Rantenstrauch, *Chem. Commun.*, 1122 (1969)) constitutes the sole published reference to an "unrestricted" 1-benzazepine.
(19) A substance believed to be the *N*-cyano counterpart of **25** was prepared in these laboratories by H. Yamamoto (Ph.D. Dissertation, 1973).
(20) All melting points and boiling points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer 137B spectrophotometer, NMR spectra were recorded on a Varian A-60 or XL-100 spectophotometer, ultraviolet spectra were determined on a Cary 18 spectrophotometer, and mass spectra were obtained with a Hitachi Perkin-Elmer Model RMU-6E single-focusing spectrometer. Gas chromatographic analyses were performed on a Varian Aerograph A90-P3 instrument operating under the following conditions: (A) 7 ft × 0.25 in aluminum column packed with SE-30 on Chromosorb W at 188 °C with the vaporizer at 205 °C, the detector at 210 °C, and a helium flow of 100 cm^3/min; (B) same as in (A) except the column temperature was 177 °C; (C) 6 ft × 0.25 in aluminum column packed with SF-96 on Chromosorb W at 140 °C with the vaporizer at 150 °C, the detector at 170 °C, and a helium flow of 85 cm^3/min. Microanalyses were performed by Galbraith Laboratories Knoxville, Tenn. All solvents were ACS Reagent Grade and were used without further purification, except for ethyl ether and tetrahydrofuran which were freshly distilled from lithium aluminum hydride.
(21) This procedure constitutes a modification of that described in ref 10.
(22) Proper analysis of this spectrum required the use of double irradiation.
(23) B. D. Astill and V. Boekelheide, *J. Am. Chem. Soc.*, **77**, 4079 (1955).
(24) This procedure represents a modification of that described in ref 11.
(25) A. Balasubramanian, J. M. McIntosh, and V. Snieckus, *J. Org. Chem.*, **35**, 433 (1970); T. Sasaki, K. Kanematsu, A. Kakehi. I. Ichikawa, and K. Hayakawa, *ibid.*, **35**, 426 (1970).
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(28) C. F. Allen, R. W. Ryan, and J. A. Van Allen, *J. Org. Chem.*, **27**, 778 (1962), and references cited therein.
(29) It is essential that the α-pyrone employed in this reaction be freshly distilled from potassium carbonate. Failure to do so results in the exothermic rearrangement of **15** to phenol.

Benzo- and Indoloquinolizine Derivatives. 13.[1] Conformation of the Perhydrobenzo[*c*]quinolizines

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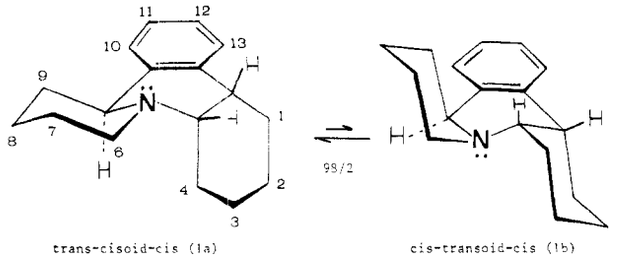
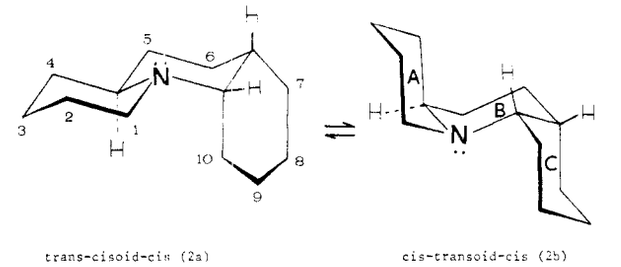
The conformation of three isomers of perhydrobenzo[*c*]quinolizine is determined by the study of their ^{13}C and 270-MHz ^1H NMR spectra. The previous cis-transoid-cis conformation assignment for one of the isomers is shown to be erroneous. The proposed trans-cisoid-cis conformation is further corroborated by molecular-mechanics calculations.

We recently were able to show by variable-temperature ^{13}C NMR that in the *rel*-(4a*β*,9a*α*,13b*β*) isomer (1) of 1,2,3,4,4a,6,7,8,9,13b-decahydro-9a*H*-pyrido[1,2-*f*]phenanthridine the trans-cisoid-cis conformation (**1a**) is strongly



favored over the cis-transoid-cis one (**1b**)[1] ($\Delta G°_{243}$ = 7.5 kJ/mol (1.8 kcal/mol)).

On the other hand, Ohki[2] reported the cis-transoid-cis isomer (**2b**)[3] as the preferred conformation for the analogous isomer of perhydrobenzo[*c*]quinolizine (**2**). This result seemed

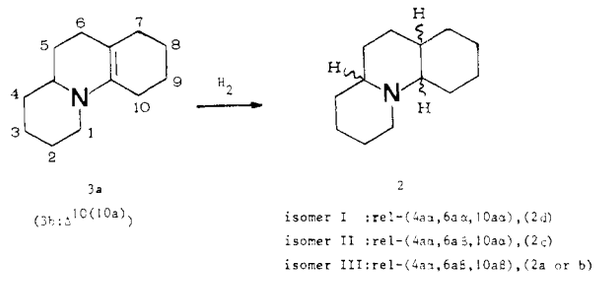


improbable to us since the trans-cisoid-cis conformation **2a** does not experience the destabilizing allylic strain[6] which occurs between the C-9 and C-10 protons and between the C-1 and C-13 protons in **1a**. Therefore, we expected the trans-cisoid-cis conformation to be even more favored in **2** than **1**.

In the carbocyclic analogues, the trans-cisoid-cis conformation of perhydrophenanthrene has been calculated to be more stable than the cis-transoid-cis isomer by 6.7–7.5 kJ/mol (1.6–1.8 kcal/mol).[7,8] We parametrized the molecular-mechanics calculations for the introduction of a nitrogen atom,[9] taking into account the lone-pair influence as described by Allinger[10] for oxygen compounds. These calculations indicate a net preference for **2a** over **2b** by 5.4–6.7 kJ/mol (1.3–1.6 kcal/mol), depending on the importance of the lone-pair interaction parameters.

In order to solve the ambiguity, we reinvestigated the conformational equilibrium in **2**, mainly by the use of ^{13}C NMR.

Synthesis of Compounds. Three isomers (I–III) of **2** were



obtained by the reduction of the enamine **3**[2] or its perchlorate salt (Table I). The fourth isomer, which was present in a very minute amount, could not be isolated.

The excellent agreement in the isomeric composition for the catalytic and the sodium borohydride reductions, along with the gas liquid chromatographic data, established the identity of the isomers as those reported by Ohki.[2]

Conformational Analysis. Infrared Spectroscopy. As already observed by Ohki,[2] isomers I and II show strong Bohlmann bands in the 2700–2800-cm^{-1} region of their in-

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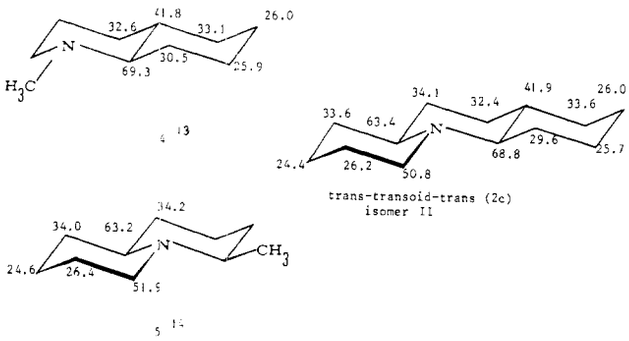
Table I. Reduction Results of 3

Compd	Catalyst	Isomer ratio[a] I	II	III	IV
3	PtO_2/H_2	63	30	5	2
	$NaBH_4$/AcOH	40	42	10	8
3·$HClO_4$	$LiAlH_4$	40	57	3	
	K-selectride (−50 °C)	47	11	42	

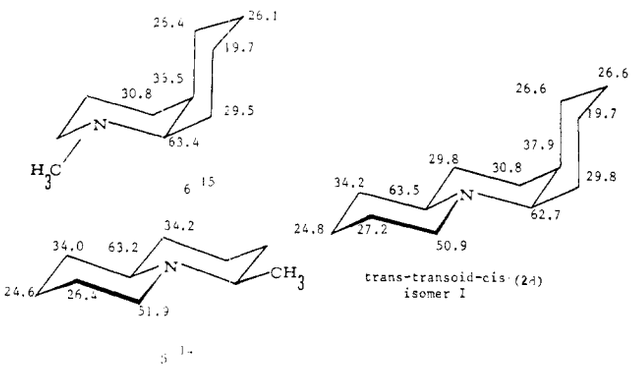
[a] The relative ratios were determined by GLC. The isomer numbers (I–IV) correspond to the order of elution from the column.[2]

frared spectra, whereas the spectrum of isomer III shows only very weak absorptions in this region. This, however, does not allow the conclusion that the quinolizidine conformation of isomer III is cis, as was done previously.[2] A *trans*-quinolizidine with an axial substituent on the carbon α to the nitrogen, as is the case in the trans-cisoid-cis conformation (**2a**) of isomer III, is expected to absorb weakly in the Bohlmann region.[11,12]



^{13}C NMR. The signals of the three methine carbons were distinguished on the basis of their multiplicity in the gated decoupled spectra, while the lowest field triplet signal was assigned to C-1.

The spectrum of isomer II, which was assigned the *rel*-(4aα,6aβ,10aα) configuration by Ohki,[2] was interpreted with the aid of the published chemical shifts for *N*-methyl-*trans*-perhydroquinoline (**4**)[13] and for *cis*-4-methylquinolizidine (**5**).[14] Excellent agreement with the experimental values is obtained, thus confirming trans-transoid-trans conformation



2c for this compound.

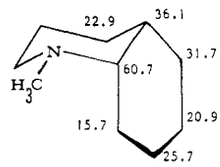
In the same way, the signals of isomer I were assigned and the trans-transoid-cis conformation **2d** could be confirmed.

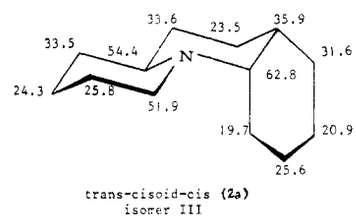
The good agreement between the models and the experimental values for these two isomers prove the reliability of these comparisons. This method can therefore be used to determine the preferred conformation of isomer III (**2a** or **2b**). The ^{13}C spectrum of this latter isomer is temperature independent over a range from +50 to −50 °C, except for a general −0.3-ppm shift. This indicates that the compound is even more conformationally homogeneous than **1**. The chemical shifts are in close agreement with those of *cis*-4-methylquinolizidine (**5**)[14] and the *N*-methyl-*cis*-perhydroquinoline conformer (**7**, Figure 6).[15]

Table II. 270-MHz ^{1}H NMR Parameters for Isomer III

Shift, δ	Assignment	Multiplicity (J, Hz)[a]
2.86	H-10a	d (12.4) of t (4.4)
2.71	H-1_{eq}	Broad d (11.5)
2.59	H-1_{ax}	t (11.5) of d (3.1)
2.40	H-4a	t (10.6) of t (2.7)
2.18	H-10_{eq}	Multiplet

[a] The spacings were read directly from the spectrum.





As models for the cis-transoid-cis conformation (**2b**) of isomer III, the ring C values of **2d** were taken, together with the ring A values of the *rel*-(4aα,9aβ,13bβ) isomer of **1**, which has the cis-transoid-trans conformation.[1] The C-10a value of **2d** has to be corrected then for a double γ interaction.[17] In no way, however, can these model shifts be matched to the experimental ones without giving at least two or three strongly deviating values. Therefore, this conformer can be excluded.

A comparison of the chemical shifts of isomers I and II with those of their carboxcyclic analogues[17] reveals the presence of the shielding effect of the nitrogen atom on antiperiplanar γ carbons.[18] As also noted by Eliel,[13,15] the antiperiplanar lone-pair shifts C-10 in **2a** upfield by 3.9 ppm, compared to the perhydrophenanthrene value.[17] No indication was found, however, for a deshielding of the syn-axial carbons by the lone pair[19] in **2d**. The approximate equality of a nitrogen lone pair and a carbon–hydrogen γ effect was also observed by Wenkert.[20]

270-MHz ^{1}H NMR. The ^{1}H NMR spectra of isomers I and II are very uninformative. In both cases, the only signal which can be assigned is the H-1 equatorial signal at δ 3.10 and 3.35, respectively. This agrees with the chemical shift of the equivalent proton in the isomers of **1**.[11] For isomer II, another equatorial proton signal at δ 2.15 is separated from the broad hump between 1 and 2 ppm. For isomer I, a three-proton signal resonates between δ 1.95 and 2.15. The spectrum of isomer III, however, shows several well-separated signals which were assigned by double-resonance experiments (Table II).

The chemical shift of H-10a is almost exactly the same as in **1a**.[11] The multiplicity indicates its axial position in the C ring and thus also confirms the trans-cisoid-cis conformation for this isomer. The small chemical-shift difference between the H-1_{eq} and H-1_{ax} signals, which is also observed in the trans-cisoid-cis conformation (**1a**),[11] is exceptional for a *trans*-quinolizidine. The geminal coupling of 11 Hz is, however, in agreement with the trans conformation.[11,21] The angular quinolizidine proton H-4a is deshielded from the normal quinolizidine value (1.7–2.0 ppm[22]) by the C10–C10a bond.[23]

In summary, the study of the ^{13}C and ^{1}H NMR spectra of the perhydrobenzo[*c*]quinolizines (**2**) has enabled us to show that in this compound, as in the benzo-substituted analogue (**1**), the preferred conformation is the trans-cisoid-cis one. This is in agreement with the energies obtained by molecular-mechanics calculations. Once more,[24] it has been shown that an assignment of a *cis*-quinolizidine conformation, based upon the absence of strong Bohlmann absorptions in the infrared spectrum, should be made with due caution.

Experimental Section

The NMR spectra were recorded on Bruker HX 270 (^{1}H) and Bruker WH 90(^{13}C) pulsed-Fourier-transform spectrometers in $CDCl_3$ solutions as described previously.[1] The infrared spectra were recorded on a Perkin-Elmer 257 spectrometer as dispersions in KBr.

2-(2-Pyridylethyl)cyclohexanone Ethylene Ketal (8) was prepared as described by Ohki[2] using ~0.33 equiv of *p*-toluenesulfonic acid; yield 60%.

2-(2-Piperidylethyl)cyclohexanone Ethylene Ketal (9). To a solution of 10 g of **8** in 100 mL of absolute ethanol, 15 g of sodium was added in portions. This required about 2 h. Water was then added, and most of the ethanol was evaporated under vacuum. Extraction with benzene, drying over $MgSO_4$, and distillation gave 7.8 g (76%) of a colorless oil; bp 132 °C (0.8 mm).

Δ^{6a}- and $\Delta^{10(10a)}$-Dehydroperhydrobenzo[*c*]quinolizine (3a, b) was prepared as described by Ohki[2] by refluxing **9** in 20% HCl for 2 h. Distillation of the enamine at 70 °C (0.5 mm) yielded 71% of a colorless oil. The ^{1}H NMR (270 MHz, $CDCl_3$) indicated the vinylic proton of the $\Delta^{10(10a)}$ isomer at δ 4.6, integrating for about 10% of a proton. The ^{13}C spectrum (22.63 MHz, $CDCl_3$) showed two sets of signals in a 90:10 proportion. The literature[2,25] reports a 4:1 composition of the isomeric mixture.

Perhydrobenzo[*c*]quinolizine (Perhydropyrido[1,2-*a*]quinoline) (2). Method 1. Catalytic and $NaBH_4$ reductions of **3a** or **3b** were carried out under the previously described conditions.[2] The composition of the reaction mixture was determined on a Varian 1520 B gas chromatograph (5% SE 30 Chromosorb W, 160 °C column, 290 °C detector, and N_2 and H_2 flow rates of 25 mL/min).

Method 2. $LiAlH_4$ reduction of 500 mg of the perchlorate salt of **3a** or **3b** was carried out in 200 mL of dry tetrahydrofuran. After a 4-h reflux, water was added and most of the tetrahydrofuran was evaporated. After extraction with ether, drying over $MgSO_4$, and evaporation of the solvent, the residue was examined by GLC (Table I). The isomers were separated by column chromatography over Al_2O_3 (Fluka, Type 507 C, Activity I) with ether elution.

Method 3. Reduction with K-selectride (5 equiv of a 0.5 M solution in THF, Aldrich) of 1 g of the perchlorate salt of **3a** or **3b** in 50 mL of dry THF was carried out at −50 °C for 15 h. The reaction was worked up as described for the $LiAlH_4$ reduction, followed by an acid–base extraction.

About 20% unreduced enamine was further reduced by the PtO_2/H_2 procedure.

Acknowledgment. We wish to thank the Fonds voor Fundamenteel Kollektief Onderzoek and the Nationale Raad voor Wetenschapsbeleid for their contribution to the equipment of our laboratory.

Registry No.—**2,** isomer I, 64161-72-4; **2,** isomer II, 64161-73-5; **2,** isomer III, 64161-74-6; **3a,** 944-68-3; **3a**·$HClO_4$, 64114-15-4; **3b,** 944-67-2; **3b**·$HClO_4$, 64114-16-5; **8,** 1023-99-0; **9,** 1444-15-1.

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Use of α-Cyano Amines for the Regiospecific Synthesis of Multisubstituted Pyridines. Preparation of Nicotine Analogues[1]

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A general synthesis of 2-alkyl-3-acylpyridines and 2-alkyl-3-formylpyridines via [2,3] sigmatropic rearrangements of α-pyrrolidinyl-2-alkylpyridines is described. The initially obtained α-cyano amine can be hydrolyzed to an aldehyde, reductively cleaved to an amine, or alkylated and hydrolyzed to a ketone. These procedures are applied toward the synthesis of pyridine-substituted nicotine, nornicotine, and anabasine derivatives. In certain cases, the Stevens rearrangement product was observed along with the desired Sommelet–Hauser product, and studies indicated that sodium amide/NH_3 gave the largest preference for the latter rearrangement pathway.

The importance of the pharmacology of nicotine (**1**) and the nicotiana alkaloids is demonstrated by the intensive study they have received over the past century.[2] Some time ago Haglid reported that 6-methylnicotine (**3**) retained virtually full nicotinic activity, whereas 4-methylnicotine (**2**) displayed no activity on isolated muscle preparations.[3] This finding was rationalized by assuming that the 4-methyl group prevented the compound from adopting the conformation necessary for interaction with the receptor. As part of our interest in the structure, chemistry, and pharmacology of nicotine,[4,5] we

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