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Synthesis and Structure of 4-Substituted Decahydroisoquinoline Derivatives

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Four possible racemates of 4-hydroxymethyldecahydroisoquinolines, hitherto unknown in the literature, were synthesized and their stereochemistry was specified and characterized. Hydrochloride salts of their benzoylesters were also prepared and their local anesthetic activity was tested, but none was proved to be useful.

In 1960 Sokolov, *et al.*[2] reported the synthesis of 4-substituted decahydroquinoline and found that they manifested local anesthetic activity, which depended much upon their stereostructure.

Thus, it appeared worthwhile to study the structure-activity relationship in the corresponding isoquinoline derivatives, 2-methyl-4-hydroxymethyldecahydroisoquinoline, whose chemistry and pharmacology have hitherto never been investigated.

For the projected synthesis, ethyl 2-ethoxycarbonylcyclohexylidenecyanoacetate (I), which was prepared from ethyl 2-oxocyclohexanecarboxylate and ethyl cyanoacetate according to the Grewe's method,[3] formed a suitable starting material.

Location of the double bond in I was decduced to be exo according to the following evidence.

Compound I gave a singlet infrared (IR) absorption band for CN at 2250 cm^{-1} (Fig. 1), indicating that the double bond in I is located either in exo- or endo-cyclic position. After hydrogenation, however, ν_{CN} shifted to a higher wave number, 2290 cm^{-1}, which appeared to be reasonable as referred to ν_{CN} 2300 cm^{-1} of ethyl *o*-ethoxycarbonylphenylcyanoacetate (XVI).

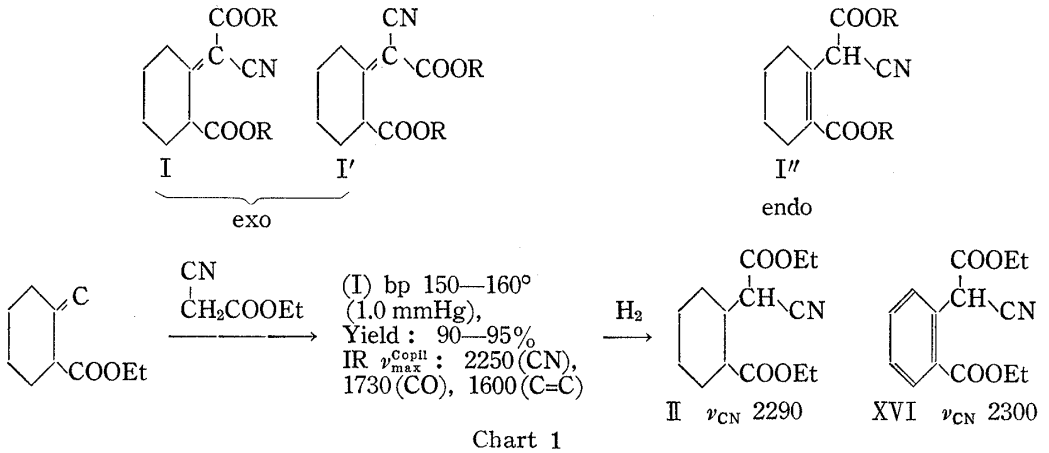


Chart 1

Hence it may be construed that the double bond in I is assuming exo-cyclic position conjugated to CN-group as shown in I and/or I'.

Further corraboration was furnished from the data of nuclear magnetic resonance (NMR) spectrum of I.

1) Location: *3073 Shimotoda, Toda, Saitama.*
2) D.V. Sokolov, G.S. Litvinenko, and K.I. Khuludneva, *J. General Chem.* (U.S.S.R.), **30**, 844 (1960).
3) R. Grewe and A. Mondon, *Ber.*, **81**, 279 (1948).

Kasturi and Surinivasan[4] ran NMR spectrum of methyl 2–methoxycarbonylcyclopentylidenecyanoacetate and found that H of two methyl groups appeared as a pair of doublet, which they ascribed to the presence of *cis* and *trans* isomeric mixture of exo–cyclic olefinic compound.

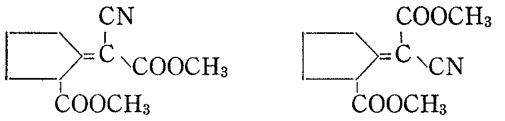


Chart 2

Ethyl 2–methoxycarbonylcyclohexylidenecyanoacetate related to I behaved similarly on NMR measurement, showing a doublet at 3.75 (ppm) ascribed to methyl hydrogen, in conformity with above mentioned case. Exo–cyclic location of the double bond in I was thus supported[5] (Chart 2).

The compound (I) obtained by condensing ethyl 2–oxocyclohexanecarboxylate with ethyl cyanoacetate showed a single absorption at ν_{CN} 2250 cm^{-1} (Fig. 1) which is probably a *cis* and *trans* mixture of 2–ethoxycarbonylcyclohexylidenecyanoacetic acid ester.

The latter yielded ethyl 2–ethoxycarbonylcyclohexylcyanoacetate (II) with ν_{CN} 2290 cm^{-1}, when reduced over Pd–catalyst.

Reduction of compound II was then carried out with Raney–Ni catalyst (100 at., 60—80°), and from the product, were isolated two crystalline ethyl 1–oxodecahydro–4–isoquinolinecarboxylate with mp 182° (IIIA), and mp 82° (IIID) in 25% and 20% yields respectively.

These two compounds were conjectured to be isomeric from their elemental analysis, molecular weight determination and IR spectral data (Fig. 2, 3).

Isomerization of these two lactams was found to be effected by refluxing with $POCl_3$ for a prolonged period of time.

Thus compound IIIA yielded compound IIIC with mp 136° in 10—15% yield and from IIID was obtained IIIB of mp 158° in 20—25% yield.

These four ethyl 1–oxodecahydro–4–isoquinolinecarboxylate (III; A, B, C and D) could be obtained in a state of high purity as was evidenced from their gas chromatography (SE–52), retention time of 3.2, 3.5, 4.5 and 3.6 sec respectively.

On reduction with $LiAlH_4$ in tetrahydrofurane (T.H.F.) followed by N–methylation,[6] these compounds were converted to 2–methyl–4–hydroxymethyldecahydroisoquinoline (V; A, B, C and D), which were purified by distillation *in vacuo* (bp 120—125° (1—2 mmHg)) to afford crystalline A (mp 89°), B (mp 65.5°) and C (mp 73°) after being crystallized from benzene–*n*–hexane.

VD, however, could not be induced to crystallize even after being purified *via* crystalline picrate of its benzoyl derivative.

For pharmacological evaluation, (V; A, B, C and D) were benzoylated, whose hydrochloride salts were prepared (Chart 3).

The local anaesthetic activity of the four foregoing isomers of 2–methyl–4–benzoyloxymethyldecahydroisoquinoline (VI; A, B, C and D) were tested with their hydrochloride salts, taking "lidocaine" as a standard compound.

The results will be reported in detail elswhere.

Here will be made only a brief description.

I) Activity (ED 50) (Potency)

1) Surface and Infiltration Anesthetic Actions

Hydrochloride salts of (VI; A, B and C) manifested almost an equal order magnitude of potency, a little stronger than "lidocaine," while VID hydrochloride seemed slightly less active.

4) T.R. Kasturi and A. Srinivasan, *Tetrahedron*, **22**, 2575 (1966).
5) NMR and IR spectra of similar type of various compounds will be discussed and reported in detail separately.
6) H. Henecka, U. Hörlein, and K.H. Risse, *Angew. Chem.*, **72**, 960 (1960).

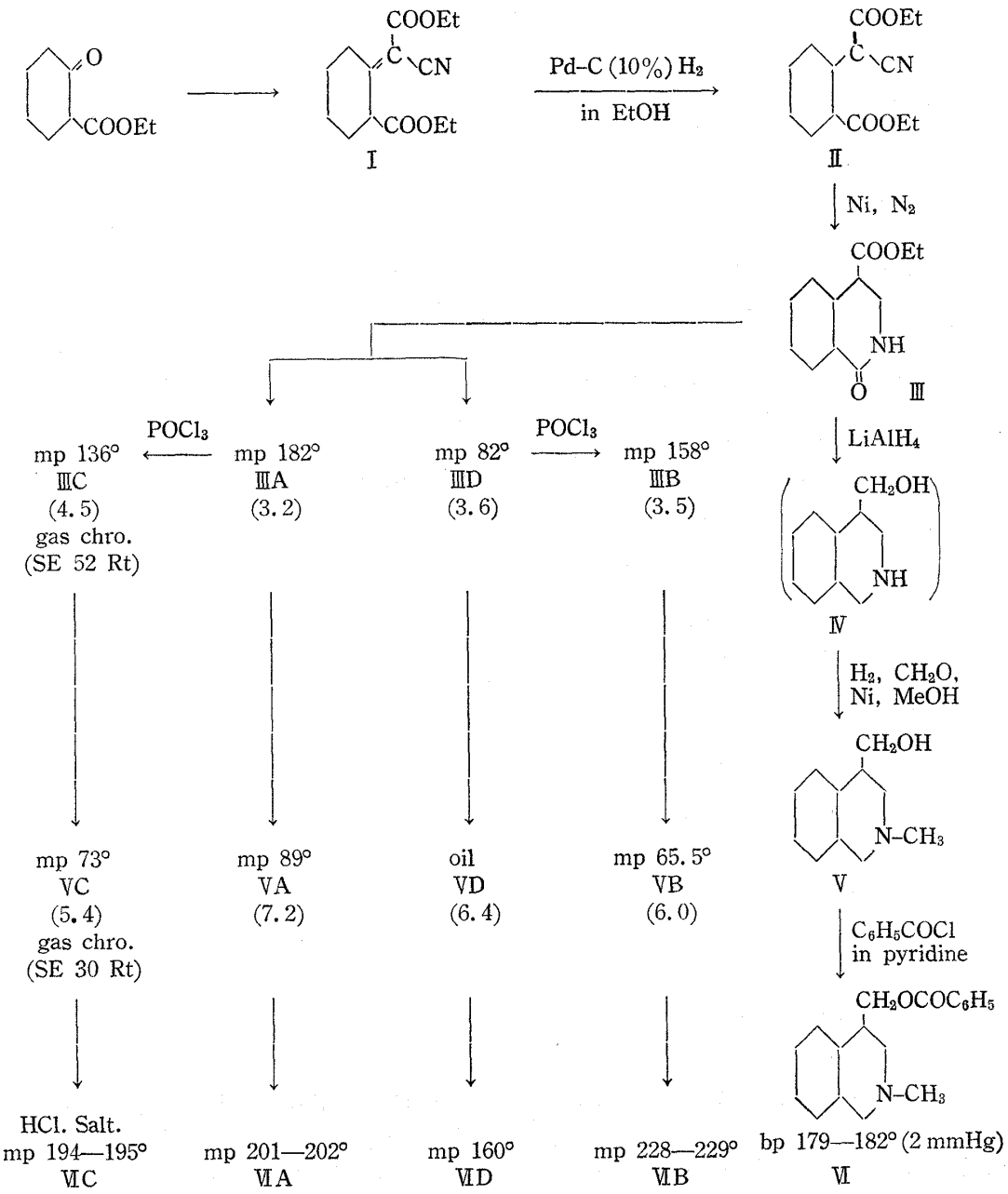


Chart 3

2) Conduction Anesthetic Action

Four isomers were almost equally, and somewhat less active than "lidocaine."

The above results showed that the action of these four isomers on nerves are almost equal, and the slight difference in surface and infiltration anesthetic activities are probably due to differences in absorption of these isomers from the site of application.

II) Toxicity

1) Local Irritability

All the four isomers showed stronger irritabilities than "lidocaine," causing necrosis when applied as 2% aq. solution, though (VIC) appeared somewhat less irritable.

2) Acute Toxicity

(VI; A, B, and C) are nearly toxic, slightly stronger than "lidocaine," (VID) was proved to be somewhat less toxic than lidocaine.

The above mentioned results may be tabulated as follows:

Table I

Compounds	Activity(ED 50) (concent. %)			Irritability	Acute toxicity
	Surface A.A.	Infilt. A.A.	Conduct. A.A.		
VIA	0.18	0.11	0.021	++++	28
VIB	0.17	0.11	0.023	++++	28
VIC	0.14	0.06	0.022	++	32
VID	0.24	0.25	0.023	+++	48
Lidocaine	0.47	0.17	0.018	+−	38

In the foregoing section it was reported that all the four possible stereoisomeric racemates of III and V, designated as A, B, C, and D, were prepared.

From the data of their IR spectra (Fig. 2—13), and gas chromatography it could be deduced that the conversion of III (A, B, C and D) to V (A, B, C and D) was effected with retention of configuration (Chart 4).

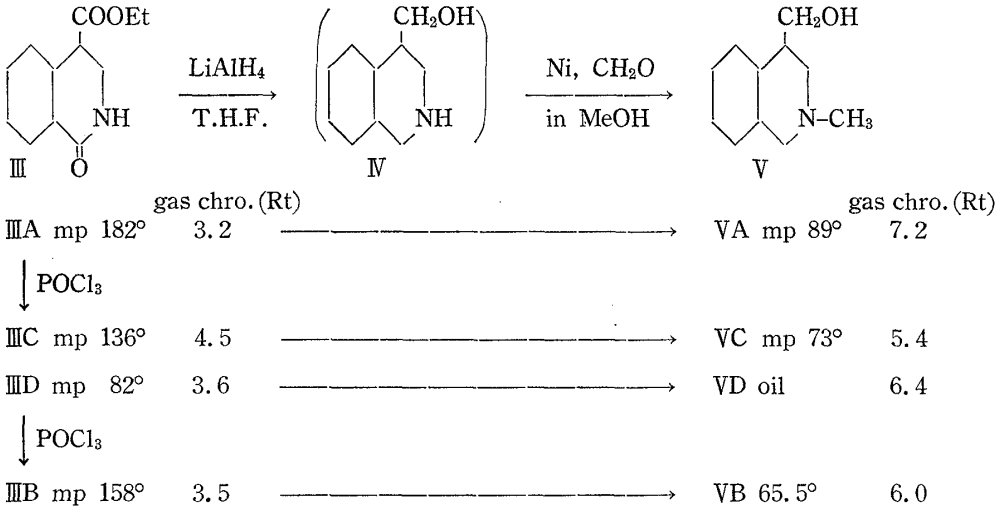


Chart 4

Thus, it became possible to discuss and specify the stereochemistry of these compounds.

When III (A, B, C and D) were treated with sodium ethoxide (10% ethanolic solution), A, C and D, all isomerized to give B, where as the latter was found to be quite indifferent toward this reagent. This fact proves that these are stereoisomers, of which IIIB exists in the most stable stereo disposition (Chart 5).

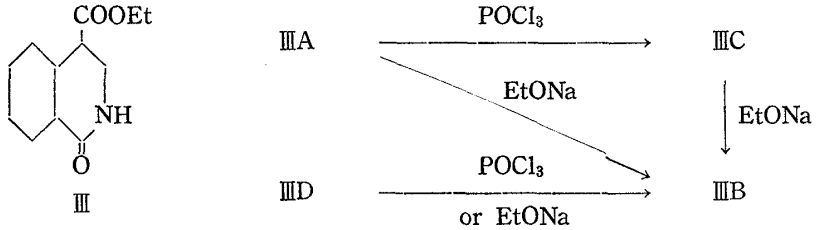


Chart 5

In order to establish the ring juncture of these compounds, V (A, B, C and D) were treated with conc. hydrobromic acid, and resultant 4-bromomethyl derivatives were condensed with trimethylamine to yield the corresponding ammonium bromides (VIII).

The latter were then submitted to the Hofmann degradation reaction to give the corresponding vinylidene derivatives 2-methyl-4-vinylidenedecahydroisoquinoline (IX; A,

B, C and D), of which A and B were found to be identical with D and C respectively by direct comparison of their picrated (mixture mp and IR spectra) (Fig. 18—21).

The plane structure of IX was verified by converting it into the corresponding 4-oxo (X) and 2,4-dimethyldecahydroisoquinoline (XI) derivatives through ozonization and catalytic hydrogenation respectively (Chart 6).

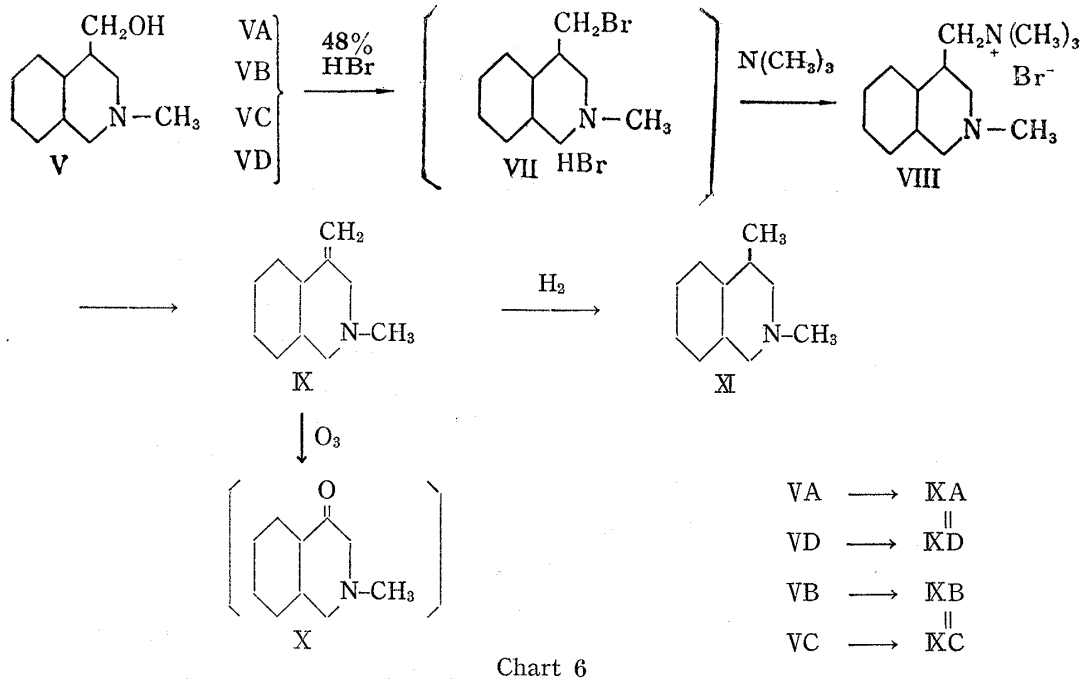


Chart 6

From the above results it was now made clear that in III and V, the compounds of series A and B were assuming the same disposition of the ring juncture as that of series D and C respectively.

Now, the next problem is to specify the ring juncture of these compounds. For that purpose inspection of the streching vibration of the OH group of the four stereoisomers A, B, C and D of V was made, which allowed discussion on the situration of intramolecular hydrogen bond (–N...H–O).

Thus in VA and VB, such a hydrogen bond is absent, whereas in VC the HO–group exists completely in a chelate state.

However, in VD were recognized both free and chelated states of the HO–group.

pK_a data of these four isomers also rend support to the above view (Chart 7).

From the foregoing discussion it could now be deduced that VC is a derivative of *trans* decahydroisoquinoline with a fixed 4–axial CH_2OH group, and VD the 4–CH_2OH group is freely convertible between axial and equatorial dispositions, which ensures from the *cis* ring juncture with hydrogens at 4– and 10–position antisituated.

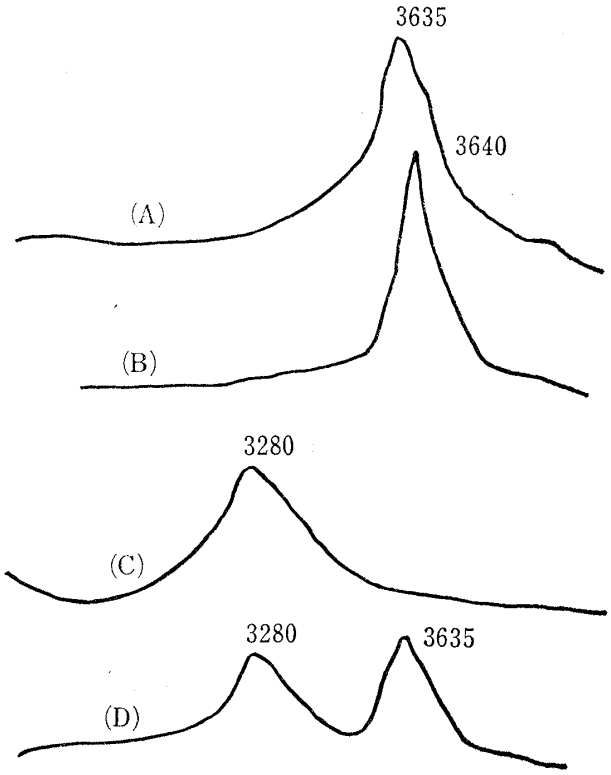
The following work was then carried out to elucidate the stereochemistry of VA and VC.

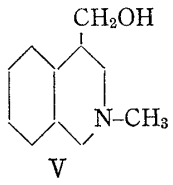
It is well established that catalytic hydrogenation of polysubstituted aromatic compounds over Pt–catalyst at room temperature yields the corresponding *cis* hydro compounds.

Thus diethyl *o*–homophthalate[7] (XII) gave diethyl *cis*–hexahydro–*o*–homophthalate[8] (XIII) in good yield.

In a similar manner 2–methyl–4–hydroxymethyl–1,2,3,4–tetrahydroisoquinoline (XVIII), prepared from *o*–cyanomethylbenzoic acid as shown in Chart 9 gave rise to IIIA in good yield, when reduced over Pt–catalyst in acetic acid.

7) C. Prise, *Org. Synth.*, **22**, 61 (1942).
8) W.E. Bachmann, *J. Org. Chem.*, **19**, 222 (1954).

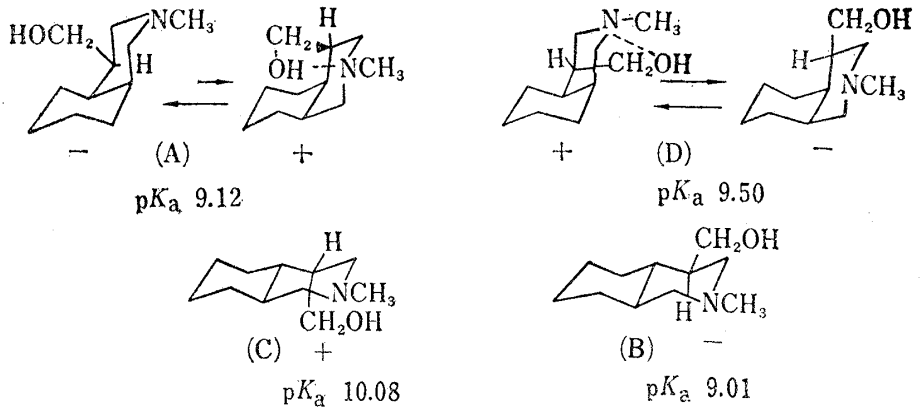




V

(A) 3635 cm^{-1}
(B) 3640
(C) 3280
(D) 3280 3635 cm^{-1}

Intramolecular hydrogen bonding ($-\overset{|}{N}\cdots HOCH_2-$) was examined in the four isomer of V from the stretching vibration of OH in their IR spectra (in CCl_4: 0.002 mole/liter).



\+ Intramolecular hydrogen bonding was deduced as possible on model.
− Intramolecular hydrogen bonding was deduced as impossible on model.

Chart 7

Hence the compounds of A-series were proved to belong to *cis* decahydroisoquinoline (Chart 8).

2-Ethoxycarbonyl-6-hydroxydecahydro-4-isoquinolinecarboxylic acid lactone (XXXV) was prepared according to the processes described in Chart 10.

Inspection of the molecular model of this compound showed that this compound exists only in one form with *cis* ring juncture, *cis* lactone ring and syn disposed hydrogens at 4 and 10. This lactone was reduced with $LiAlH_4$ to yield 2-methyl-4-hydroxymethyl-6-hydroxydecahydroisoquinoline (XXXVI) (Chart 8), which was partially dehydrated and the product was reduced over Pt catalyst.

The compound thus obtained was found to be identical with VA. Since any isomerization during these reactions (XXXV to VA) appears improbable, the compound VA should have the same configuration as XXXV, *i.e.*, *cis* ring juncture and syn disposed hydrogen at 4 and 10.

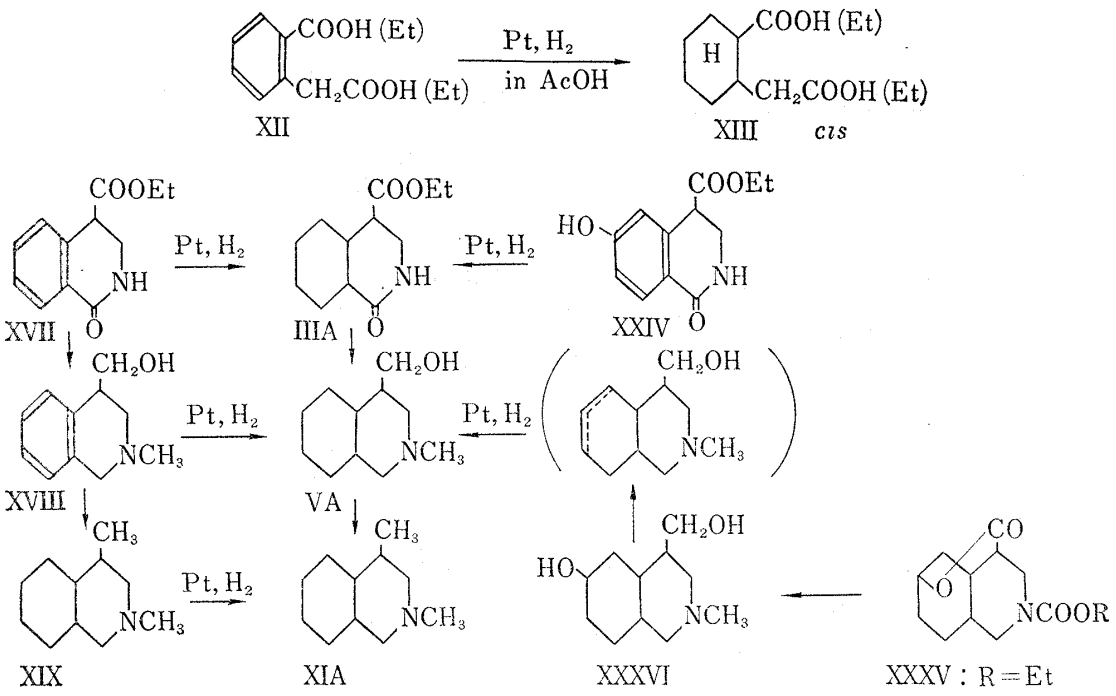


Chart 8

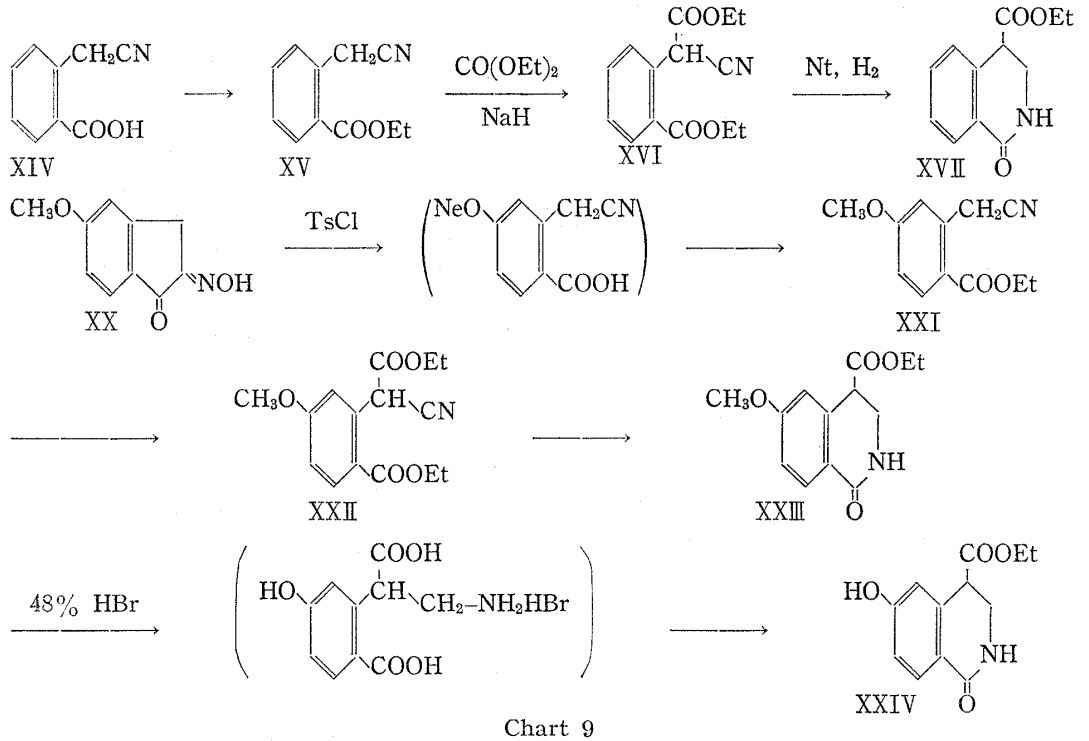


Chart 9

As was already described in the foregoing section isomerization of IIIA and IIID with $POCl_3$ occurred only at ring juncture 9 with exemption of 4-position to yield IIIC and IIIB respectively.

Hence the compounds of series A and C, and B and D have the same configuration at 4 and 10 positions. At the same time the above mentioned conjecture of *cis* ring juncture in series A and D, and *trans* in B and C was also corraborated.

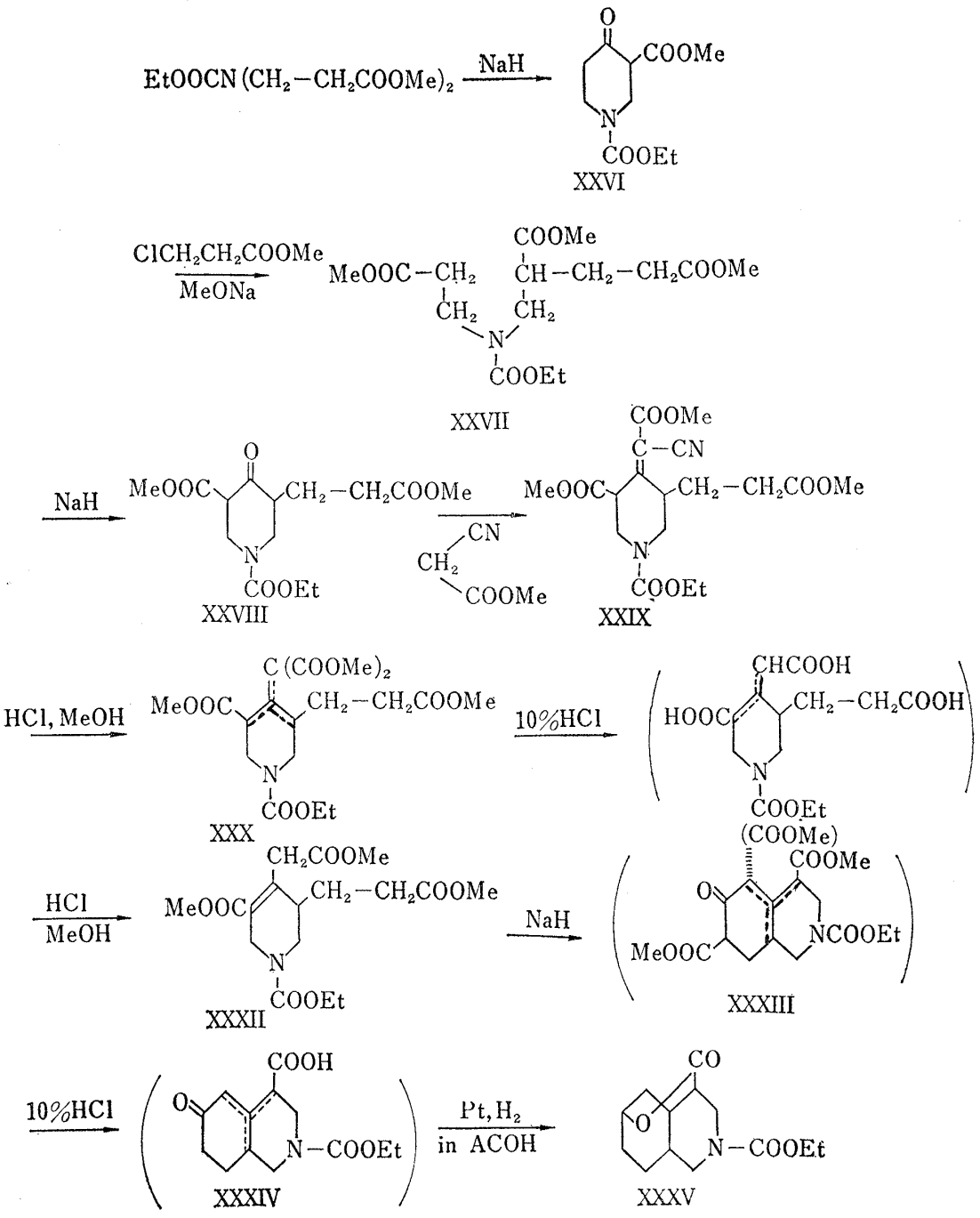


Chart 10

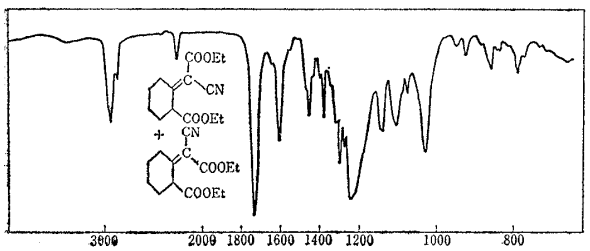


Fig. 1

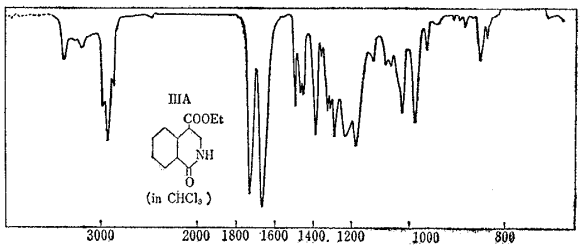


Fig. 2

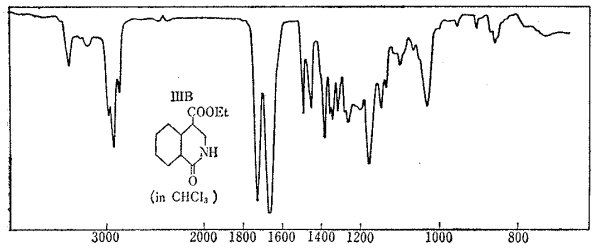


Fig. 3

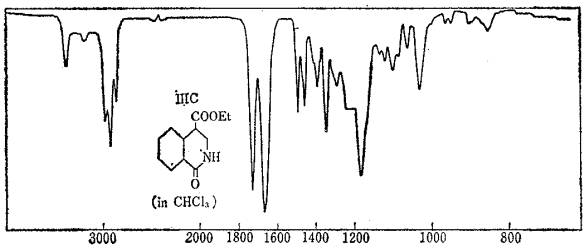


Fig. 4

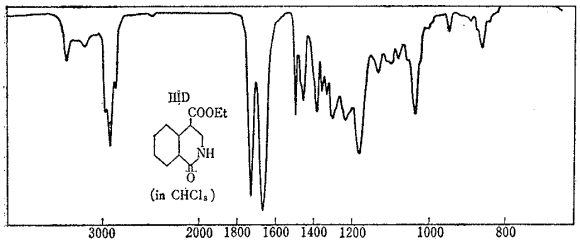


Fig. 5

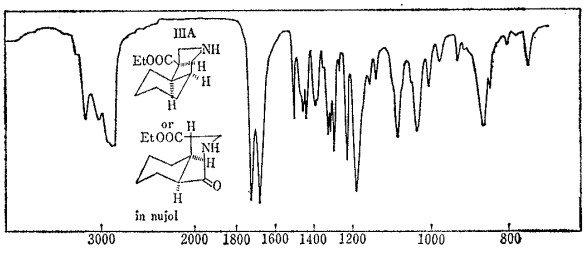


Fig. 6

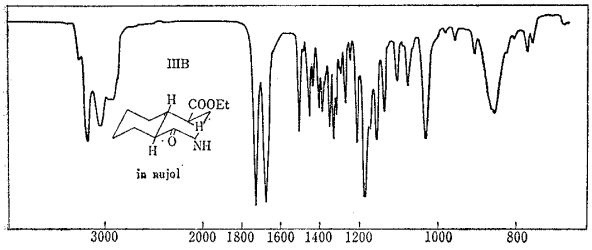


Fig. 7

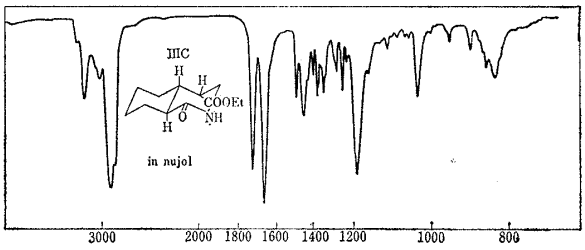


Fig. 8

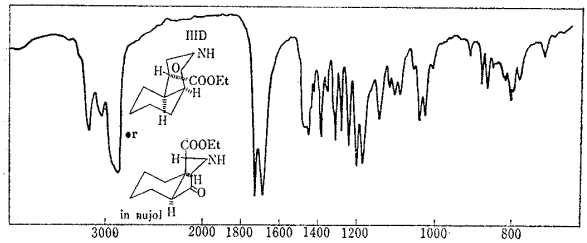


Fig. 9

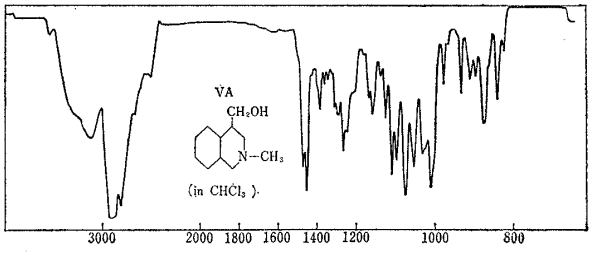
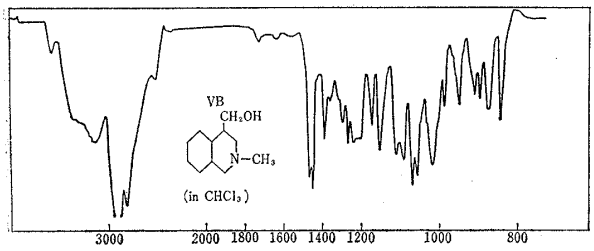


Fig. 10



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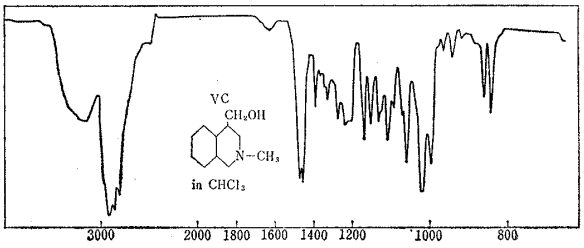


Fig. 12

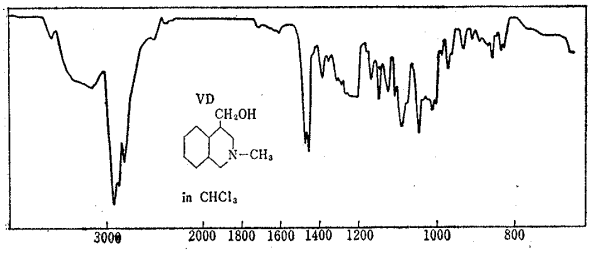


Fig. 13

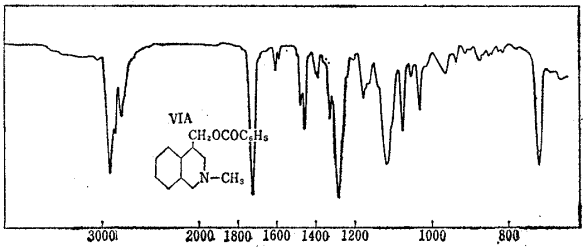


Fig. 14

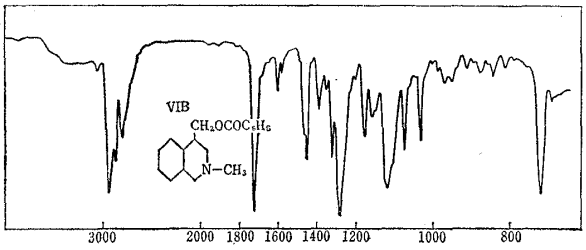


Fig. 15

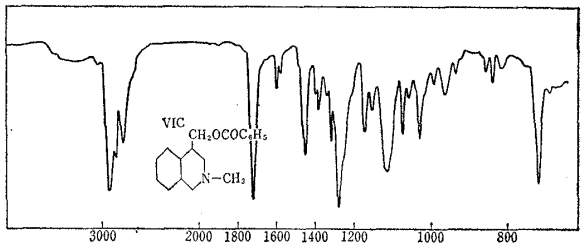


Fig. 16

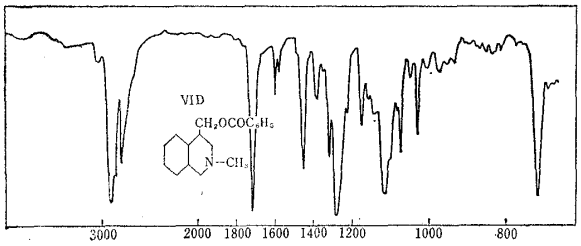


Fig. 17

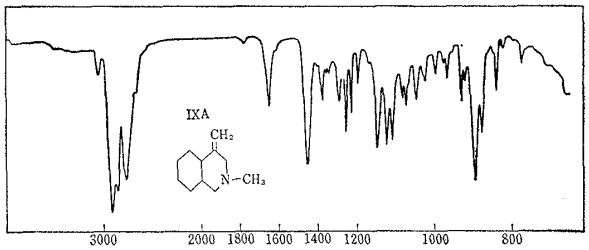


Fig. 18

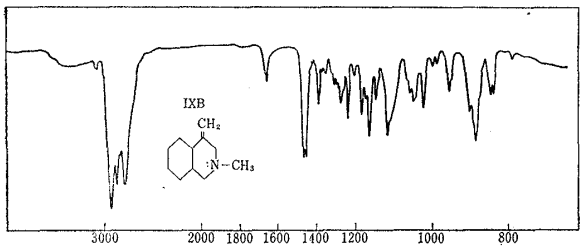


Fig. 19

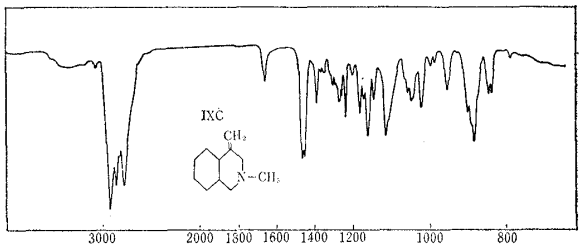


Fig. 20

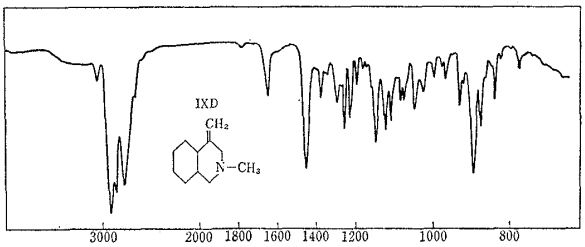


Fig. 21

Experimentals

Ethyl 2-Ethoxycarbonylcyclohexylcyanoacetate(II)——Ethyl 2-ethoxycarbonylcyclohexylcyanoacetate (I) (100 g) was hydrogenated in EtOH (200 ml) over 10% Pd-C (3.0 g) at room temperature. The hydrogenation was stopped after one mole of hydrogen (2 hr) had been absorbed. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residual product was extracted with benzene. The extract was dried, the solvent was removed, and the residue was purified by distillation *in vacuo*. bp 150—155° (1—2 mmHg) (94.0 g or 93% yield) II. IR (Fig. 1).

Ethyl 1-Oxodecahydro-4-isoquinolinecarboxylate(III)——A solution of ethyl 2-ethoxycarbonylcyclohexylcyanoacetate II (100 g) in EtOH (200 ml) was shaken in the presence of Raney-Ni (7.5 g) catalyst with hydrogen at 60—80° and 100 atm. pressure. The reaction was stopped when two moles of H_2 had been absorbed. The catalyst was removed by filtration and the solvent evaporated leaving a semi-solid material. Recrystallization from EtOH afforded III (A) (20.2 g or 25%) mp 182° and III (D) (17.0g or 20%) mp 82°. IR (Fig. 2, 6, 5, 9). *Anal.* Calcd. for $C_{12}H_{19}O_3N$: C, 63.97; H, 8.50; N, 6.22. Found: IIIA; C, 63.82; H, 8.41; N, 6.10, IIID; C, 63.59; H, 8.32; N, 6.31. M.W. (Rast) Calcd. 225; Found: IIIA, 227.2; IIID 226.1.

Ethyl 1-Oxo-1,2,3,4-tetrahydro-4-isoquinolinecarboxylate (XVII)——In a like manner 20 g of cyanodiester XVI, furnished 12 g of the objective XVII as colorless needles mp 106° (from EtOH). IR $\nu_{max}^{CHCl_3}$: 3400

(NH), 1730 (ester, C=O), 1680 (amide, C=O). *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.69; H, 5.92; N, 6.44.

Ethyl 1-Oxo-6-methoxy-1,2,3,4-tetrahydro-4-isoquinolinecarboxylate (XXIII)——A solution of cyano-diester (XXII) (15 g) in EtOH (30 ml) was treated as described above, giving colorless needles, mp 160° (from EtOH); yield, 8.2 g or 63%. IR ν_{max}^{Nujol}: 3160 (NH), 1740 (ester C=O), 1670 (amide C=O). *Anal.* Calcd. for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.41; H, 5.94; N, 5.39.

Isomerization of IIIA and IIID——The compound IIIA (1.0 g) was heated with $POCl_3$ (2 ml) under reflux for 8 hr and excess $POCl_3$ was removed by distialltion under reduced pressure to give semi-solid residue, which was triturated with water. After standing at room temperature overnight, the solution turned yellow and crystlas separated out, which were a mixture of the staring matieral IIIa and the isomerized product (IIIC). Their separation was best effected through crystallization from EtOH. Thus the mixture (0.8 g) was dissolved in hot EtOH (20 ml) and the solution was allowed to cool, separating a mixture of colorless needles, of IIIA, and colorless fine needles of IIIC. These were collected and swirled with cold EtOH, when the latter gradually went into solution, leaving the former undissolved. Pure IIIA (0.5 g) was thus recovered. Alcoholic mother liquor and washing were combined and evaporated to a small volume. In case IIIC separated from the cooled solution was contaminated with IIIA, treatment with cold EtOH was repeated to remove the more sparingly soluble IIIA. 0.15 g (or 15%) of pure IIIC was ultimately obtained, which formed colorless fine needles, mp 136°, from EtOH.

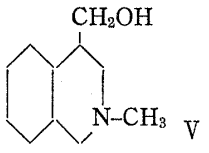
The compound IIID (1.0 g) was heated with $POCl_3$ (2 ml) under reflux for 6 hr. After cooling the mixture was treated as above, giving an orange semi-solid. Recrystallization from EtOH gave pure IIIB (0.2—0.25 g) as colorless needles mp 158°, and IIID (starting material) was collected as colorless fine needles, mp 82°, from the mother liquor in the yield or 0.3—0.4 g. IR of IIIB and IIIC (Fig. 2,7,4,8). *Anal.* Calcd. for $C_{12}H_{19}O_3N$; C, 63.97; H, 8.50; N, 6.22. Found: IIIB; C, 64.28; H, 8.54; N, 6.22, IIIC; C, 64.18; H, 8.18; N, 6.12. M.W. (Rast) Calcd. 225: Found; IIIB 226; IIIC 225.6.

Isomerization of the Compounds IIIA, IIIC and IIID by Sodium Ethoxide——A solution of IIIA (1.0 g) EtONa (Na, 1.0 g; EtOH, 10 ml) was heated on water bath for 6 hr. After evaporation of the solvent, the brown residue obtained was dissolved in benzene, washed with H_2O and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a colorless solid. Recrystallization from EtOH gave pure product (0.12 g, 12%) as colorless needles mp 158°. The compound thus obtained was shown to be identical through mixed mp and IR (in $CHCl_3$) data with the sample prepared by treating the compound IIID with $POCl_3$.

By the procedure described above, IIIC and IIID gave IIIB as colorless needles mp 158° (from EtOH) in 32% and 24% yield respectively.

2-Methoxy-4-hydroxymethyldecahydroisoquinoline (V)——To a suspention of $LiAlH_4$ (14 g) in dehyd. T.H.F. (200 ml) was added dropwise with stirring a solution of IIIA (50 g) in dehyd. T.H.F. (400 ml) under ice-cooling. The mixture was refluxed gently for 24 hr. After cooling, the complex salt was decomposed by H_2O (20 ml) and the inorganic salt was filtered off. The filtrate was concentrated and the residue was dissolved in AcOEt, dried (K_2CO_3) and evaporated. The residue obtained (40 g) was dissolved in MeOH (300 ml), added with aq. CH_2O (37%, 35 ml) and AcOH (3.5 ml) and was reduced catalytically at 60 atm. pressure and 80—90° over Raney-Ni (40 g of alloy was activated) catalyst. Ni was removed by filtration and the filtrate was removed and the residue was dissolved in a mixture of benzene (100 ml) and Ac_2O (50 g), and heated at 120—130° for 3 hr. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in 10% HCl and washed with ether. The aqueous layer was washed with benzene and treated with charcoal. The filtrate was basified with K_2CO_3 and extracted with benzene, the benzene

TABLE II.



V

No.	bp (°C/mmHg)	mp (from benzene–hexane)	Yield (%)	Analysis (%) $C_{11}H_{21}ON$ Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VA	140—145/1—2	89	41	72.08	11.55	7.64	72.12	11.41	7.71
VB	139—143/1	65.5	42				71.96	11.24	7.53
VC	140—145/2	73	39				71.92	11.36	7.41
VD	139—140/2	oil	40				72.12	11.45	7.54

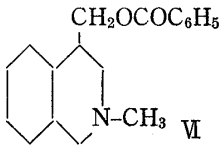
layer was dried over K_2CO_3. The solvent was evaporated to give a brown oil, which was distilled *in vacuo*, bp 120—125° (1—2 mmHg). Yield 28.2 g (2-methyl-4-acetoxymethyldecahydroisoquinoline).

A mixture of the foregoing product (28.2 g) and KOH solution (KOH, 15 g in MeOH (250 ml) and H_2O (20 ml)) was refluxed for 3 hr. The solvent was evaporated under reduced pressure to leave a viscous oil, which was dissolved in water and extracted with ether. The extract was dried (K_2CO_3) and concentrated. The residual oil was purified by distillation to give VA (20.5 g) as colorless oil (Table II). IR (Fig. 10,13). Gas chromat. SE-30 (Column) temp. 190° t_R; VA 7.2; VB, 6.0; VC, 5.4; VD, 6.4.

2-Methyl-4-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (XVIII)——To a suspension of $LiAlH_4$ (14 g) in dehyd. T.H.F. (200 ml) was added dropwise with stirring a solution of isoquinoline (XVII) (50 g) dissolved in dehyd. T.H.F. (200 ml) under ice-cooling. The mixture was treated as described above, giving colorless viscous oil, bp 130—135° (1 mmHg); yield 24 g or 60%; formed colorless prisms from benzene-hexane, mp 86°. IR $\nu_{max}^{CHCl_3}$: 3440 (OH, broad) cm^{-1}. *Anal.* Calcd. for $C_{11}H_{15}ON$; C, 74.54; H, 8.53; N, 7.90. Found: C, 74.43; H, 8.29; N, 8.10.

2-Methyl-4-benzoyloxymethyldecahydroisoquinoline (VI)——A mixture of V (1.0 g), pyridine (5 ml) and benzoyl chloride (1.0 g) was allowed to stand at room temperature for 24 hr. After removal of pyridine under reduced pressure, water was added to the residue. The resulting red aqueous solution was made alkaline with K_2CO_3, and extracted with benzene. After removal of benzene, the residue was distilled *in vacuo* (Table III). IR (Fig. 14—17).

Table III.

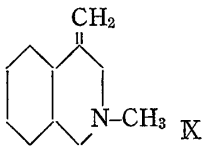


VI

No.	bp (°C/mmHg)	Yield (%)	mp (from EtOH) (°C)	Analysis (hydrochloride) $C_{18}H_{25}O_2N \cdot HCl$ Calcd. C	H	N	Cl	Found C	H	N	Cl
VIA	180—182/2	98	201—202	66.77	8.03	4.32	10.97	66.56	8.12	4.35	11.28
VIB	174—182/2	98	160					66.15	7.79	4.74	11.09
VIC	182—184/2	94	194—195					67.02	7.94	4.42	10.99
VID	179—181/2	96	228—229 (decomp.)					66.62	7.86	4.56	11.58

2-Methyl-4-vinylidenedecahydroisoquinoline (IX)——A solution of V (5 g) in aq. HBr (48%, 60 ml) was refluxed for 3 hr. After cooling, excess HBr was removed under reduced pressure on a steam bath and the residue was poured into ice-water (10 g), into which was the added aq. $(CH_3)_3N$ (30%, 10 g) and the mixture was allowed to stand overnight at room temperature. The reaction mixture was shaken with Ag_2O (prepared from 10 g of $AgNO_3$) and the inorganic salt was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by distillation *in vacuo* (Table IV). IR (Fig. 18—21).

Table IV.

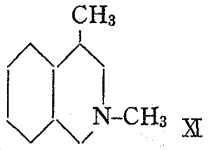


IX

No.	bp (°C/mmHg)	Yield (%)	Picrate mp (from EtOH) (°C)	Analysis (picrate: %) $C_{17}H_{22}O_7N_4$ Calcd. C	H	N	Found C	H	N
IXA	115/3	22.2	145—146	51.77	5.62	14.21	51.67	5.22	14.14
IXB	112/3	24.0	148—149				51.52	5.21	14.39
IXC	115—117/3	19.4	148—149				51.82	5.46	14.01
IXD	114/3	21.0	145—146				51.59	5.61	14.46

2,4-Dimethyldecahydroisoquinoline (XI)——To a solution of VA (0.2 g) in pyridine (2 ml) cooled in ice, tosyl chloride (0.2 g) in pyridine (1.5 ml) was added slowly. After allowing to stand overnight, tosyl chloride (1.0 g) in pyridine (1.5 ml) was added again to this mixture and left standing for 48 hr at room temperature. After removal of pyridine under reduced pressure at 45° or lower, the residue was dissolved in 10% K_2CO_3 and extracted with ether. After drying over K_2CO_3, ether was removed *in vacuo*. The residue was obtained as a viscous oil. IR ν_{max}^{oil}: 1180, 960 (S=O). To a solution of $LiAlH_4$ (0.2 g) in dehyd. ether (30 ml), while cooling with ice, a solution of the residue in dehyd. ether (30 ml) was added dropwise slowly. After standing overnight, hydr. ether and then water were added to decompose the excess of $LiAlH_4$. After filtration, the ether solution was dried, ether was evaporated and the residue was distilled *in vacuo* (Table V).

Table V.



XI

No.	bp (°C/mmHg)	Yield (%)	Picrate (from EtOH) (°C)	Analysis (picrate) $C_{17}H_{24}O_7N_4$ Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIA	100/10	62	175	51.51	6.10	14.14	51.28	5.91	14.21
XIB	100/10	68	152—153				51.62	6.42	13.96
XIC	100/10	58	178—179				51.37	6.32	14.01
XID	100/10	60	138—139				51.78	5.87	14.43

Ozonolysis of 2-Methyl-4-vinylidinedecahydroisoquinoline——Into a solution of the foregoing vinyliden IX (3 g) in aq. HCl (2.3%, 30 ml) was bubbled ozono gas (4—5%) at 10° for 10 hr. The solution was made alkaline with K_2CO_3, extracted with ether and dried over K_2CO_3. The solvent was evaporated to give a colorless viscous oil (X) (1.5 g), which darkened in air. IR $\nu_{max}^{Capil.}$: 1720 cm^{-1} (C=O).

Reduction of Vinylidene Compound——The compound IXA (0.5 g) was dissolved in a mixture of EtOH (15 ml) and HCl (10%, 0.2 ml) and was reduced over PtO_2 (0.1 g) for 15 min (1 mole hydrogen was absorbed). The catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was purified by ditillation under reduced pressure, bp 100° (10 mmHg); yield (0.5 g).

The picatare was crystallized from EtOH as yellow needles, mp 175° and found to be identical with XIA through, mixed mp and IR spectrum.

By the procedure described above, XIB (picrate mp 152—153°, from EtOH) and XIC (picrate; mp 179—180°, from EtOH) were obtained from IXB.

Ethyl *o*-Cyanomethylbenzoate (XV)——A solution of *o*-cyanomethylbenzoic acid (XIV) (24.5 g) in aq. NH_3 (2.6%, 100 g) was added to aq. $AgNO_3$ (26%, 100 g). The separated colorless crystals were collected and washed with EtOH and ether. To a stirred suspension of the crystals in abs. EtOH (100 ml) was added at 20—25° a solution of EtI (20 g) in abs. EtOH (80 ml). The mixture was refluxed for 12 hr. After cooling, the inorganic salt was filtered off. The solvent was removed leaving an orange oil which was distilled to give XII (17 g) as colorless oil, bp 130—135° (2 mmHg). IR $\nu_{max}^{Capil.}$: 2290 (CN), 1720 (ester C=O).

Ethyl *o*-Ethoxycarbonylphenylcyanoacetate (XVI)——To a stirred suspension of NaH (51.2%, 5 g) in dehyd. ether (200 ml) was added dropwise a mixture of cyano ester XV (20 g) and diethylcarbonate (20 g). The mixture was stirred for 1 hr at room temperature and then refluxed for 5 hr. After cooling, the sodium salt was dissolved in H_2O and acidified with AcOH. The separated oil was taken up in benzene and dried over Na_2SO_4. The solvent to give XVI (26 g or 95%) as a slightly yellow oil, bp 170° (2 mmHg). IR $\nu_{max}^{Capil.}$: 2300 (CN), 1750, 1720 (doublet) (ester C=O).

Ethyl 2-Ethoxycarbonyl-5-methoxyphenylcyanoacetate (XXII)——To a stirred suspension of NaH (51.2%, 5 g) in dehyd. ether (200 ml) was added dropwise a mixture of cyano ester XXI (11.5 g) and diethylcarbonate (10 g). The mixture was treated as above, giving colorless prisms, mp 84—85° (from hexane): yield, 15 g or 98%. IR $\nu_{max}^{CCl_4}$: 2300 (CN), 1750, 1710 (ester C=O). *Anal.* Calcd. for $C_{15}H_{17}O_5N$; C, 61.85; H, 5.88; N, 4.81. Found: C, 61.87; H, 5.75; N, 5.10.

2,4-Diemethyl-1,2,3,4-tetrahydroisoquinoline (XIX)——A mixture of XVIII (2 g) and aq. HBr (48%, 30 ml) was heated at 130° for 6 hr. After cooling, the mixture was diluted with water and the solution was concentrated to give a red viscous oil. The residue was dissolved in EtOH, and AcONa (4 g) was added. The mixture was shaken with H_2 at room temperature and atmospheric pressure in the presence of Pd–C (10%, 0.2 g). About 300 ml of H_2 was absorbed in 30 min and then absorption stopped. The catalyst and

the inorganic salt were filtered off and the solvent was removed *in vacuo*, leaving a colorless viscous oil. The residue was dissolved in water, made alkaline with K_2CO_3 and extracted with ether. The extract was dried over K_2CO_3, the solvent was removed and the residual oil was purified by distillation to give XIX (1.5 g) as colorless oil, bp 103° (10 mmHg). *Anal.* Calcd. for $C_{11}H_{15}N$; C, 81.93; H, 9.38; N, 8.67. Found: C, 82.08; H, 9.56; N, 8.26.

Ethyl *o*-Cyanomethyl-*p*-methoxybenzoate (XXI)——A mixture of hydroxyimino-5-methoxyindanone[9] (XX) (15 g), aq. NaOH (6.8%, 100 ml) and tosyl chloride (9.5 g) was warmed at 50—55° for 2 hr with stirring. After cooling, the separated brown solid was removed by filtration and the filtrate was acidified with 10% HCl to separate a solid, which was collected and washed with H_2O.

The solid was dissolved in aq. NH_3 (5%, 20 ml) and $AgNO_3$ (26%, 40 g) was added. The separated colorless solid was collected and washed with EtOH, ether and dried. To a stirred suspension of the solid in abs. EtOH (50 ml) was added at 20—25° a solution of EtI (10 g) in abs. EtOH (40 ml). The mixture was stirred for 2 hr. At room temperature, then refluxed for 2 hr. After cooling the inorganic salt was filtered off. The solvent was removed, leaving a yellow oil which was distilled to give XXI (11.5 g or 68%) as colorless oil, bp 170—174° (5 mmHg). IR $\nu_{max}^{CCl_4}$: 2290 (CN), 1715 (ester C=O).

Ethyl 1-Oxo-6-hydroxy-1,2,3,4-tetrahydro-4-isoquinolinecarboxylate (XXIV)——A mixture of lactam ester XXIII (1.0 g) and aq. HBr (48%, 10 ml) was heated at 130—140° for 3 hr. The reaction mixture was concentrated to give a brown oil. The residue was dissolved in ethanolic HCl (20%, 10 ml) and the solution was heated on water-bath for 3 hr. After removal of the solvents, the residue was dissolved in water, made alkaline with $NaHCO_3$ and extracted with AcOEt. The AcOEt layer was then extracted with 10% NaOH, and the aqueous layer was washed with benzene, filtered, acidified with 10% HCl and extracted with AcOEt. The extract was dired over Na_2SO_4. The solvent was evaporated to give a yellow viscous oil XXIV (0.5 g).

Reduction of an aromatic nucleus

i) Product from ethyl 1-oxo-decahydro-4-isoquinolinecarboxylate (IIIA)

a) Reduction of ethyl 1-oxo-1,2,3,4-tetrahydro-4-isoquinolinecarboxylate (XVII)

The foregoing tetrahydroisoquinoline (XVIII) (0.5 g) in AcOH (20 ml) was shaken with PtO_2 (0.5 g) in H_2 atmosphere at room temperature (20—25°) for about 20 min. After removal of the catalyst and the solvent, the residue was dissolved in water and made alkaline with $NaHCO_3$, and the crystals formed were separated. Recrystallization from EtOH gave ethyl 1-oxodecahydro-4-isoquinolinecarboxylate (IIIA), as colorless needles, mp 180—182°; yield 0.48 g or 98%.

b) Reduction of ethyl 1-oxo-6-hydroxy-1,2,3,4-tetrahydro-4-isoquinolinecarboxylate (XXIV)

The crude ethyl 1-oxo-6-hydroxy-1,2,3,4-tetrahydro-4-isoquinolinecarboxylate (XXIV) (0.5 g) in AcOH (20 ml) was hydrogenated as above, giving colorless crystals. Recrystallization from EtOH gave ethyl 1-oxodecahydro-4-isoquinolinecarboxylate (IIIA) as colorless needles, mp 180—182°; yield 82%.

ii) Preparation of 2-methyl-4-hydroxymethyldecahydroisoquinoline (VA). Reduction of 2-methyl-4-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (XVIII).

2-Methyl-4-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (XVIII) (0.5 g) in AcOH (50 ml) was shaken with PtO_2 (0.5 g) in H_2 atmosphere at room temperature (20—25°) for about 1 hr. After removal of the catalyst and the solvent, the residue was dissolved in water, made alkaline with K_2CO_3 and extracted with AcOEt. The extract was dried over K_2CO_3. After evaporation of the solvent, the residue was distilled *in vacuo* to give a colorless oil bp 140—141° (2 mmHg). This oil crystallized while standing at room temp. Recrystallization from benzene-hexane, gave 2-methyl-4-hydroxymethyl-decahydroisoquinoline (VA) as colorless needles, mp 89°; yield 0.4 g or 89%.

iii) Preparation of 2,4-dimethyldecahydroisoquinoline (XIA). Reduction of 2,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (XIX).

2,4-Dimethyl-1,2,3,4-tetrahydroisoquinoline (XIX) (0.5 g) in AcOH (50 ml) was shaken with PtO_2 (0.5 g) in H_2 atmosphere at room temperature (20—25°) for about 1 hr. The mixture was worked up as above, giving colorless oil bp 101° (10 mmHg); yield 0.42 g. The picrate was crystallized from EtOH as yellow needles, mp 175° and found to be identical with XIA.

Methyl 1-Ethoxycarbonyl-4-oxo-piperidinecarboxylate (XXVI)——To a solution of methyl 2-[N-ethoxycarbonyl-N-(2-methoxycarbonylethyl)amino]propionate (XXV) (5 g) in benzene (50 ml), NaH (51.2%, 1.0 g) was added slowly and the mixture was refluxed on a water bath until the evolution of H_2 had ceased (*ca.* 2 hr). After cooling, the reaction mixture was acidified with AcOH and extracted with benzene. The benzene extract was washed with $NaHCO_3$, H_2O and dried. The solvent was removed, and the residue was purified by distillation *in vacuo*, bp 145—150° (3 mmHg). Yield 4.2 g. IR $\nu_{max}^{Capil.}$: 1700 (N-COOEt, C=O), 1670, 1630 (keto ester C=O). *Anal.* Calcd. for $C_{10}H_{15}O_5N$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.64; H, 6.83; N, 6.02.

Dimethyl 1-[N-Ethoxycarbonyl-N-(2-methoxycarbonylethyl)aminomethyl]glutarate (XXVII)——A solution of sodium methoxide (from 4.5 g of sodium) in MeOH (120 ml) was slowly added with shaking to a mixture of XXVI (42 g), methyl β-chloropropionate (27 g), abs. MeOH (50 ml) and sodium iodide (0.5 g), with cooling

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in a bath of cold water. The reaction was allowed to proceed at room temperature for 2 hr, and after refluxing for additional 2 hr, a major portion of the MeOH was evaporated. The residue was poured into ice–water (1000 ml) and the precipitated oil was extracted with benzene. On distilation XXVII came at bp 187—190° (0.5 mmHg) as an almost colorless oil, which gave a negative ferric chloride reaction; (yield 49 g or 78%). IR $\nu_{max}^{Capil.}$: 1740 (ester C=O), 1700 (NCOOEt C=O). *Anal.* Calcd. for $C_{15}H_{25}O_8N$: C, 51.86; H, 7.25; N, 4.03. Found: C, 52.14; H, 7.56; N, 3.94.

Methyl 1-Ethoxycarbonyl-4-oxo-5-(2-methoxycarbonylethyl)-3-piperidinecarboxylate (XXVIII)——To a solution of the tetra ester XXVII (49 g) in benzene (800 ml) NaH (51.2%, 7 g) was added and the mixture was refluxed on a water bath until the evolution of H_2had ceased (*ca.* 4 hr). After cooling, the reaction mixture was acidified with AcOH and extracted with benzene. The benzene extract was washed with 5% $NaHCO_3$, H_2O and dried over Na_2SO_4. The solvent was removed and the residue was purified by distillation *in vacuo*, bp 205° (0.5 mmHg); yield 25 g or 57%. IR $\nu_{max}^{Capil.}$: 1740 (ester C=O), 1700 (NCOOEt), 1670, 1625 (keto ester C=O) cm^{-1}. *Anal.* Calcd. for $C_{14}H_{21}O_7N$; C, 53.32; H, 6.71; N, 4.44. Found: C, 53.61; H, 6.94; N, 4.12.

Ethyl 3-Methyloxycarbonyl-4-cyano(methoxycarbonyl)methylene-5-(2-methoxycarbonylethyl)-1-piperidinecarboxylate (XXIX)——A mixture of methyl cyanoacetate (15 g), the keto ester (XXVIII) (35 g), ammonium acetate (3 g), glacial AcOH (5 g) and benzene (40 ml) was heated under reflux until no more water was separated (70 hr). The cooled reaction mixture was washed several times with 10% NaOH and H_2O, and the benzene was removed *in vacuo*. The residue was purified by distillation *in vacuo*, to give a yellow viscous oil. bp 225—230° (0.5 mmHg) (ferric reaction, negative) (yield, 9 g or 21%). IR $\nu_{max}^{Capil.}$: 1740,1680 (ester C=O), 1700 (NCOOEt, C=O). *Anal.* Calcd. for $C_{18}H_{24}O_8N_2$: C, 54.54; H, 6.10; N, 7.07. Found: C, 54.91; H, 6.45; N, 6.83.

Ethyl 3-Methoxycarbonyl-4-di(methoxycarbonyl)methylene-5-(2-methoxycarbonylethyl)-1-piperidinecarboxylate (XXX)——A solution of the cyano ester (XXIX) (10 g) in HCl–MeOH (30%, 50 ml) was left standing for 48 hr at room temperature. After removal of HCl–MeOH under reduced pressure, the residue was dissolved in H_2O, made alkaline with $NaHCO_3$ and extracted with benzene. After drying over Na_2SO_4, the solvent was removed under reduced pressure and then the residue was distilled, bp 210—215° (0.1 mmHg); yield, 7.5 g or 69%. IR $\nu_{max}^{Capil.}$: 1740, 1710 (ester C=O), 1700 (NCOOEt, C=O).

Ethyl 3-Methoxycarbonyl-4-methoxycarbonylmethyl-5-(2-methoxycarbonylethyl)-1,2,5,6-tetrahydro-1-piperidinecarboxylate (XXXII)——The penta ester (XXX) (5 g) was refluxed with HCl (10%, 50 ml) for 4 hr. During the initial 30 min of heating, evolution of CO_2 was observed. The solution was evaporated under reduced pressure to give a brown viscous oil (XXXI). This oil was boiled with HCl–MeOH (30%, 20 ml) for 4 hr, and HCl–MeOH was distilled off under reduced pressure. The residue was mixed with water, made alkaline with $NaHCO_3$ and extracted with benzene. The extract was dired (Na_2SO_4) and concentrated to give a yellow viscous oil, which was distilled *in vacuo*, bp 200—204° (0.1 mmHg); yield, 2.4 g or 56%. IR $\nu_{max}^{Capil.}$: 1730, 1670 (ketoester, C=O), 1700 (NCOOEt, C=O). *Anal.* Calcd. for $C_{17}H_{25}O_8N$: C, 54.98; H, 6.79; N, 3.77. Found: C, 55.37; H, 7.10; N, 3.54.

2-Ethoxycarbonyl-6-hydroxydecahydro-4-isoquinolinecarboxylic Acid δ-Lactone (XXXV)——To a solution of the tetra ester (XXXII) (5 g) in benzene (50 ml) NaH (51.2%, 0.6 g) was added and the mixture was refluxed on a water bath until the evolution of H_2 had ceased (*ca.* 6 hr). After cooling, the reaction mixture was acidified with AcOH and extracted with benzene. The solvent was evaporated and the residue was boiled with HCl (10%, 20 ml) for 4 hr to effect ketonic fission and the mixture was extracted with AcOEt and washed with water. The AcOEt solution was extracted with dil. $NaHCO_3$ soln. The aqueous layer was washed with benzene and filtered with charcoal. The yellow filtrate was acidified with HCl (10%), and extracted with AcOEt. The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated to give a slightly yellow viscous oil. yield, 1.2 g (XXXIV). The crude product (XXXIV) (1.0 g) was hydrogenated over PtO_2 (0.1 g) in glac. AcOH (30 ml) at atmospheric pressure and room temperature. The hydrogenation was stopped after two moles of H_2 (30 min) had been absorbed. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in benzene, washed with 2% $NaHCO_3$ and water, and dried over Na_2SO_4. The solvent was evaporated to leave a pale yellow viscous oil, which was distilled *in vacuo*, bp 190—200° (1.0 mmHg); yield, 0.18 g or 20%. Crystallized as colorless prisms from benzene–hexane, mp 40—41°. IR $\nu_{max}^{CHCl_3}$: 1720 (-lactone, C=O), 1700 (NCOOEt, C=O). *Anal.* Calcd. for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.24; H, 7.16; N, 5.85. M.W. (Rast), Calcd. 253; Found: 248.

Preparation of 2-Methyl-4-hydroxymethyldecahydroisoquinoline (VA) from 2-Methoxycarbonyl-6-hydroxydecahydro-4-isoquinoline Carboxylic Acid δ-Lactone (XXXV)——To a stirred suspension of $LiAlH_4$ (0.2 g) in dioxane (20 ml) was added a solution of the foregoing lactone (XXXV) (0.5 g) in dioxane (50 ml). After stirring for 1 hr at 20—25°, and mixture was refluxed for 20 hr. The reaction mixture was decomposed by addition of H_2O (20 ml) and the inorganic salt was filtered off. The filtrate was concentrated to dryness to give a residue which was taken up in AcOEt. The AcOEt solution was extracted with dil. HCl. The aqueous layer was basified with K_2CO_3, extracted with AcOEt, and the extract was dried over K_2CO_3. Evaporation of the AcOEt gave an orange viscous oil which was chromatographed over Al_2O_3 with AcOEt. Elution with AcOEt gave the diol (XXXVI) (0.2 g) as colorless viscous oil. IR $\nu_{max}^{Capil.}$: 3320 (broad, OH).

A mixture of crude diol (XXXVI) (0.2 g) $CHCl_3$ (10 ml) and P_2O_5 (0.2 g) was refluxed for 3 hr. The solvent was evaporated, the residue was dissolved in water, made alkaline with K_2CO_3 and extracted with AcOEt. The extract was dried over K_2CO_3. The solvent was evaporated to give a colorless viscous oil, which was chromatographed on 10 g of Al_2O_3. Elution with *n*–hexane afforded 0.11 g (XXXVII) of colorless viscous oil. IR $\nu_{max}^{capil.}$: 3280 (broad, OH), 1640 (C=C).

The crude alcohol (XXXVII) (0.1 g) was hydrogenated in EtOH (5 ml) over PtO_2 (0.05 g) at room temperature. The hydrogenation was stopped after one mole of H_2 (2 hr) had been absorbed. The catalyst was removed by filtration, and the solvent was evaporated *in vacuo*, leaving a slightly yellow oil which was distilled to give VA (0.05 g or 14%) as a colorless oil, bp 139—140° (1.0 mmHg); Crystallized as colorless prisms from *n*–hexane, mp 88—89°.

The compound thus obtained was shown to be identical through mixed mp and IR ($CHCl_3$) spectra with the sample prepared from the compound IIIA.

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