MeOH/EtOAc (40:1:2.5) as the solvent system and the following compounds were isolated.

1. 4-Bromo-13β-methyl-13aα*H*-tetrahydropseudoepiberberine (17). Fractions 3–7 were combined and evaporated and the solid obtained was crystallized from benzene–hexane to yield pale yellow needles: 30 mg; mp 146 °C; IR (KBr) 2900–2750 cm^{-1} (Bohlmann bands); UV (EtOH) 288 nm (log ε 3.88); NMR data as given in the discussion; mass spectrum *m/e* 433 and 431 (M^+), 272, 270 and 162. Anal. Calcd for $C_{21}H_{22}NO_4Br$: C, 59.55; H, 5.08; N, 3.23. Found: C, 59.42; H, 5.05 N, 3.27.

2. 13β-Methyl-13aα*H*-tetrahydropseudoepiberberine (7). Fractions 9–16 were combined and evaporated to yield a solid which was crystallized from benzene as yellow needles: 300 mg; mp 197–198 °C; found to be identical (IR, mp, mmp, and spectra) with an authentic sample prepared as reported.[1]

3. 4-Bromo-13α-methyl-13aα*H*-tetrahydropseudoepiberberine (18). Fractions 20–30 were combined and evaporated to give a yellow residue. This was crystallized from benzene–hexane as yellow needles: 420 mg; mp 160 °C; UV (EtOH) 288 nm (log ε 3.88); NMR data as given in the discussion; mass spectrum *m/e* 433 and 431 (M^+), 272, 270, and 162. Anal. Calcd for $C_{21}H_{22}NO_4Br$: C, 59.55; H, 5.08; N, 3.23. Found: C, 59.34; H, 5.35; N, 3.22.

4. 13-α-Methyl-13aα*H*-tetrahydropseudoepiberberine (8). Fractions 31–34 gave a compound which was crystallized from benzene as colorless crystals: 60 mg; mp 132 °C; found to be identical with an authentic sample.[1]

Cyclization of 4 Using PBr_5 and P_2O_5. The *N*-formyl derivative **4** was cyclized as described above and the products were separated by chromatography.

1. 4-Bromo-13β-methyl-13aα*H*-tetrahydropseudocoptisine (19). Fractions 4–8 were combined and evaporated to give a colorless solid which was crystallized from benzene as colorless crystals: 55 mg; mp 205–206 °C; IR (Nujol) 2800–2700 cm^{-1} (Bohlmann bands); UV (EtOH) 292 nm (log ε 4.00); NMR ($CDCl_3$) δ 0.93 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.20–4.20 (8 H), 5.93 (s, 2 H, OCH_2O), 6.05 (s, 2 H, OCH_2O), 6.57, 6.67, 6.70 (3s, 3 H, aromatic protons); mass spectrum, *m/e* 417, 415 (M^+), 256, 254, and 162. Anal. Calcd for $C_{20}H_{18}NO_4Br$: C, 57.70; H, 4.33; N, 3.36. Found: C, 57.81, H, 4.30; N, 3.36.

2. 13β-Methyl-13aα*H*-tetrahydropseudocoptisine (9). Fractions 10–16 were combined and crystallized from benzene as pale yellow crystals: 380 mg; mp 195 °C; identical with an authentic sample.[3]

3. 4-Bromo-13α-methyl-13aα*H*-tetrahydropseudocoptisine (20). Fractions 18–27 when combined and evaporated gave a yellow solid which was crystallized from benzene–hexane as yellow crystals: 400 mg; mp 179 °C; UV (EtOH) 291 nm (log ε 3.98); NMR ($CDCl_3$) δ 1.43 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.57–3.00 (4 H), 3.30–4.35 (4 H), 5.92 (s, 2 H, OCH_2O), 6.01 (s, 2 H, OCH_2O), 6.52 (1 H, aromatic proton), 6.73 (s, 2 H, aromatic protons); mass spectrum *m/e* 417, 415 (M^+), 256, 254, and 162. Anal. Calcd for $C_{20}H_{18}NO_4Br$: C, 57.69; H, 4.33; N, 3.37. Found: C, 57.40; H, 4.30; N, 3.64.

4. 13α-Methyl-13aα*H*-tetrahydropseudocoptisine (10). Fractions 30–35 gave a compound which was crystallized from benzene–hexane as colorless needles: 75 mg; mp 131 °C. This compound was identical with an authentic synthetic sample.[3]

Catalytic Debromination of 17, 18, 19, and 20. The bromo compounds (250 mg each) were dissolved in methanol (75 mL) and Pd-C (10%, 150 mg) was added to the solution and hydrogenated at room temperature in a paar reduction apparatus for 5 h. The catalyst was then filtered off, the solution was neutralized with dilute NH_4OH solution, and the methanol was distilled off. The residue was then extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with water, dried (Na_2SO_4), and evaporated. The solid residue was crystallized. Thus compounds **17**, **18**, **19**, and **20** gave **7**, **8**, **9**, and **10**, respectively.

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Registry No.—**3**, 65366-54-3; **4**, 65366-55-4; **5**, 65366-56-5; **6**, 65366-57-6; PBr_5, 7789-69-7; P_2O_5, 1314-56-3.

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(4) $POBr_3$ was prepared as reported in "Inorganic Synthesis", Vol II, C. Firnelius, Ed., McGraw-Hill, New York, N.Y., 1946, p. 151. $POBr_3$ was used earlier successfully for the synthesis of some 9,10-substituted tetrahydroprotoberberines in this laboratory—Cf. R. Rajaraman, B. R. Pai, M. S. Premila and H. Suguna, *Indian J. Chem.*, **15B**, 878 (1977).
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Studies in Protoberberine Alkaloids. 15. Some Aspects on the Rate of Methiodide Formation in Protoberberine Chemistry

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The rates of methiodide formation of several synthetic tetrahydroprotoberberines and some 13-methyltetrahydroprotoberberines have been determined. The effect of the substitution pattern and the geometry of fusion of the **B/C** ring system on the rate constants of the compounds studied is briefly discussed. It is also observed that alkaloids having free phenolic hydroxyl groups have larger reaction rates when compared to their O-alkyl derivatives.

Two important methods being used at present to assign conformation to quinolizidine and indolizidine systems are a study of their NMR spectra[1] and determination of their rate of quaternization with methyl iodide.[2] In the course of our work on protoberberine alkaloids we had prepared a large number of synthetic tetrahydroprotoberberines and a few 13-methyltetrahydroprotoberberines. We established the structures and stereochemistry of these compounds on the basis of their IR, NMR, and mass spectral data. Thus a variety of substrates of known stereochemistry were readily available to us and we thought it worthwhile to study their rate of quaternization with a view to study the limitations of this

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Table I

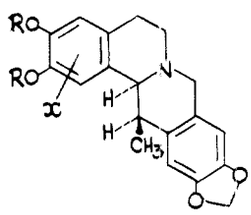
	trans-Quinolizidines				*cis*-Quinolizidines			
	1a[b]	**3a**[c]	**1b**[d]	**3b**[e]	**2a**[f]	**4a**[g]	**2b**[h]	**4b**[i]
$k \times 10^4$ s^{-1} 31.5 °C	1.3 (1.3)[c]	6.4	1.2	9.5	99.62 (341)[a]	98.70	60.32	69.07

[a] Rate constants reported by Shamma et al.[2] for these compounds determined at 25 °C. [b] Registry no. 24306-61-4. [c] Registry no. 65391-28-8. [d] Registry no. 65494-22-6. [e] Registry no. 65442-06-0. [f] Registry no. 24314-69-0. [g] Registry no. 65391-29-9. [h] Registry no. 65442-05-9. [i] Registry no. 65494-23-7.

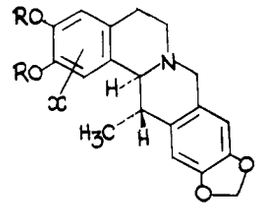
method if any which have not been commented upon by earlier workers. Our observations of the *cis*- and *trans*-quinolizidines of the 13-methyltetrahydroprotoberberines are in general agreement with the earlier findings of Shamma et al.[2] However, we noticed certain aspects which we feel are important and should be taken into consideration in the interpretation of the results of rate of quaternization.

Table I gives the rate constants for the methiodide formation of four 13-methyltetrahydroprotoberberines[2,3] (**1a, 2a, 3a,** and **4a**) and their corresponding bromo derivatives[4] (**1b, 2b, 3b,** and **4b**). It is clear that the *cis*-quinolizidine compounds react at a much faster rate than their corresponding trans compounds. The value of k for the trans compound studied (**1a**) does not change significantly with temperature and the most likely conformation is that represented by A. The cis compound can exist in conformations B and C[5] and is perhaps an equilibrium mixture in solution. At lower temperatures C is expected to be in preponderance, where the lone pair on nitrogen is sterically not hindered, while at higher temperatures the major conformation perhaps has to move to B where the axial methyl group comes in proximity to the nitrogen lone pair and thus makes the rate of quaternization slower. This is evident from the rate constants of **2a** at two different temperatures.

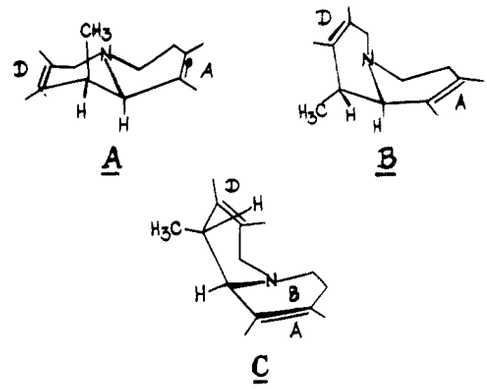
It is also noted from Table I that for the *trans*-quinolizidine compounds the rate constants do not change much when there is a bromine atom present in ring **A** (compare the rates of **1a** and **3a** with those of **1b** and **3b**). However, there is an appreciable decrease in the rate of methiodide formation of the *cis*-quinolizidine compounds as is evident when the rate constants of **2a** and **4a** are compared with those of **2b** and **4b.** In these bromo compounds the position of bromine is not yet settled between the two possibilities of 1 and 4. Bromine in position 1 in the case of cis compounds may cause distortion in the geometry to produce more hindrance to the nucleophilic nitrogen resulting in the rate being decreased.



1a R=CH$_3$; X=H
1b R=CH$_3$; X=Br
3a RR=CH$_2$; X=H
3b RR=CH$_2$; X=Br



2a R=CH$_3$; X=H
2b R=CH$_3$; X=Br
4a RR=CH$_2$; X=H
4b RR=CH$_2$; X=Br



A **B** **C**

The kinetic data on the quaternization of the tetrahydroprotoberberines **5, 6, 7, 8, 9,** and **10** are presented in Table II. All these compounds have relatively lower reaction rates comparable to the *trans*-quinolizidine conformers of the 13-methyl series. Hence in accordance with the general view all these compounds may be said to exist in solution with their **B/C** rings in trans fusion. The rate of quaternization of the tertiary nitrogen in these compounds would depend upon the

Table II

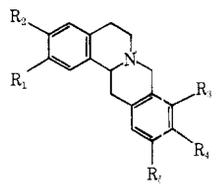
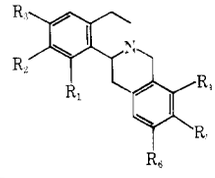
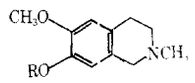
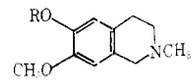
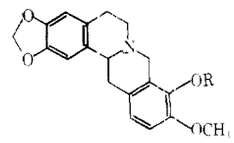
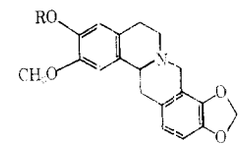
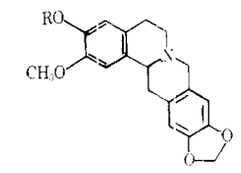
(±)-Compound		Registry No.	Substituents R_1	R_2	R_3	R_4	R_5	$k \times 10^4$ s^{-1} at 31.5 °C
	**(5)**	53898-94-5	OCH_3	OCH_3	H	OCH_2O		17.9
	(6)	38853-67-7	OCH_3	OCH_3	OCH_2O		H	7.2
	(7)	36295-42-8	OCH_2O		H	OCH_2O		10.67
	(8)	4312-32-7	OCH_2O		OCH_2O		H	7.34
	(9)	28319-96-4	OCH_2O		H	OCH_3	OCH_3	21.11
	(10)	29074-38-2	OCH_2O		OCH_3	OCH_3	H	18.69

Table III

(±)-Compound		Registry no.	Substituents R_1	R_2	R_3	R_4	R_5	R_6	$k \times 10^4$ s^{-1} at 31.5 °C
	**(11)**	17388-17-9	H	OCH_2O		OH	OCH_3	H	29.52
	(12)	7762-76-7	H	OCH_3	OCH_3	OH	OCH_3	H	32.00
	(13)	60229-61-0	H	OCH_3	OH	H	OCH_2O		40.30
	(14)	33746-81-5	OH	OCH_3	H	H	OCH_3	OCH_3	44.00
	(15)		OH	OCH_3	OCH_3	OCH_3	OCH_3	H	(78.00)[a]
	(16)		OH	OCH_3	OCH_3	OCH_3	OH	H	(85.00)[a]

[a] Rate constants reported by Shamma et al.[2] for these compounds.

Table IV

Compd	R	Registry no.	$k \times 10^4$ s^{-1} at 31.5 °C
	H	450-14-6	172.7
	CH_2Ph	15778-79-7	67.2
	H	13871-59-5	216.4
	CH_2Ph	56633-08-0	61.4
	H		29.5
	CH_3		18.7
	H	41431-80-5	14.0
	CH_3		7.2
	H		40.3
	CH_3		18.0

basicity also. So the effect of substitution pattern on the basicity of nitrogen becomes another important factor, besides stereochemical considerations of the different conformations. Here it must be borne in mind however that the stereochemistry by itself can influence the basicity. Table II indicates a trend toward faster rates for the 10,11-substituted compounds, compared to those of the corresponding 9,10-substituted ones as is revealed by the comparison of the pairs **5–6**, **7–8**, and **9–10**. It is to be noted that all these compounds are likely to have trans conformation and the differences in their rates are only due to the varying substitution pattern.

In Table III are given the rates of quaternization of a few tetrahydroprotoberberines (**11**, **12**, **13**, and **14**) which contain a phenolic group. All four compounds have faster rates of quaternization than those compounds in Table II. Their rate constants, particularly of compounds **13** and (±)-caseadine (**14**), approach more toward the values that would be expected for the *cis*-quinolizidines of the 13-methyl series.

Shamma and co-workers[2] reported that the higher rates of quaternization of capaurine (**15**) and capaurimine (**16**) were indicative of the predominance of *cis*-quinolizidine conformations and this was borne out by x-ray crystallographic studies.[6] However, a scrutiny of Table IV (which gives the kinetic data for some phenolic bases and their corresponding *O*-alkylated compounds) indicates that the rate of quaternization is considerably enhanced by the presence of free phenolic hydroxyl groups. The tetrahydroprotoberberines listed therein have the stable trans configuration (cf. Shamma[7]). The nature of the substituents, whether they are free phenolic or *O*-alkylated, will not alter the stereochemistry of **B/C** ring fusion. So, the difference in the rate for this set of compounds can be ascribed only to the presence or absence of a phenolic substituent. Hence, in our view the rates of quaternization have to be used with caution to assign conformation in the quinolizidine and indolizidine systems having free phenolic groups.

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