (>N–C=O). NMR (in $CDCl_3$) δ: 1.07 (3H, d, J=7.5 Hz, C_3–CH_3). NMR (in C_6H_6) δ: 0.94 (3H, d, J=7.5 Hz,

C_3–CH_3). Mass Spectrum *m/e*: 153 (M^+). *Anal.* Calcd. for $C_9H_{15}ON$: C, 70.53; H, 9.87; N, 9.14. Found: C, 70.46; H, 9.71; N, 9.02.

3-Methyl-*trans*-octahydroindole (IVb)——A mixture of VIIb (0.1 g) and $LiAlH_4$ (0.05 g) in dry ether (5 ml) was refluxed for 2 hr, and treated successively with moist ether, water and 10% sodium hydroxide solution. The ethereal layer was then separated. The aqueous layer was extracted with ether. The combined ethereal solution was dried (Na_2SO_4), and evaporated. The oily residue of IVb was characterised by the preparation of picrate, 0.18 g (74.3%), mp 160.5—162°. Yellow needles (benzene), mp 161.5—162.5°. *Anal.* Calcd. for $C_{15}H_{20}O_7N_4$: C, 48.88; H, 5.47; N, 15.21. Found: C, 49.02; H, 5.62; N, 15.20.

3-Methyl-*trans*-octahydroindole (IVa)——A mixture of VIIa (0.35 g) and $LiAlH_4$ (0.15 g) in dry ether (10 ml) was refluxed for 1.5 hr, and treated successively with moist ether, water and 10% sodium hydroxide solution. The ethereal layer was then separated. Aqueous layer was extracted with ether. The combined ethereal solution was dried (Na_2SO_4), and evaporated. The oily residue of IVa was characterised by the preparation of picrate, 0.58 g (69.0%), mp 172—175°. Yellow plates (EtOH), mp 177—178°.

Treatment of VIIa with Potassium *t*-Butoxide——To a solution of potassium *t*-butoxide (potassium 0.076 g) in *t*-BuOH (10 ml), VIIa (0.3 g) was added and refluxed for 14 hr. The solution was evaporated to dryness. To the residue water (3 ml) was added and an insoluble substance was extracted with ether. The ethereal layer was dried (Na_2SO_4) and evaporated to recover, 0.27 g (90%) of VIIa, mp 131—133°.

Isomerization of VIIb——To a solution of potassium *t*-butoxide (potassium, 0.076 g) in *t*-BuOH (10 ml), VIIb (0.3 g) was added and refluxed for 14 hr. The solution was evaporated to dryness. After adding of H_2O (3 ml), an insoluble substance was extracted with ether. The ethereal layer was dried (Na_2SO_4), and evaporated. Recrystallization of the crystalline residue (0.26 g, mp 124—127°) from water gave colorless needles of VIIa, 0.185 g (62%), mp 133—134°. The product was identified with the authentic sample of VIIa by mixed mp and IR (KBr) comparison.

1-Benzylsulfonyl-2-oxo-3-methyl-3-ethoxycarbonyl-*trans*-octahydroindole (XI)——To a NaOEt–EtOH solution prepared from Na (0.07 g) and abs. EtOH (10 ml), was evaporated to dryness. To the residue (EtONa) was added X (1 g) in dry diethyl carbonate (20 ml), and the produced EtOH was distilled at atmospheric pressure until bp reaches to 124° (*ca.* 4 ml). After cooling the solution, CH_3I (1.17 g) was added, and stirred for 22 hr at room temperature. The solvent was removed by distillation *in vacuo*. To the residue water was added, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried (Na_2SO_4). After evaporating the $CHCl_3$, the residue was purified by silica gel column chromatography eluting with $CHCl_3$ and 0.435 g (41.9%) of XI was obtained, mp 116—118°. Colorless prisms (ether–pet. ether), mp 118—119°. IR ν_{max}^{KBr} cm^{-1}: 1759 (>N–C=O), 1731 (EtO–C=O), 1357, 1139 (SO_2). NMR (in $CDCl_3$) δ: 1.24 (3H, s, C_3–CH_3). NMR (in C_6H_6) δ: 1.09 (3H, s, C_3–CH_3). Mass Spectrum *m/e*: 379 (M^+). *Anal.* Calcd. for $C_{19}H_{25}O_5NS$: C, 60.13; H, 6.64; N, 3.69. Found: C, 60.35; H, 6.75; N, 3.64.

Desulfurization of XI——A suspension of Raney Ni w-4 (2 ml) in EtOH was added to XI (0.2 g) under stirring, and stirred for 5 hr at room temp. After filtering of the Ni, the EtOH was evaporated *in vacuo* to give Vb as crystals, 0.099 g (83.9%), mp 99—103°. Colorless needles (ether–pet. ether), mp 106—106.5°, were identified with the authentic sample of Vb by mixed mp and IR (KBr) comparison.

2-Oxo-1,3-diethoxycarbonyl-*trans*-octahydroindole (XII)——To the dried EtONa which was prepared from Na (0.055 g) was added a solution of I (0.56 g) in dry diethyl carbonate (10 ml), and the produced EtOH was distilled off at atmospheric pressure until bp 124° (*ca.* 3 ml) is shown. After refluxing the solution for 1 hr, the solvent was removed, and to the residue water was added. The resulting mixture was neutralized with dil. AcOH, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried (Na_2SO_4), and evaporated. The oily residue was purified by silica gel column chromatography eluting with $CHCl_3$ to give 0.534 g (71.2%) of XII, mp 41—43°. IR ν_{max}^{KBr} cm^{-1}: 1797 (>N–COOEt), 1760 (>N–C=O), 1738 (C_3–COOEt). NMR (in $CDCl_3$) δ: 3.15 (1H, d, $J=12$ Hz, C_3–H). Mass Spectrum *m/e*: 283 (M^+). *Anal.* Calcd. for $C_{14}H_{21}O_5N$: C, 59.31; H, 7.47; N, 4.85. Found: C, 59.35; H, 7.47; N, 4.94.

2-Oxo-1,3-diethoxylcarbonyl-3-methyl-*trans*-octahydroindole (XIII)——To the dried EtONa which was prepared from Na (0.109 g) was added a solution of XII (1.34 g) in dry diethyl carbonate (10 ml), and the produced EtOH was distilled off at atmospheric pressure until bp 120° (*ca.* 8.9 ml) is shown. After cooling, CH_3I (2 g) was added. White precipitate of NaI appeared. After allowing to stand for 30 min at room temperature, the solution was washed with H_2O (five times) to remove NaI. The diethyl carbonate was evaporated *in vacuo*. The oily residue was purified by silica gel column chromatography eluting with $CHCl_3$ to give 1.197 g (85.1%) of XIII as oil, bp 181—184°/7 mmHg. The oil solidified on standing in dry ice-acetone bath, mp 40—42°. IR ν_{max}^{KBr} cm^{-1}: 1767 (>N–COOEt), 1745 (>N–C=O), 1729 (C_3–COOEt). NMR (in $CDCl_3$) δ: 1.31 (3H, s, C_3–CH_3). Mass Spectrum *m/e*: 297 (M^+). *Anal.* Calcd. for $C_{15}H_{23}O_5N$: C, 60.64; H, 7.97; N, 4.64. Found: C, 60.59; H, 7.80; N, 4.71.

2-Oxo-3-methyl-3-carboxy-*trans*-octahydroindole (VIa)——After allowing to stand a solution of XIII (1.197 g) in 5 N NaOH (10 ml) and EtOH (3 ml) for 5 hr, the solution was neutralized with dil. HCl and precipitated crystals were collected, washed with water and dried to give 0.535 g (67.3%) of VIa, mp 178—179° (decomp.). Recrystallization from water gave colorless needles (VIa), mp 181.5—182° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3465 (OH), 3210, 3090 (NH), 2500, 1703 (HO–C=O), 1683 (>N–C=O). NMR (in DMSO-d_6) δ: 1.18 (3H,

s, C_3–CH_3). Mass Spectrum *m/e*: 197 (M^+). *Anal.* Calcd. for $C_{10}H_{15}O_3N$: C, 60.96; H, 7.98; N, 7.09. Found: C, 60.89; H, 7.67; N, 7.10.

2-Oxo-3-methyl-3-ethoxycarbonyl-*trans*-octahydroindole (Va)——After refluxing a solution of VIa (0.4 g) in 15% ethanolic HCl (10 ml) for 5 hr, the solvent was evaporated to dryness. The residue was crystallized by treating with pet. ether to give 0.379 g (83.1%) of Va, mp 107.5—110°. Colorless needles (ether–pet. ether), mp 112—114.5°. IR ν_{max}^{KBr} cm^{-1}: 3233, 3132 (NH), 1737 (EtO–C=O), 1703 (>N–C=O). NMR (in $CDCl_3$) δ: 1.40 (3H, s, C_3–CH_3). NMR (in C_6H_6) δ: 1.49 (3H, s, C_3–CH_3). Mass Spectrum *m/e*: 225 (M^+). *Anal.* Calcd. for $C_{12}H_{19}O_3N$: C, 63.52; H, 8.38; N, 6.07. Found: C, 63.67; H, 8.50; N, 6.22.

Decarboxylation of VIa——An 0.1 g of VIa was heated for 4 min at 190—200°. After cooling, the decomposed residue was dissolved in ether (10 ml), and insoluble substance was filtered off. The solvent was evaporated to give crystals of VIIa, 0.067 g (84.8%), mp 125—128°. Recrystallization from ether–pet. ether gave colorless needles, mp 131—133°.

Hydrolysis of VIa——After refluxing a solution of VIa (0.4 g) in 20% HCl (15 ml) for 5 hr, the solvent was evaporated to dryness. The crystalline residue was washed with ether, and dried to give 0.357 g (84.8%) of VIIIb, mp 200—202° (decomp.). Recrystallization from EtOH–ether gave colorless needles of mp 201—202° (decomp.).

2-(*trans*-2-Aminocyclohexyl)-propionic Acid·HCl (VIIIa)——After refluxing a solution of VIIa (0.15 g) in 20% HCl (10 ml) for 5 hr, the solvent was removed *in vacuo*. The crystalline residue was washed with ether and dried to give 0.18 g (88.5%) of VIIIa, mp 195—196° (decomp.). Recrystallization from EtOH–ether gave colorless plates of mp 195—196° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 3132, 3053 (NH_3^+), 2730—2530, 1723 (COOH). *Anal.* Calcd. for $C_9H_{18}O_2NCl$: C, 52.02; H, 8.73; N, 6.74. Found: C, 52.09; H, 8.96; N, 6.64.

Formation of VIIa from VIIIa——After refluxing a solution of VIIIa (0.2 g) in 15% ethanolic HCl (5 ml) for 5 hr at 140° on an oil bath, the solvent was removed *in vacuo*. The residue was dissolved in water (0.5 ml) and neutralized with 5% NaOH. An oily substance separated, extracted with 10 ml portions of ether (three times) and dried (Na_2SO_4). The ether was evaporated to give 0.124 g (84.3%) of VIIa, mp 130—133°. Recrystallization from water gave colorless needles of mp 132—134°, which was identified with the authentic sample of VIIa by mixed mp and IR (KBr) comparison.

Hydrolysis of VIIb——After refluxing a solution of VIIb (0.1 g) in 20% HCl (7 ml) for 3 hr, the solvent was evaporated to dryness. The crystalline residue was washed with ether, and dried to give 0.09 g (66.6%) of VIIIb, mp 200—201° (decomp.). Recrystallization from EtOH–ether gave colorless needles (VIIIb), mp 201—202° (decomp.).

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