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Synthesis of Quinolizine Derivatives. XX.[1] Synthesis and Stereochemistry of Perhydrobenzo[*c*]quinolizine[2]

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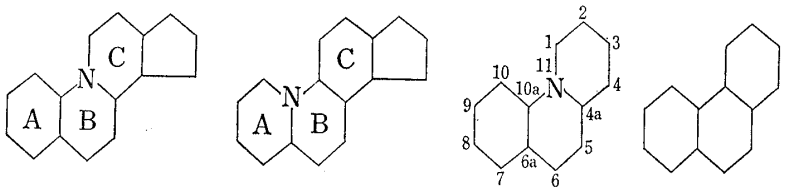
The four kinds of stereoisomers of perhydrobenzo[*c*]quinolizine were isolated as picrates of mp 203—205°, mp 182—184°, mp 171°, and mp 155°, whose stereostructures were elucidated as IIIa, IIIb, IIIg, and IIId (or IIIh), though the last one was not determined conclusively due to the minute quantity available.

In connection with the synthesis of 9- (I) and 10-azasteroids (II), synthesis of perhydrobenzo [*c*]quinolizine (III) and its stereochemistry were examined. III contains the same system as the A–B–C ring system of I and II so that elucidation of the stereochemistry of III would be of interest in reference to various methods for its synthesis.



I II III IV

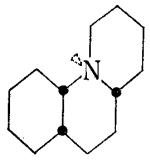
The perhydrophenanthrene (IV) corresponding to III forms the main skeleton of numerous steroids and terpenes and six of its stereoisomers have been examined in detail by Linstead and others.[4] In contrast, eight kinds of isomers (IIIa–h) will be possible for III due to the presence of nitrogen, as shown in Chart 1, if no consideration is given to the inversion of the bridgehead nitrogen.

(I) Formation of the Stereoisomers of III and Their Separation

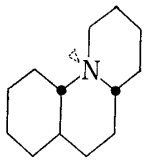
III had been synthesized by Clemo, *et al.*,[5] and by Jampolsky and Solodar.[6] The former worker obtained it as a picrate of mp 148° and the latter, picrate of mp 178—180°. This means that two kinds of stereoisomer have been recorded to date. The method used by Jampolsky and Solodar was the reductive cyclization of 2-[β-(2-pyridyl)ethyl]cyclohexanone (V) in acidity, and they had obtained as a by-product 2-[β-(2-piperidyl)ethyl]cyclohexanol (VI), mp 144—146°, and a minute amount of a substance of mp 83—88° (Chart 2). According to present series of experiments, cyclization reaction of VI, mp 144—145°, to III was difficult. This fact seems to suggest that the reductive cyclization of V to III passes,

1) Part XIX: K. Sugimoto, S. Ohki and N. Shibata, *Yakugaku Zasshi*, **88**, 900 (1968).
2) This work was presented at the 87th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1967.
3) Location: *Women's Division, Ueno Sakuragi 1-chome, Daito-ku, Tokyo.*
4) R.P. Linstead, *et al.*, *J. Am. Chem. Soc.*, **64**, 1985 (1942); *J. Chem. Soc.*, **1950**, 1425, 1428; E.L.Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, 1962, p. 282.
5) R. Clemo, J.G. Cook and R. Raper, *J. Chem. Soc.*, **1938**, 1318.
6) M. Jampolsky and W.E. Solodar, *J. Am. Chem. Soc.*, **75**, 5427 (1953).

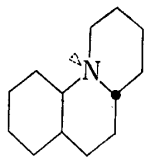
trans–Quinolizidine series



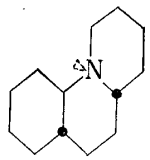
IIIa *cis–anti–trans*



IIIb *trans–anti–trans*

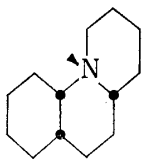


IIIc *cis–syn–trans*

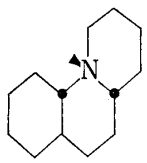


IIId *trans–syn–trans*

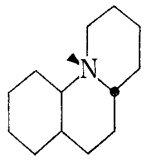
cis–Quinolizidine series



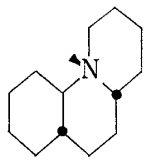
IIIe *cis–syn–cis*



IIIf *trans–syn–cis*



IIIg *cis–anti–cis*



IIIh *trans–anti–cis*

Chart 1

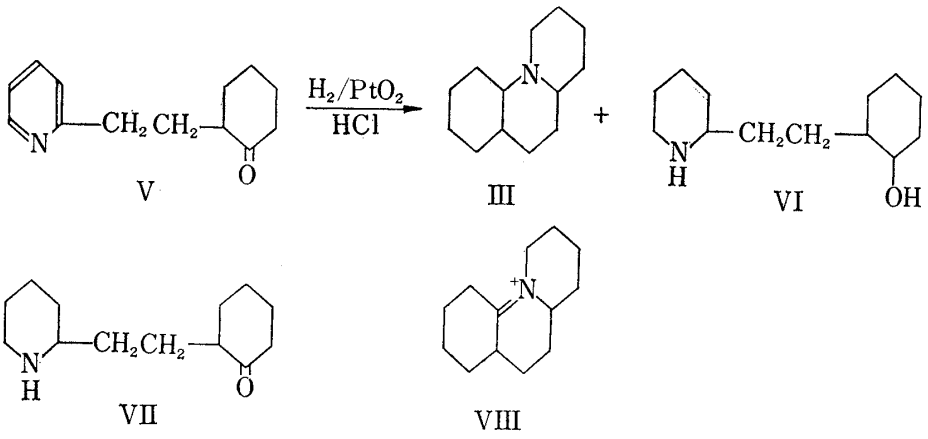


Chart 2

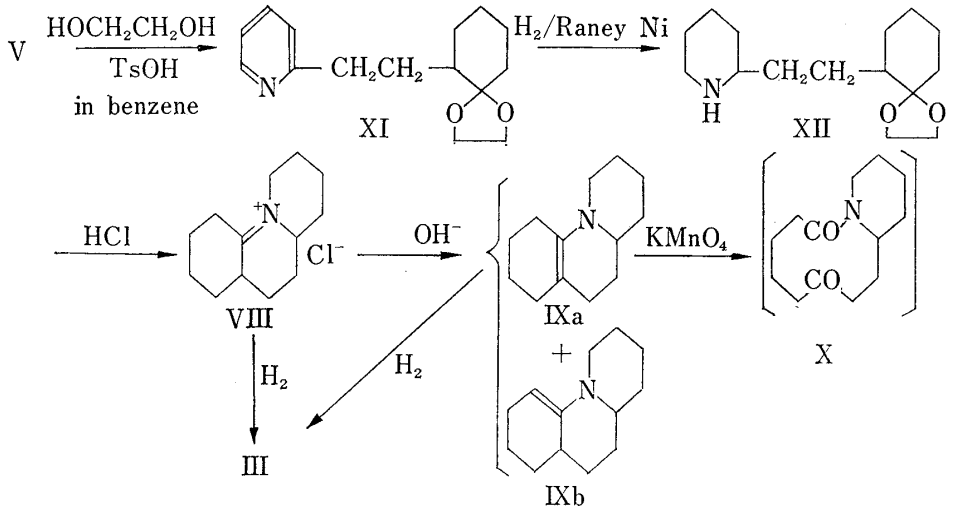


Chart 3

not VI, but through piperidylethylcyclohexanone (VII) and 10a,11-dehydroquinolizidinium salt (VIII). Accordingly, VIII was synthesized by the route shown in Chart 3 and catalytic reduction and reduction with sodium borohydride were carried out on VIII to compare with Jampolsky's result. At the same time, synthesis of III through catalytic reduction of the cyclic enamine (IX), derived from VIII, was also examined. IX is considered to be a mixture of IXa and IXb. Its oxidation with potassium permanganate gives an alkali-insoluble substance as the main product which is assumed to be X by the presence of absorptions for a lactam and a ketone in its infrared spectrum. Consequently, IXa was thought to be predominant in this mixture.

During the course of the present experiment, Danishefsky and others[7] reported the synthesis of VIII and IX by approximately the same method, and stated that the ratio of IXa to IXb was about 4:1 from the measurement of nuclear magnetic resonance (NMR) spectrum. The same result as theirs was obtained on following this method.

The reduction products (III) of VIII and IXa,b are given in Table I and II. Four kinds of picrate of mp 203—205°, 182—184°, 171°, and 155°, were obtained as the finally purified product. These were obtained by separation of the free base of III by column chromatography and purification of each isomer as a picrate. Separation of the free base by gas chromatography is shown in Fig. 1. Besides the foregoing four picrates, a picrate of mp 164° and of mp 176—178°, both showing comparatively sharp melting point during the purifi-

Table I. Perhydrobenzo[*c*]quinolizine

Picrate of III (mp, °C)	Analysis (%) C	H	N	IR (cm^{-1})	Bohlmann band
203—205	53.86	6.36	13.32	2778, 2755	+
182—184	54.14	6.58	13.32	2770, 2732	+
171	54.27	6.50	13.27		−
155	—	—	—[a]		
(Cacld.)	54.02	6.20	13.26		(±?)

a) Not analyzed.

Table II. Formation Ratio[a] of III Isomers

Method of reduction	Picrate of III (mp, °C) 203—205	182—184	171	155
VIII $\xrightarrow[\text{HCl acidity}]{H_2/PtO_2}$ III	10	8	1	0
VIII $\xrightarrow[\text{HCl acidity}]{NaBH_4}$ III	11	13.5	2.1	1
IXa,b $\xrightarrow[\text{or } H_2/PtO_2]{H_2/Rh-C}$ III	24	13	2	1
V $\xrightarrow[\text{AcOH acidity (Jampolsky's method)}]{H_2/PtO_2}$ III	3	8	1	0

a) Measured by gas liquid chromatography of the free base.

7) *a*) S. Danishefsky and M. Feldmann, *Tetrahedron Letters*, **1964**, 2249; *b*) *Idem*, *ibid.*, **1965**, 1131.

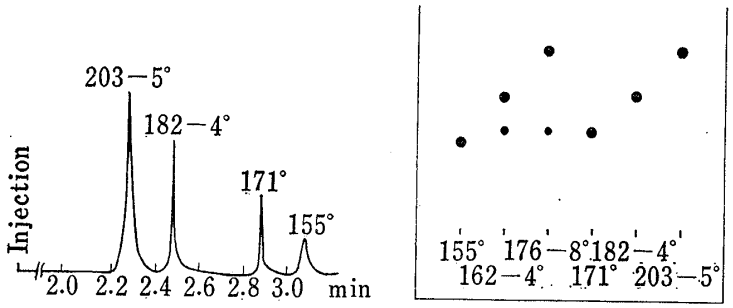


Fig. 1

Gas–Liquid Chromatogram of III

column temp. 160°
detector temp. 250°
N_2 flow rate 45 ml/min
H_2 flow rate 45 ml/min
1.0% SE-30 Chromasorb W

Thin–Layer Chromatogram (on Silica Gel) of III

solvent system
benzene–ethanol–diethylamine
(18:1:1, v/v)

(Each isomer of III is indicated as melting point of picrate.)

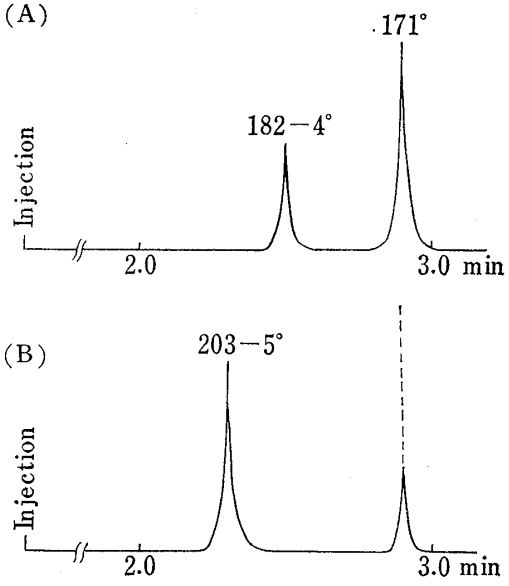


Fig. 2. Gas–Liquid Chromatogram of Free Base forming a Picrate of mp 164° (A) and of mp 176–178° (B)

cation process and assumed as a unit, were also obtained. However, these picrates were found to be a mixture, respectively, of mp 182—184° and mp 171°, and of mp 171°, and mp 203—205°, from the result of gas liquid chromatography and thin-layer chromatography of the free base (Fig. 1,2). The picrate of mp 178—180° obtained by Jampolsky must be the picrate mixture of mp 176—178° or of mp 182—184° obtained in the present series of work. The follow-up examination of Jampolsky's method gave the results shown in Table II, affording three kinds of a picrate. The substance recorded by Clemo and others is also considered to be a mixture.[8]

The picrate of mp 155° was obtained only in a minute amount and its authenticity could not be confirmed through elemental analysis, *etc.* Since the infrared spectrum of its free base was similar to those of other three isomers, and since it was derived from the substance forming a picrate of mp 203—205° by oxidation and following reduction (Chart 6), it seems certain that the substance is one of the stereoisomers of III but its confirmation must await further experiment.

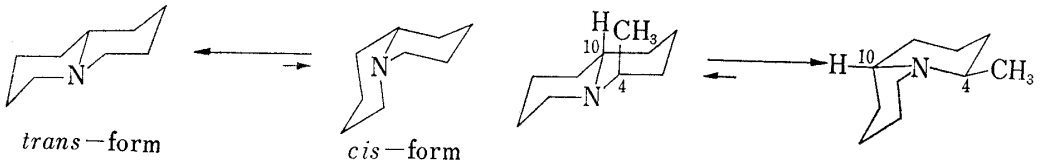
(II) Stereochemical Assignment of the Isomers of III

The free bases of III giving a picrate of mp 203—205° and of mp 182—184°, show the Bohlmann band[9] in their infrared (IR) spectra, while that forming a picrate of mp 171° does not (Table I). Based on these evidences, the former two are considered to have the *trans*- and the latter *cis*-quinolizidine ring. The quinolizidine ring undergoes easy interconversion between the *cis* and *trans* forms and, in general, the equilibrium tends toward a stable *trans* form.

According to Moynehan,[10] however, 4-ax.-methylquinolizidine (XIII) is markedly inclined to the *cis* form due to the 1,3-diaxial interaction of 4-CH_3 and 10-H.

8) Clemo and others obtained III by the Wolff–Kischner reduction of 1-oxoperhydro-5,6-benzo (*c*) quinolizine and its picrate melted at 148° (R. Clemo, J. G. Cook, and R. Raper, *J. Chem. Soc.*, **1938**, 1318). The Clemmensen reduction of the same compound gave a substance forming a picrate of mp 128—130° which was found not to be III but a structural isomer attended with extension and contraction of the ring.

9) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957).



XIII

Aaron[11] doubted whether the energy barrier between these *trans* and *cis* forms could be broken in this kind of interaction but, if Moynehan's view is taken into consideration and with reference to Johnson's rule regarding perhydrophenanthrenes[12] the eight kinds of isomer of III (IIIa–h) can be classified into the following four species of IIIa, IIIb, IIIg, and IIIh (or IIId) (Chart 4). It is still unknown which of IIId or IIIh is the more preferred conformation

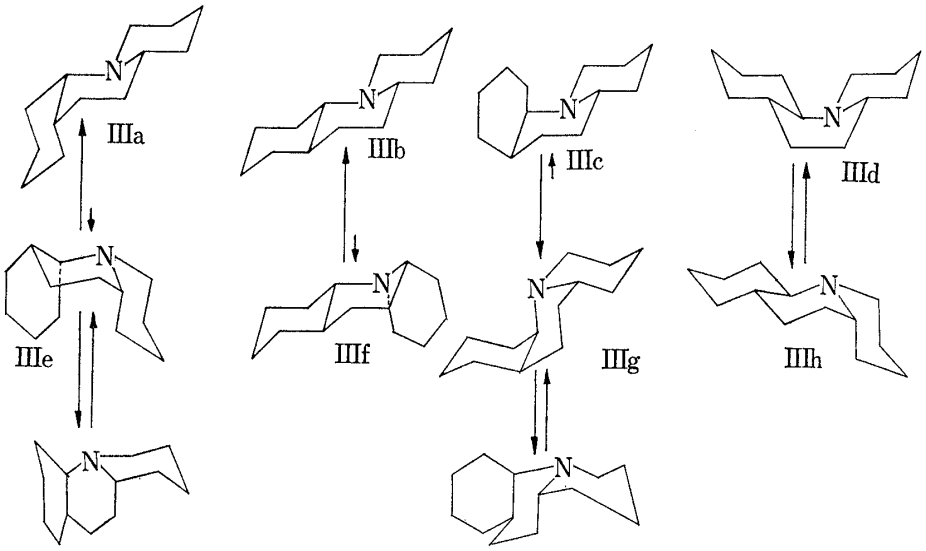


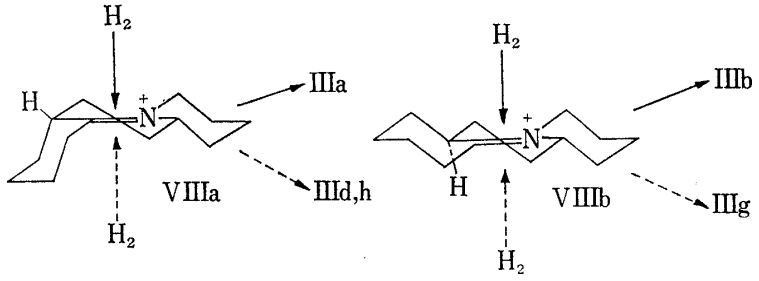
Chart 4

but since the boat form is generally unstable, IIIh seems to be the more likely. However, such conclusive decision cannot be made at present because there is still a possibility that the C–ring of sparteine may be in a boat form.[13]

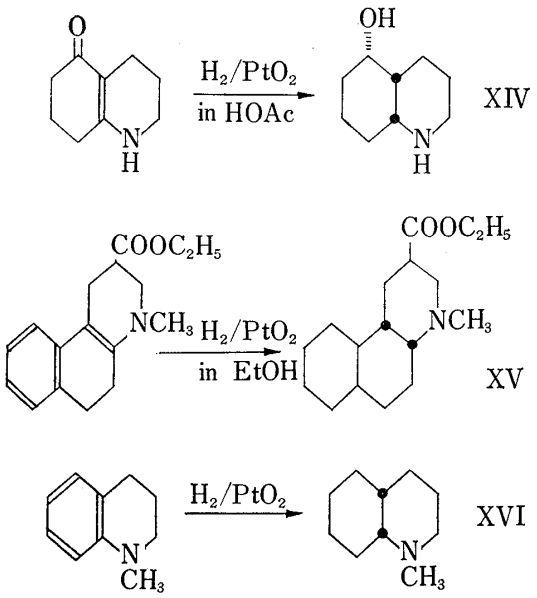
From the Bohlmann band, therefore, the bases forming the picrate of mp 203—205° and of mp 182—184° would probably correspond to IIIa or IIIb in which the *trans* form is a stable type, and that forming a picrate of mp 171° would correspond to IIIg in which the *cis* form would be stable. That these are not IIId or IIIh will be proved in the following section.

As shown in Table II, the following four kinds of isomer will be possible from VIII (possibly a mixture of VIIIa and VIIIb).

Four kinds of isomer will also be formed from IXa and



10) T.M. Moynehan, K. Shofield, and R.A.Y. Jones, *J. Chem. Soc.*, **1962**, 2637.
11) H.S. Aaron, *Chem. Ind.* (London), **1965**, 1338.
12) W.S. Johnson, *J. Am. Chem. Soc*, **75**, 1498 (1953)
13) F. Bohlmann, *et al.*, *Tetrahedron Letters*, **1965**, 2433, 2705.



IXb. In this case also, if IXb is not mixed in IX, formation of IIIa and IIIg alone might be expected from the *cis*–addition rule for catalytic reduction. It cannot be said that hydrogen always undergoes *cis* addition in the catalytic reduction of the cyclic carbon–carbon double bond[14] but in most cases, *cis* addition takes preference. For example, formation of *cis*–decahydroquinolines (XIV,[15] XV,[16] XVI[17]) may be cited.

Therefore, benzo(*c*)quinolizidine[18] (XXII) was synthesized from diethyl *β*–(2–quinolyl)–ethylmalonate[19] (XVII) and catalytic reduction of XXII was carried out.

Actually, two kinds of isomer giving a picrate of mp 203—205° and of mp 171° were

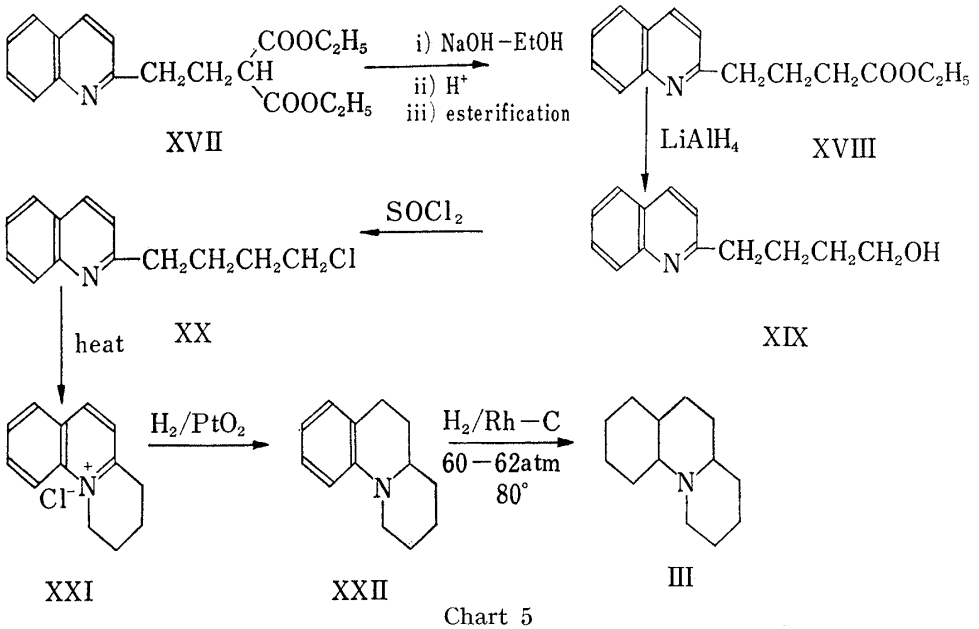


Chart 5

obtained, with the latter predominating. If there had been *cis* addition of hydrogen, the picrate, mp 203—205°, of the *trans* form would be IIIa and that of mp 171° of the *cis* form would be IIIg. The remaining stable *trans* form would then be IIIb which should correspond to the picrate of mp 182—184°.

In order to confirm the assignment of the three kinds of isomer of III, made on the basis of Bohlmann absorptions in the infrared spectra and of *cis* addition of hydrogen, the following experiments were carried out.

(a) Reduction of the Oxidation Product of III (picrate, mp 203—205°): In general, *trans*–quinolizidines are oxidized with mercuric acetate into dehydroquinolizidinium salt[20]

14) S.Siegel and B. Dmochovsky, *J. Am. Chem. Soc.*, **86**, 2192 (1964).
15) G.A. Grob and H.R. Kiefer, *Helv. Chim. Acta*, **48**, 799 (1965).
16) Z. Horii and T.Kurihara, *Chem. Pharm. Bull.* (Tokyo), **14**, 1227 (1966).
17) N. J. Leonard and L.A. Miller, *J. Am. Chem. Soc.*, **78**, 3463 (1956).
18) G. Jones and J. Wood, *Tetrahedron*, **21**, 2529 (1965).
19) V. Boekelheide and G. Marinett, *J. Am. Chem. Soc.*, **73**, 4015 (1951).
20) *cf.* N.J. Leonard, P.D. Tomas, and V.W. Gash, *J. Am. Chem. Soc.*, **77**, 1552 (1955).

but the *cis* compound is not oxidized. III (picrate, mp 203—205°) was easily oxidized by mercuric acetate and reduction of its oxidation product with sodium borohydride or catalytic reduction over platinum oxide gave three kinds of isomer giving picrates of mp 203—205°, 171°, and 155° (Fig. 3). If the picrate of mp 203—205° were to correspond to IIIa, formation of each of these isomers through the oxidation products (XXIII and XXIV), as shown in Chart 6, would be understood. It should especially be noted here that a substance giving a picrate of mp 182—184° was not obtained while that of mp 155° was detected. Formation of IIIb cannot be expected from the above

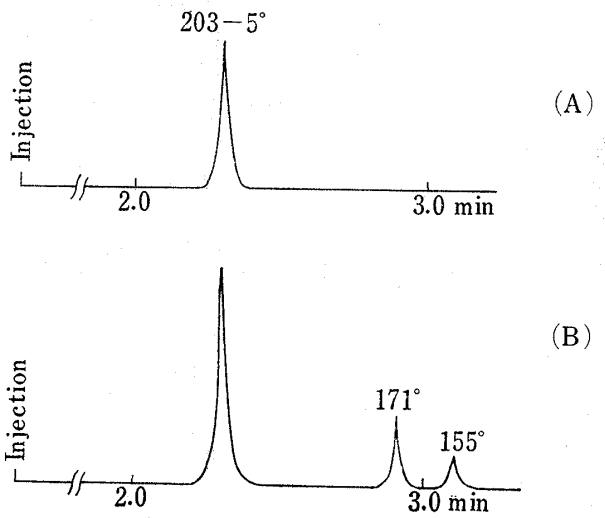


Fig. 3. Gas–Liquid Chromatogram of the Reduction Product (B) and the Starting Compound III (Picrate: mp 203—205°) (A)

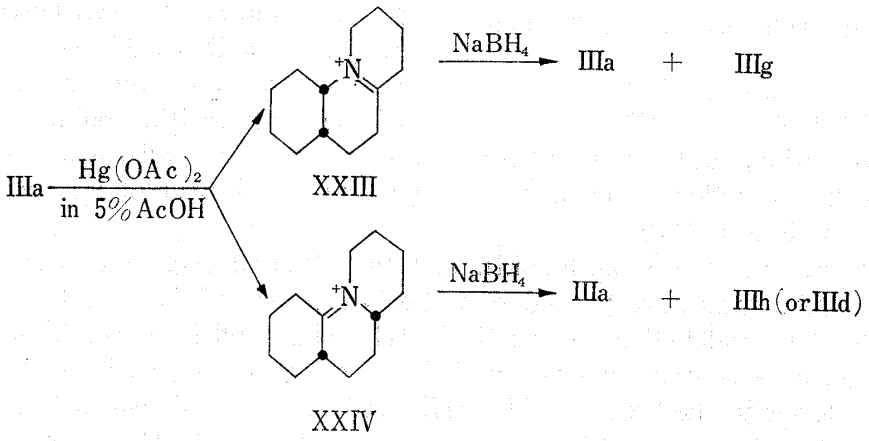
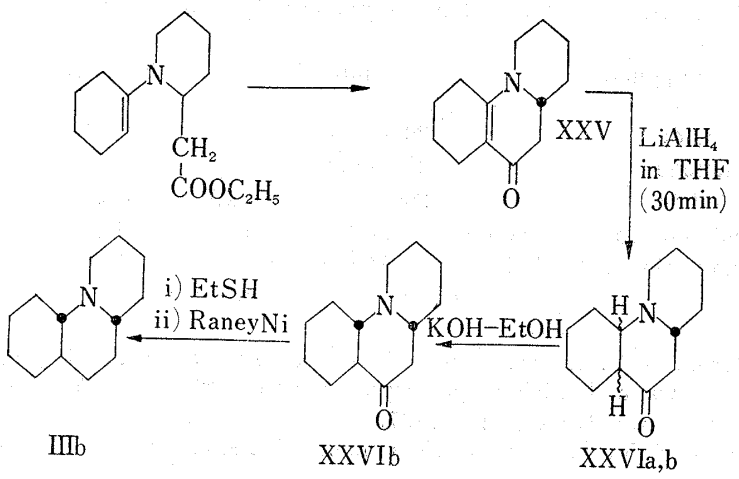


Chart 6

formulae but that of IIIh (or IIId) can. Consequently, the picrate of mp 155° is very likely to be that of IIIh (or IIId).

The isomer of III giving a picrate of mp 171° is not oxidized at all by treatment with mercuric acetate and should therefore be the *cis* form, corresponding to IIIg.



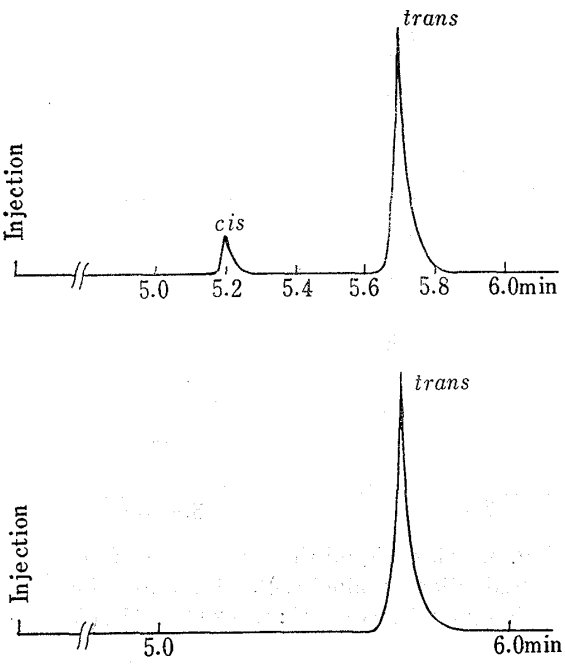


Fig. 4. Gas–Liquid Chromatogram of XXVIa,b and XXVIa

column temp. 160°; detector temp. 250°; N_2 flow rate 35 ml/min; H_2 flow rate 50 ml/min; SE-30 Chromosorb W

(b) Synthesis of IIIb: Conclusive evidence that IIIb, which was considered to be the most stable form, taking an all-chair, all-*trans* form, is the isomer of III forming a picrate of mp 182—184°, was obtained in the following way.

Horii and others reported that one of the reduction products (XXVI) of 6a,-10a-dehydro-6-oxoperhydrobenzo(*c*)quinolizine[21a] (XXV), the *cis*-decahydroquinoline (XXVIa), easily underwent isomerization to the *trans*-decahydroquinoline[21b] (XXVIb) due to the presence of a ketone group. The variation in the amount of this *cis* compound (XXVIa) was detected by gas chromatography (Fig. 4).

The ketone group in *trans* compound (XXVIb) was reduced to the methylene group[22] and III was synthesized as a unity. Its picrate melted at 182—184° which showed no depression on admixture with the picrate of the same melting point obtained earlier. This method is nothing but a method for synthesis of all-chair, all-*trans* form of IIIb, and this experiment has provided a conclusive evidence that the isomer of III forming a picrate of mp 182—184° is indeed IIIb.

(c) Formation Rate of the Methiodides of IIIa, IIIb, and IIIg, and their NMR Spectra: The foregoing experiments have proved that the isomers of III forming the picrates of mp 203—205°, 182—184°, and 171° are respectively IIIa, IIIb, and IIIg, and in order to endorse these evidences, another experiment was added. The formation velocity of the methiodides of III becomes slower in the order of IIIg, IIIb, and IIIa. As shown in Chart 4, the lone-pair electrons of the ring nitrogen is sterically most deshielded in IIIg and most shielded in IIIa. This is the reason why the formation of the methiodide becomes more difficult in IIIa at a low temperature. Such correlation can also be observed in the retention time in gas liquid chromatography and in the *Rf* values in thin-layer chromatography (Fig. 2), indicating that the location of the lone-paired electrons of ring nitrogen and adsorptivity are in parallel, and that the configurations and conformations assigned to these isomers here are appropriate. The NMR spectra of the N^+–Me protons of these methiodides are shown

Table III. Proton Resonance of N-Methylperhydrobenzo[*c*]quinolizinium Ions

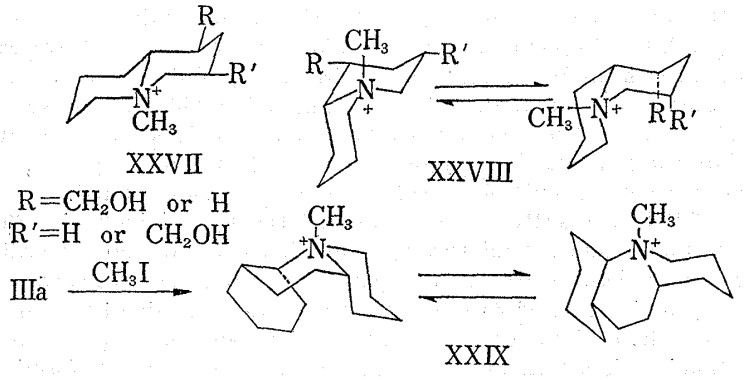
Compound	mp (°C)	N–Me (τ)	Ring fusion
IIIa methiodide	208—210	6.54	*cis*
IIIb methiodide	177—180	7.00	*trans*
IIIg methiodide	290—292 (decomp.)	6.62	*cis*
trans-Quinolizidine methiodide	320 (decomp.)	6.91	*trans*
cis-Quinolizidine methioidde	314 (decomp.)	6.70	*cis*

21) *a*) Z. Horii, K. Morikawa, Y. Tamura, and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **14**, 1399 (1966); *b*) Z. Horii, K. Morikawa, and I. Ninomiya, Paper presented at the 87th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1967.

22) We are grateful to Mr. K. Morikawa for advices about this reduction.

in Table III. The N^+–Me proton signals of the methiodides of *cis*–quinolizidine derivatives generally appear in a lower magnetic field than those of the *trans* derivatives. There are many such examples, such as the quinolizidine methiodide, [9,23] and the methiodide of its derivatives.[10,23,24] From the signals of N^+–Me listed in Table III, it may be assumed that IIIa and IIIg take the *cis*– form methiodide, and IIIb, the *trans*–form methiodide.

The methiodide of 1– or 3–eq.–hydroxymethylquinolizidine (lupinine or 3–lupinine) takes the *trans* form (XXVII) and the N–methyl takes the axial configuration. In contrast, the methiodide of 1– or 3–ax.–hydroxymethylquinolizidine (*epi*–lupinine or 3–*epi*–lupinine) is thought to take the *cis* form (XXVIII) because of the steric interference between the hydroxymethyl and N–methyl groups.[23] This is because, in the methiodide of IIIa, 1,3–



interaction occurs between the axial C_7–C_{6a} bond and N^+–Me, and consequent inversion has given the *cis* form (XXIX). Inversion of the *trans*–form free base into the *cis*–form methiodide will only occur in IIIa.

Stereostructure of the four kinds of stereoisomers of III has been determined by the foregoing various reactions. The isomers giving the picrate of mp 203—205° is IIIa, that of mp 182—184° is IIIb, that of mp 171° is IIIg, and that of mp 155° is IIId (or IIIh), although the last–named isomer was obtained in such a minute quantity that conclusive evidence is still lacking.

Experimental[25]

2-(2-Pyridylethyl)cyclohexanone Ethylene Ketal (XI)——A solution of 60 g of 2–(2-pyridylethyl)cyclohexanone, 4 ml of ethylene glycol, and a small amount of *p*–toluenesulfonic acid dissolved in 40—50 ml of benzene was refluxed with stirring for 5 hr. H_2O formed by the reaction was made to distill off outside the reaction system as an azeotropic mixture with benzene. Benzene and unreacted ethylene glycol were distilled off under a reduced pressure, the residue was neutralized with K_2CO_3, and extracted with benzene. The extract was dried over Na_2SO_4, benzene was distilled off, and the residue was submitted to vacuum distillation, affording 5.52 g (75%) of a pale yellow oil, bp 149° (4 mmHg). Picrate: Yellow needles (from EtOH), mp 122.5—123.5°. *Anal.* Calcd. for $C_{21}H_{24}O_9N_2$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.53; H, 5.58; N, 11.48. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1605 (C=N), 1086, 1050 (ketal) (absorption of $\nu_{C=O}$ at 1704 absent).

2-(2-Piperidylethyl)cyclohexanone Ethylene Ketal (XII)——A solution of 3 g of XI dissolved in 20 ml of dehyd. EtOH, added with Raney Ni catalyst, was submitted to high–pressure catalytic hydrogenation at 110° and 90 atm. After removal of the catalyst by filtration, the solvent was evaporated and the residue was distilled in vacuum to collect 2.5 g (83%) of a distillate of bp 138° (3 mmHg). IR $\nu_{max}^{liq.film}$ cm^{-1}: 3344 (=N—H), 1087, 1047 (ketal) (disappearance of absorptions at 1590, 1568, and 1473 (pyridine)).

Δ^{6a}-and $\Delta^{10(10a)}$-Dehydroperhydrobenzo[c]quinolizine (IXa and b)——A solution of 1.3 g of XII dissolved in 20% HCl was refluxed gently for 1 hr, H_2O and HCl were distilled off at a reduced pressure, the residue was neutralized with KOH, and salted out with K_2CO_3. This was extracted with ether, the ether

23) I. Matsuo, K. Sugimoto, and S. Ohki, *Chem. Pharm. Bull.* (Tokyo), **15**, 1680 (1968).
24) M. Shamma and J.M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963).
25) All melting points are uncorrected. NMR spectra were recorded at 60 Mcps in $CDCl_3$ solution, using tetramethylsilane as internal standard. Chemical shifts are reported in τ units.

layer was dried over Na_2SO_4, and ether was evaporated. The residue was distilled *in vacuum* and 0.78 g (80%) of an oily distillate of bp 108° (4 mmHg) was collected. One peak detected in gas liquid chromatography. NMR: $\tau=5.46$ (N–C(H)=C–, 1/4 proton), $\tau=5.52$ doublet (H_6–eq. 1H). Therefore, IXa–IXb=4:1. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1653 (C=C due to enamine), 2747 (Bohlmann band).

IXa and IXb would be unstable and were acidified to be stored as VIII. In order to chemically prove IXa, its oxidation with $KMnO_4$ was carried out. A mixture of IXa and IXb (0.2 g) was dissolved in acetone and oxidized with 5% $KMnO_4$ until the color no longer faded. The mixture was extracted with ether, the extract was dried over K_2CO_3, and the solvent was evaporated. The residue was chromatographed over Al_2O_3 column and 0.14 g (*ca.* 60%) of a substance was obtained. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1698 ($\nu_{C=O}$), 1621 (N–C=O). Therefore, the structure was assumed to be X. Since a considerable amount of X was produced, the mixture probably contained larger amount of IXa.

Reduction of Quinolizinium Ion (VIII) with $NaBH_4$——A solution of 1.0 g of VIII dissolved in MeOH was acidified with HCl and MeOH solution of 0.8 g of $NaBH_4$ was added dropwise with stirring, maintaining the solution just above pH 2, the dropwise addition made during 3 hr. The solvent was distilled off under a reduced pressure, the residue was basified and salted out with K_2CO_3, and extracted with ether. The extract was dried over K_2CO_3, ether was evaporated, and the residue was distilled in vacuum to collect 0.44 g (52%) of a liquid of bp 95° (4 mmHg). The rectified distillate was submitted to chromatography over Al_2O_3 column and separated into the products forming picrates of mp 203—205°, mp 184°, mp 171°, and mp 155°. During the course of purification, a mixed picrate of mp 176—178° was isolated.

Catalytic Reduction of VIII over PtO_2——One gram of VIII was acidified with 35% HCl, 0.1 g of PtO_2 and 20 ml of EtOH were added, and the mixture was submitted to reduction at ordinary pressure. After removal of the catalyst by filtration, the solvent was evaporated from the filtrate, the residue was neutralized and salted out with K_2CO_3, and extracted with ether. The extract was dried over K_2CO_3, ether was evaporated, and the residue was distilled under a reduced pressure, and 0.83 g (85%) of oil, bp 95° (4 mmHg) was obtained. Purification by Al_2O_3 column chromatography afforded products forming picrates of mp 204°, mp 180°, and mp 171°. During the course of purification, a mixed picrate of mp 162° was isolated.

Catalytic Reduction of IX over Rh-C——A mixture of 1 g of IX (a and b), 0.1 g of Rh–C, and 20 ml of dehyd. MeOH was submitted to catalytic reduction at ordinary temperature and pressure. The catalyst and solvent were removed and the residue was treated in the same way as above. Low-pressure distillation of the final residue gave 0.86 g (90%) of a liquid, bp 89° (4 mmHg). After separation by Al_2O_3 column chromatography, the products were purified as picrates. The main product was a picrate of mp 205°, accompanied with those of mp 182—184° and of mp 171°.

Catalytic Reduction of IX over PtO_2——A mixture of 1 g of IX (a and b), 0.1 g of PtO_2, and 20 ml of dehyd. EtOH was submitted to catalytic reduction at ordinary temperature and pressure. Treatment of the reaction mixture as above afforded 0.84 g (87%) of a liquid, bp 107—108° (7 mmHg). After separation by Al_2O_3 column chromatography, picrates of mp 203—204° (majority), mp 184°, and mp 171°, were obtained.

Synthesis of Benzo[*c*]quinolizidine (XXII)——i) Ethyl β-(2-Quinolyl)ethylacetate (XVIII): A solution of 1 g of diethyl β-(2-quinolyl)ethylmalonate[19] dissolved in 10 ml of NaOH–EtOH was refluxed in a water bath for 3 hr. The solvent was distilled off under a reduced pressure, the residue was acidified with 20% HCl, and the mixture was refluxed for 1 hr to effect decarboxylation. The reaction mixture was concentrated in a reduced pressure, 20 ml of dehyd. EtOH was added, and dry HCl gas was passed through this solution while refluxing on a water bath to effect esterification. After about 4 hr, the product was purified through Al_2O_3 column chromatography and 0.52 g (65%) of a substance was obtained. Picrate: Yellow scales (from EtOH), mp 127—128°. *Anal.* Calcd. for $C_{21}H_{20}O_9N_4$: C, 53.39; H, 4.27; N, 11.86. Found: C, 53.18; H, 4.11; N, 11.56. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1736 (ester).

ii) 4-(2-Quinolyl)-1-butanol (XIX): To an ice cold solution of 0.46 g of the ester (XVIII) dissolved in 10 ml of dehyd. ether, a solution of 0.2 g of $LiAlH_4$ dissolved in 20 ml of dehyd. ether was added during 1 hr with stirring. The mixture was stirred for further 2 hr, the reactant was decomposed with H_2O, salted out with K_2CO_3, and extracted with ether. The extract was dried over Na_2SO_4, ether was evaporated, and the residue was purified by Al_2O_3 column chromatography to collect 0.34 g (90%) of the product. Neither the picrate nor perchlorate crystallized. IR $\nu_{max}^{liq.film}$ cm^{-1}: 3410, 1049 (CH_2OH).

iii) 6,7-Benzo-1,2,3,4-tetrahydroquinolizinium Chloride (XXI): To a solution of 0.34 g of the alcohol (XIX) dissolved in 8 ml of dehyd. $CHCl_3$, 0.25 g of $SOCl_2$ was added with cooling and the mixture was stirred under ice cooling. The mixture was then warmed on a water bath for 1 hr, $CHCl_3$ and the unreacted $SOCl_2$ were distilled off, and a small amount of H_2O was added to the residue. The water-soluble portion was neutralized and salted out with 10% K_2CO_3 and extracted with benzene. The extract was dried over Na_2SO_4, and the solution was refluxed for 5 hr by which a precipitate formed. The precipitate was collected by filtration, the filtrate benzene solution was converted into a toluene solution, and the latter was refluxed for some time. The precipitate thereby formed was collected by filtration and combined with the former precipitate to afforded 0.25 g (70%) of a gelatinous product.

iv) Reduction of XXI: A solution of 0.25 g of the chloride (XXI) dissolved in 15 ml of EtOH, added with 0.05 g of PtO_2 was submitted to catalytic reduction. After removal of the catalyst and EtOH, the residue

was neutralized and salted out with 10% K_2CO_3 and extracted with ether. The product was purified by Al_2O_3 column chromatography and 0.12 g (60%) of XXII was obtained. Picrate: mp 160—161°, which agreed with that reported in literature.[18] IR $\nu_{max}^{liq.film}$ cm^{-1}: 2784, 2762 (Bohlmann band), 1603 (benzene).

High-Pressure Reduction of XXII to form III——A solution of 0.1 g of XXII dissolved in 8 ml of glacial AcOH, added with 0.05 g of Rh–C, was submitted to reduction at 60—62 atm. and 80°. After removal of the catalyst and the solvent, the residue was neutralized and salted out with K_2CO_3, and extracted with ether. The product obtained was distilled *in vacuum* to obtain 0.074 g (71.6%) of bp 115—120° (4 mmHg). Two spots detected in thin-layer chromatography. After separation by Al_2O_3 column chromatography, picrates of mp 171° and of mp 176—178° (a mixture of the picrates of mp 203—205° and of mp 171°) were obtained, with a larger amount of the former. Catalytic reduction of XXII at ordinary temperature ended in the recovery of the starting material, using either Rh–C or PtO_2 as a catalyst.

2-Oxoperhydro-3,4-benzoquinolizine[21b] (XXVIb)——A mixture of XXVI (a and b) in KOH–EtOH was refluxed for 30 min. The product was determined to be all-*trans* compound. Picrate (from EtOH): mp 220°.

Dithioketal of XXVIb——To a solution of 22 mg of XXVIb dissolved in 5 ml of AcOH, a small amount of BF_3-etherate and 20 mg of EtSH were added and the mixture was allowed to stand overnight. The mixture was neutralized with K_2CO_3 and further rendered alkaline and extracted with ether. The extract was dried over Na_2SO_4, ether was evaporated, and the residue was purified through Al_2O_3 column chromatography to afford 16 mg of a product, which was found to be a unity by gas liquid and thin-layer chromatography. IR spectrum showed the disappearance of $\nu_{C=O}$. Picrate: needles (from EtOH), mp 228—229°. *Anal.* Calcd. for $C_{23}H_{35}O_7N_4S_2$: C, 50.82; H, 6.44. Found: C, 50.70; H, 6.42.

Perhydrobenzo[*c*]quinolizine (IIIb)——To a solution of 52 mg of the dithioketal dissolved in 5 ml of dehyd. EtOH, a small amount of Raney Ni of strong activity was added and the mixture was refluxed for 6 hr. Purification through Al_2O_3 column chromatography gave 18 mg (56%) of III. Picrate (from EtOH), mp 182—184°, showing no depression on admixture with the picrate of III obtained by different routes.

Reduction of the Oxidation Product of IIIa——A mixture of 1.89 g of mercuric acetate in 5 ml of 5% AcOH solution was stirred at room temperature for some time to obtain a homogeneous mixture. To this mixture, 286 mg. IIIa (picrate, mp 203—205°) was added and the mixture was stirred for 1.5 hr on a water bath. Precipitate of mercurous acetate formed after about 20 min. This precipitate was filtered off, the filtrate was saturated with H_2S gas to precipitate excess Hg^+ as HgS which was removed by filtration. A solution of 160 mg of $NaBH_4$ dissolved in 5 ml of MeOH was added dropwise during 3 hr to this solution, while maintaining it at pH 3—5 and with stirring. The mixture was stirred at room temperature, neutralized with K_2CO_3 and further made alkaline, and extracted with ether. The extract was dried over Na_2SO_4, ether was distilled off, and the residue was purified through Al_2O_3 column chromatography to afford 172 mg (60%) of a product. Three peaks corresponding to the picrates of mp 203—205°, mp 171°, and mp 155°, appeared in gas liquid chromatogram (Fig. 3).

IIIg (picrate, mp 171°) was not oxidized by mercuric acetate.

Re-examination of Jampolsky's Synthesis[5] of Perhydrobenzo[*c*]quinolizine (III)——A mixture of 12 g of 2-[β-(2-pyridyl)ethyl]cyclohexanone (V), 60 ml of AcOH, and 0.5 g of PtO_2 was submitted to catalytic reduction at 30—35°. After removal of the catalyst by filtration, the filtrate was basified with Na_2CO_3 and extracted with benzene. The extract was dried over Na_2SO_4, benzene was evaporated, and ether was added to the residue. The ether solution was allowed to stand at 0—2° and the white crystals that precipitated were recrystallized from ether to 0.08 g of 2-(2-piperidylethyl)cyclohexanol. The filtrated ether solution was dried over Na_2SO_4, ether was evaporated, and the residue was distilled in vacuum to collect 6.2 g (52.6%) of a product which was separated into two distillates by fractionation. A distillate of bp 95—98° (2 mmHg) gave a mixture of picrates of mp 203—205°, mp 182—184°, and mp 171°. The distillate of bp 105° (2 mmHg) gave a mixture of picrates of mp 182—184°, mp 203—205°, and of mp 171°. These two fractions are actually a mixture of three isomers of perhydrobenzo[*c*]quinolizine and the ratio of the picrates, as revealed by gas liquid chromatography was found to be 8:3.1:1 for those of mp 182—184°, mp 203—205°, and mp 171°, respectively.

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