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127. Sadao Ohki and Yoshiya Noike : Synthesis of Quinolizine Derivatives. V.[1] Studies on Diastereoisomer of Ethyl 3-Quinolizidinecarboxylate.

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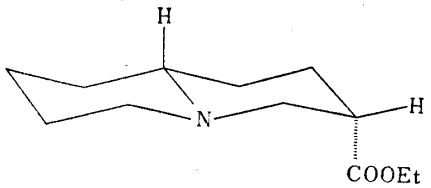
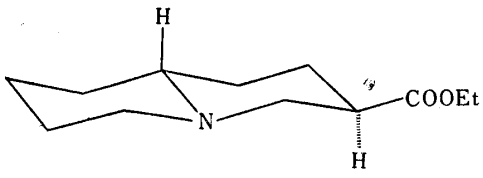
Attempted preparation of 3-aminoquinolizidine, starting with ethyl 3-quinolizidinecarboxylate (I) and via Curtius degradation of its hydrazide, afforded two kinds of hydrazide, one as an oil and the other in crystalline state, and a difference was found in the behavior of these two diastereoisomers to the Curtius degradation. It seemed of interest that such a difference should exist in simple quinolizidine derivatives owing to difference in steric configuration and studies were made to determine first the steric configuration of ethyl 3-quinolizidinecarboxylate (I). Quinolizidine ring may be considered to be present in *cis* and *trans* types corresponding to *cis* and *trans* types of decalin. As will be described later, the infrared spectra of (Ia) and (Ib) indicated absorption at 2750~2800 cm^{-1} for *trans*-quinolizidine as proposed by Bohlmann[2] and it was found that both could be considered as having *trans* type (Fig. 1). Therefore, the stereoisomer of (I) obtained in the present series of experiment can be limited to the two kinds of racemic compound, (A) and (B).



(A)



(B)

Boekelheide and others[3] synthesized (I) by the reduction of ethyl 2-cyano-4-(2-pyridyl)butyrate and they obtained two kinds of its picrate, one of m.p. 158~159° and the other of m.p. 146°. These seemed to be the respective picrate of diastereoisomers and, therefore, attempt was made to separate the stereoisomers of the picrate of (I) obtained in the present series of experiment. The picrate was prepared from the ethanolic solution of (I) and the picrate comparatively sparingly soluble in ethanol was obtained as yellow plates, m.p. 160~161°. The filtrate obtained after removal of this picrate afforded a comparatively easily solubly picrate as yellow plates, m.p. 144~146°. The formation ratio of these two kinds of picrate was 4:1. It is rather difficult to separate a fair quantity of these picrates and it is necessary to effect fractional crystallization by using a large amount of solvent which would not give a mixture of two picrates and to collect a small amount of the one of m.p. 160~161° at a time.

Treatment of the two kinds of picrate here obtained afforded the free bases, (Ia) and (Ib). In order to see which of these is more stable, basic isomerization[4] was carried out. In the case of (I) containing (Ia) and (Ib) in 4:1 ratio, this ratio changed to 3:7, while in the case of pure (Ia), 50% of it isomerized to (Ib). This fact suggested that the ethoxycarbonyl group in (Ia) takes the axial form (A-type) while that in (Ib) takes the equatorial (B) type.

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1) Paper presented at the Kanto Local Meeting of the Pharmaceutical Society of Japan, September, 1958. Part IV : This Bulletin, **1**, 391(1953).
2) F. Bohlmann : Angew. Chem., **69**, 645(1957); Chem. Ber., **91**, 2157(1958).
3) V. Boekelheide, *et al.* : J. Am. Chem. Soc., **75**, 3243(1953).
4) C. Schöpf, *et al.* : Ann., **465**, 97(1928).

Attempt was then made to reduce (Ia) and (Ib) with lithium aluminum hydride to derive them respectively to 3-lupinine (IIa), m.p. 59°, and 3-*epi*-lupinine (IIb), m.p. 30°, whose steric configuration is approximately known.

(IIa) and (IIb) have been synthesized by many workers[5] because of interest that these compounds are structural isomers of natural lupinine and *epi*-lupinine. Determination of configuration in these isomers has been made through physical means such as the measurement of infrared spectrum[5a] and dipole moment.[6]

Reduction of (Ia) and (Ib) with lithium aluminum hydride in ether afforded (IIa), m.p. 59°, and (IIb), $b.p_{0.2}$ 102°, which remained a liquid and was difficult to crystallize. (IIa) and (IIb) were identified through their picrate. The infrared spectrum of (IIa) indicated

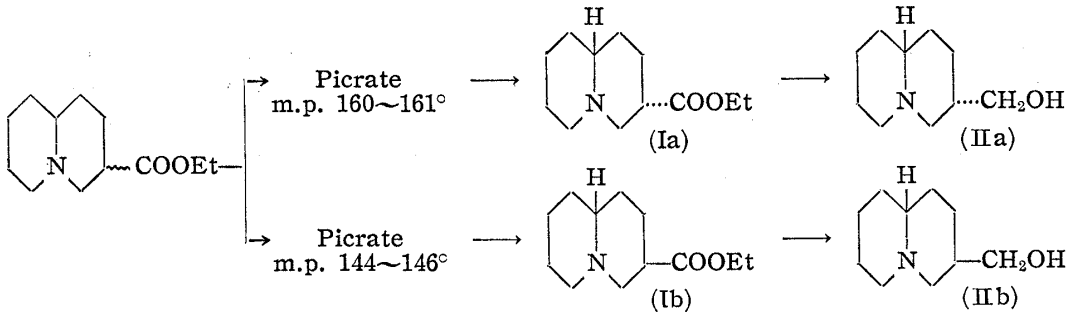


Chart 1.

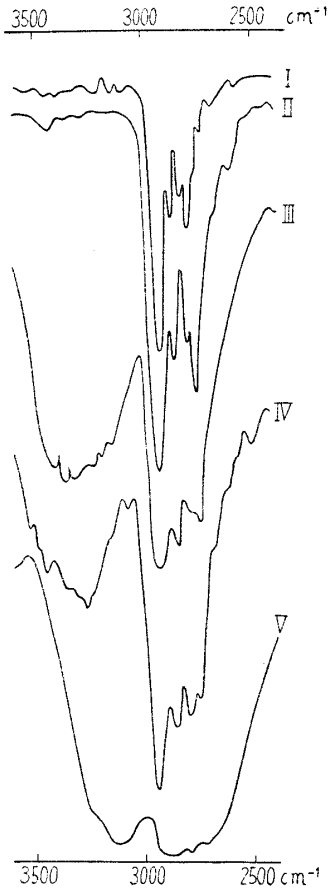


Fig. 1.
Infrared Absorption Spectra

I: (Ib)
II: (Ia)
III: (IIb)
IV: (IIa)(10% CCl_4 Soln.)
V: (IIa)(Nujol mull)

5) (a) K. Winterfeld, C. Heinen: Ann., **573**, 85(1951); **578**, 171(1952); J. Ratuský, F. Šorm: Chem. Listy, **47**, 1491(1953); (b) S. Ohki, K. Yamakawa: This Bulletin, **1**, 260(1953).

6) J. Ratuský, F. Šorm: Collection Czech. Chem. Communs., **20**, 798(1955).

the presence of a very strong hydrogen bonding and this fact suggested that the $-CH_2OH$ group in (IIa) takes the axial form, forming intramolecular hydrogen bond with the ring nitrogen. This has further confirmed the fact that the ethoxycarbonyl group in (Ia) would be in axial form while it would take the equatorial form in (Ib).

The structural configuration of (IIa) and (IIb) was further confirmed by chemical means other than by the existing physical methods.

In the determination of steric configuration of lupinine, Galinovsky[7] prepared a tosyl ester of lupinine by application of tosyl chloride, heating the ester to form intramolecular quaternary salt of a four-membered ring, and confirmed the axial form of the hydroxymethyl group in lupinine.

This method was applied in the case of (IIa) and (IIb) to examine their behavior. Tosylation of (IIa) in pyridine with tosyl chloride afforded (IIIa), m.p. 83°, which was labile to heat and changed into an extremely hygroscopic syrupy substance, insoluble in non-polar solvents, on being heated. This must indicate, as in the case of lupinine, the facile formation of an intramolecular quaternary salt due to the close proximity of tosyloxymethyl group with lone-pair electrons of ring nitrogen. This syrupy substance formed a picrate of m.p. 205°(decomp.) and its analytical values agree with those for (IV : $X=C_6H_2O_7N_3$).

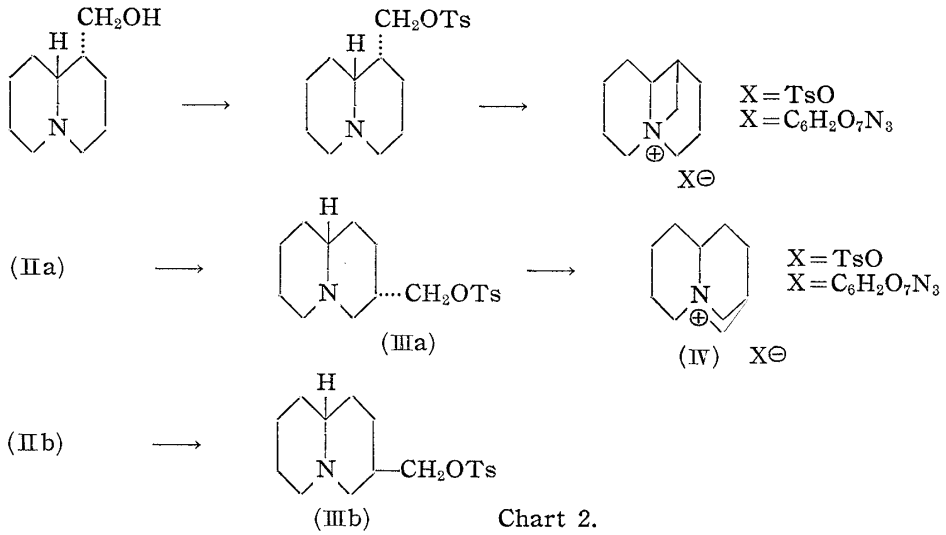


Chart 2.

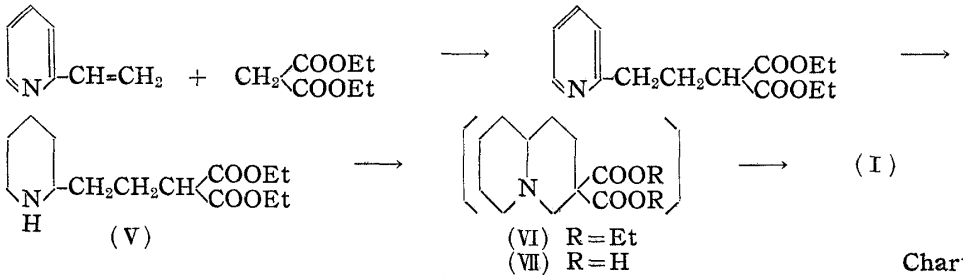
There is also a possibility for the formation of an eight-membered ring by intermolecular condensation of (IIIa) but Galinovsky and others stated that only intramolecular cyclization would occur, citing the example of the formation of a nitrogen-containing four-membered ring reported by Marvel and others.[8] In the case of (IIIa), a similar intramolecular cyclization seems to have taken place.

The same tosylation of (IIb) afforded (IIIb), m.p. 73°, which was stable to heat and did not undergo intramolecular cyclization, affording a fraction of b.$p_{0.08}$ 185~190°(bath temp.) by distillation.

The foregoing facts proved that the hydroxymethyl group in (IIa) takes the axial form, that in (IIb), the equatorial, and, consequently, the ethoxycarbonyl group in (Ia) would be in axial (A) form and that in (Ib) would be in equatorial (B) form.

Synthesis of (I) was carried out by the route shown in Chart 3.[9]

7) F. Galinovsky, H. Nesvadba : Monatsh., **85**, 1300(1954).
8) C. F. Gibbs, C. S. Marvel : J. Am. Chem. Soc., **56**, 725(1934).
9) Paper presented at the Local Meeting of the Pharmaceutical Society of Japan, November, 1955.



(V) (VI) R=Et (VII) R=H

Chart 3.

The Mannich reaction of diethyl 2-(2-piperidyl)ethylmalonate (V) in acetic or hydrochloric acidity, followed by saponification, decarboxylation, and esterification afforded (I) in 70% yield. It was later found that Šorm and his school had also synthesized this compound (I) by the same route.[6] They had carried out the Mannich reaction in pyridine and obtained (VI) in 85% yield, whose saponification with alkali, followed by decarboxylation and esterification had given (I) in 58% yield. From the present series of experiment, it was observed that the decarboxylation of (VII) from (VI) resulted in the stereospecific retension of the axial carboxyl group. This is probably analogous to the larger formation of axial carboxyl in decarboxylation of 4-phenyl-1,1-cyclohexanedicarboxylic acid reported by Zimmerman and others.[10]

The authors express their deep gratitude to Prof. S. Sugasawa for his unfailing guidance and encouragement throughout the course of this work. They are indebted to Mr. Keisuke Furuya for technical help, to Messrs. G. Chihara, K. Tanigawa, and T. Ushioda for infrared spectral measurements, and to the members of the Analysis Room of the Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd., of Women's Department, Tokyo College of Pharmacy, and of this Faculty, for elementary analytical data.

Experimental

Ethyl 3-Quinolizidinecarboxylate (I)—i) To 10.2 g. of ethyl 2-(2-piperidyl)ethylmalonate (V) 3.3 cc. of 35% HCHO solution was added, the mixture was adjusted to pH 5.5~6.0 with AcOH, and allowed to stand at room temperature for 1 week. After concentration to a small volume under reduced pressure, the residue was heated at 120~130° with 20% HCl to effect saponification and decarboxylation. The evolution of CO_2 almost stopped after heating for 5 hr. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in dehyd. EtOH. The EtOH solution was saturated with HCl and warmed on a water bath. After removal of EtOH under reduced pressure, the residue was dissolved in a small quantity of water and shaken with Et_2O to remove the substance insoluble in HCl. This solution was basified, salted out with K_2CO_3, and extracted with Et_2O, which was dried over Na_2SO_4 and evaporated. The residue was distilled *in vacuo* and colorless oil, $b.p_{0.2}$ 93~96°, was obtained. Yield, 5.6 g. or 70.7%.

ii) To a solution of 7.3 g. of the hydrochloride of (V) in water 2.6 cc. of 35% HCHO solution was added and the mixture was allowed to stand for 4 days. This solution was treated as in the foregoing case. Yield of (I), 2.2 g. or 44%.

iii) To a solution of 10.7 g. of the hydrochloride of (V) in 50 cc. of EtOH, 2.1 g. of paraformaldehyde was added and the mixture was refluxed gently on a water bath for 15 hr. The solution was treated as in the foregoing. Yield of (I), 1.5 g. or 20.4%.

Separation of the Diastereoisomers of (I)—To 5 g. of (I) in EtOH (5 cc.) 6.5 g. of picric acid in EtOH was added. The picrate was obtained as 6.7 g. of yellow plates, m.p. 160~161°, after several recrystallization from a large quantity of EtOH. The EtOH mother liquor was concentrated and another picrate separated as 1.7 g. of yellow plates, m.p. 144~146°, after several recrystallizations from EtOH. *Anal.* Calcd. for $C_{12}H_{21}O_2N \cdot C_6H_3O_7N_3$: C, 49.09; H, 5.49; N, 12.72. Found (in the picrate of m.p. 160~161°): C, 49.44; H, 5.67; N, 12.96. Found (in the picrate of m.p. 144~146°): C, 49.06; H, 5.08; N, 12.82.

To a mixture of Et_2O and 5% HCl a solution of the foregoing picrate in acetone was added. After shaking, the aqueous layer was separated, basified, and salted out with K_2CO_3. The organic layer was extracted with Et_2O. After drying over Na_2SO_4, Et_2O was removed and the residue was distilled *in vacuo*. There were obtained colorless oil of $b.p_{0.5}$ 102~105° (Ia), derived from the picrate of m.p. 160~161°, and of $b.p_{0.5}$ 104~106° (Ib), derived from the picrate of m.p. 144~146°. From these

10) H. E. Zimmerman, H. J. Giallombardo: J. Am. Chem. Soc., 78, 6259(1956).

oils, (Ia) and (Ib), the picrates of m.p. 160~161° and m.p. 144~146° were prepared quantitatively.

Epimerization of (I)—i) EtOH solution of NaOEt was prepared from 3 mg. of metallic Na and 0.1 cc. of dehyd. EtOH, to which 200 mg. of (I) ((Ia) and (Ib) mixed in approx. 4:1 ratio) was added and the mixture was warmed at 60~65° for 1 hr. After cool, water was added and extracted with Et_2O. The Et_2O solution was dried, evaporated, and the residue was distilled *in vacuo*. Colorless oil, $b.p_{0.5}$ 103~106°; yield, 170 mg. This oil formed two kinds of picrate, 80 mg. of (Ia)-picrate and 200 mg. of (Ib)-picrate.

ii) Following the same method described above, the epimerization of (Ia) was carried out and, from 100 mg. of (Ia), there were obtained 70 mg. each of (Ia)-picrate and (Ib)-picrate.

3-Lupinine (IIa)—To a solution of 0.81 g. of $LiAlH_4$ in 30 cc. of dehyd. Et_2O, while chilled with ice, a solution of 3 g. of (Ia) in 50 cc. of dehyd. Et_2O was dropped in slowly. After allowing to stand over night, hydr. Et_2O and then water were added to decompose the excess of $LiAlH_4$. After filtration, Et_2O solution was dried over K_2CO_3 and Et_2O removed by which the residue solidified. This was recrystallized from petr. ether to (IIa) as colorless plates, m.p. 58~59°; yield, 1.8 g. or 75%. The picrate of (IIa) formed in Et_2O and was obtained by recrystallizaition from AcOEt as yellow prisms, m.p. 137~138°.*2 *Anal.* Calcd. for $C_{10}H_{19}ON \cdot C_6H_3O_7N_3$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.02; H, 5.77; N, 13.86.

3-*epi*-Lupinine (IIb)—To a solution of 0.27 g. of $LiAlH_4$ in dehyd. Et_2O a solution of (Ib) in dehyd. Et_2O was added and the mixture was treated as in the foregoing. There was obtained colorless viscous oil, $b.p_{1.0}$ 103~104°; yield, 0.6 g. or 75%. The picrate of (IIb) formed in Et_2O and was obtained by recrystallization from AcOEt as yellow prisms, m.p. 154~155°. *Anal.* Calcd. for $C_{10}H_{19}ON \cdot C_6H_3O_7N_3$: C, 48.24; H, 5.57; N, 14.07. Found : C, 48.11; H, 5.66; N, 14.04.

3-Quinolizidinylmethyl Tosylate (IIIa)—To a solution of 1 g. of (IIa) in 8 cc. of pyridine, chilled in ice, a solution of 1 g. of tosyl chloride in 6 cc. of pyridine was added slowly. After allowing to stand over night, a solution of 1 g. of tosyl chloride in 6 cc. of pyridine was added again to this mixture and left standing for 48 hr. at room temperature. After the removal of pyridine under reduced pressure at 45° or lower, the residue was dissolved in 10% Na_2CO_3 and extracted with Et_2O. After drying over KOH, Et_2O was removed under reduced pressure by which the residue solidified. This was crystallized from petr. ether as colorless needles, m.p. 82~83°; yield, 1.63 g. or 85.3%. The picrate of (IIIa) formed in Et_2O and was obtained by recrystallization from EtOH as yellow plates, m.p. 149~150°. *Anal.* Calcd. for $C_{17}H_{25}O_3NS \cdot C_6H_3O_7N_3$: C, 49.99; H, 5.11; N, 10.14. Found : C, 49.76; H, 5.33; N, 10.42.

3-*epi*-Quinolizidinylmethyl Tosylate (IIIb)—By the procedure described above, from 1 g. of (IIb) 1.65 g. of the objective (IIIb) was obtained as colorless plates, m.p. 72~73° (from petr. ether), $b.p_{0.08}$ 185~190°(bath temp.). The picrate of (IIIb) formed in Et_2O and was obtained by recrystallization from EtOH as yellow plates, m.p. 181~182°. *Anal.* Calcd. for $C_{17}H_{25}O_3NS \cdot C_6H_3O_7N_3$: C, 49.99; H, 5.11; N, 10.14. Found : C, 49.97; H, 5.10; N, 10.04.

3,5-Methanoquinolizidinium Salt (IV)—The heating of 0.6 g. of (IIIa) in a boiling water bath under reduced pressure (12 mm. Hg) for 4 hr. gave viscous oil (IV : X=TsO), which was washed several times with Et_2O. Yield. 0.5 g. This viscous oil was deliquescent and insoluble in nonpolar solvents.

The picrate (IV : $X=C_6H_2O_7N_3$), yellow prisms, m.p. 205°(decomp.), formed when equimolar amounts of (IV : X=TsO) and picric acid were mixed in EtOH. Yield, 0.3 g. (from 0.5 g. of (IV : X=TsO)). *Anal.* Calcd. for $C_{16}H_{20}O_7N_4$: C, 50.52; H, 5.30. Found : C, 50.10; H, 5.28.

Summary

Steric configuration of the two diastereoisomers of ethyl 3-quinolizidinecarboxylate (I) was examined and it was proved from following facts that (Ia) (picrate, m.p. 160~161°) has the A-type and (Ib) (picrate, m.p. 144~146°) has the B-type orientation. It was shown that (i) quinolizidine ring is in *trans* type; (ii) basic isomerization of (I) and (Ia) afforded a fair amount of (Ib); and that (iii) reduction of (Ia) and (Ib) with lithium aluminum hydride resulted in their derivation to 3-lupinine (IIa) and 3-*epi*-lupinine (IIb), respctively. The steric configuration of (IIa) and (IIb) had previously been approximately determined from measurement of their infrared spectra and dipole moment. It was confirmed through preparation of the tosylates of (IIa) and (IIb), and comparison of their chemical properties that (IIa) had an axial $-CH_2OH$ group and (IIb), the equatorial $-CH_2OH$.

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*2 The picrate of *dl*-3-lupinine was reported previously (This Bulletin, **1**, 260(1953)) as yellow plates, m.p. 126°, but this was found to have been a mixture of *epi* compounds and not a unity, and the data are herewith corrected.