plication of this theory seems, however, to be premature; the calculated relative stability is about 2 kcal/mole as compared to about 0.2 kcal/mole found experimentally. It seems that other effects, such as modification of the σ electrons and H-bond energies, should also be considered.[20]

(iii) Finally, there seems to be a small but systematic tendency of a methyl group, relative to a hydrogen atom, to stabilize that enol form in which the methyl is adjacent to a carbonyl group.

Acknowledgment. We wish to thank J. Reuben for help in recording some of the ^{17}O nmr spectra.

Intramolecular Catalysis. X.[1] Facilitation of Acylation of Tertiary Hydroxyl Groups in Alicyclic 1,3-Diaxial Glycols[2,3]

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Abstract: Evidence is presented for a facilitation of acylation of tertiary hydroxyl groups in alicyclic 1,3-diaxial diols, and for the argument that, in suitable systems, the acylation may be subject also to intramolecular catalysis by a tertiary nitrogen atom. Treatment of the perhydrobenzo[*b*]quinolizine tetrol **1** with acetic anhydride in pyridine at room temperature yielded the triacetate **3** in practically quantitative yield, and similar acetylation of the triol **36** gave the diacetate **37**. Potentiometric, spectroscopic, and chemical evidence for the configuration of **1** and its derivatives is presented. Treatment of **1** with phosgene yielded the 9,10a-carbonate **19**. An alternate route to **19** proceeded *via* conversion of **1** to the ethyl tetrol carbonate **7** and conversion of **7** to **19** by base treatment. Acetylation of **19** yielded the diacetate **20**. Acylation of **19** with ethyl chloroformate gave the 9,10a-carbonate 8-ethyl carbonate **23**. Acetylation of **7** yielded the 6a,8,9-triacetoxy-10a-ethyl carbonate **8**. Acetylation of **1** with acetic anhydride–perchloric acid, followed immediately by termination of the reaction with excess methanol, gave the 8,9,10a-triacetate **5**; reaction for a longer period gave the tetraacetate **9**. Methanolyis of **3** at room temperature smoothly yielded the diacetate **4** and similar solvolysis of **5** gave **6**. Oxalic acid hydrolysis of enol ether **30** gave the unsaturated ketone **33**, and hydrogenation of **33** followed by hydroxylation with performic acid gave triol **36**. Mineral acid hydrolysis of **30** gave **31**. Lithium and ammonia reduction of **31**, followed by chromic acid oxidation, gave **41**. Reduction with lithium aluminum hydride gave the β-equatorial alcohol **34**, whereas catalytic hydrogenation with ruthenium gave a mixture of **34** and **39**. Treatment of triol **36** with 1 molar equiv of acetic anhydride yielded the 6a-monoacetate **38**, and similar acylation of **19** yielded **21**. Arguments are advanced in support of the view that the facile acylation of the C-6a tertiary hydroxyl group is a bifunctionally catalyzed direct acylation. The buffer ratio–rate profile indicated *intermolecular* basic catalysis of the pseudo-first-order solvolysis of **3**, **5**, and **22** over the pH′ range studied. A similar study of the solvolysis of the triol monoacetate **38** indicated *intramolecular* basic catalysis, and rate enhancement approximately 10,000-fold over that expected. Possible mechanisms for the facile acylations and deacylations among perhydrobenzo[*b*]quinolizine polyol derivatives are discussed.

Facilitation of the alkaline solvolysis of an alicyclic axial acetate by a hydroxyl group bearing a 1,3-diaxial juxtaposition to the acetate is a well-established fact.[5–10] Furthermore, in suitably constituted molecules, the solvolysis may be subject also to intramolecular general base catalysis by a tertiary nitrogen atom.[1,11] We report herewith our observation of facilitation of acylation of tertiary hydroxyl groups in alicyclic 1,3-diaxial diols and evidence for the argument that, in suitable systems, the acylation may be subject also to intramolecular catalysis by a tertiary nitrogen atom.

Treatment of 1,3,4,6,6a,7,8,9,10,10a,11,11a-dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol (**1**)[12,13] with acetic anhydride in pyridine at room temperature yielded the 6a,8,9-triacetate **3**, in practically quantitative yield. Acetyl determination indicated that **3** was a triacetate, and the nmr spectrum shows three acetate methyl signals, at τ 7.91, 7.97, and 7.99. The infrared spectrum in Nujol shows carbonyl absorption nicely resolved into three bands at 5.74, 5.80, and 5.90 μ.

(1) Part IX: S. M. Kupchan, S. P. Eriksen, and Y.-T. S. Liang, *J. Am. Chem. Soc.*, **88**, 347 (1966).

(2) This work was presented, in part, at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, Abstracts, p 101K.

(3) This investigation was supported by Public Health Service Research Grant HE-02275, from the National Heart Institute.

(4) National Institutes of Health Predoctoral Fellow, 1963–1966.

(5) S. M. Kupchan and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 3864 (1956).

(6) H. B. Henbest and B. J. Lovell, *Chem. Ind.* (London), 278 (1956); *J. Chem. Soc.*, 1965 (1957).

(7) S. M. Kupchan, W. S. Johnson, and S. Rajagopalan, *Tetrahedron*, 7, 47 (1959).

(8) S. M. Kupchan and C. R. Narayanan, *J. Am. Chem. Soc.*, **81**, 1913 (1959).

(9) R. West, J. J. Korst, and W. S. Johnson, *J. Org. Chem.*, **25**, 1976 (1960).

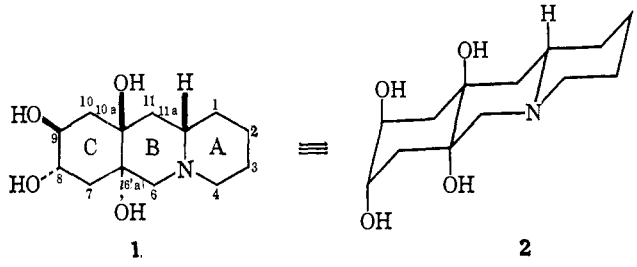
(10) S. M. Kupchan, S. P. Eriksen, and M. Friedman, *J. Am. Chem. Soc.*, **84**, 4159 (1962); **88**, 343 (1966).

(11) S. M. Kupchan, S. P. Eriksen, and Y.-T. Shen, *ibid.*, **85**, 350 (1963).

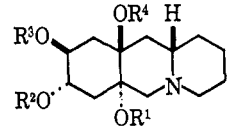
(12) S. M. Kupchan, G. R. Flouret, and C. A. Matuszak, *J. Org. Chem.*, **31**, 1707 (1966).

(13) All asymmetric synthetic products described are racemic mixtures. Only one optical antipode for each is drawn for convenience of representation and discussion. In the representation of the quinolizidine derivatives the electron pair on nitrogen is understood to project downward, and a heavy-line bond to the 11a hydrogen indicates the *trans*-quinolizidine configuration.

In a similar manner, acetylation of the 6a,8,10a-triol **36** yielded the 6a,8-diacetate **37**, which shows acetate methyl signals at τ 7.94 and 8.01. In contrast, attempted acetylation of the ditertiary glycol **13**[12] under the same conditions resulted in almost complete recovery of starting material; partial acylation to **14** could be effected only by prolonged acylation at elevated temperature. The latter observations support the view that the hydroxyl group at C-8 facilitates the acetylation of the C-6a hydroxyl group in **1** and **36**. Furthermore, the ease of acylation of the tertiary hydroxyl group at C-6a in **1** and **36** contrasts markedly



1 **2**



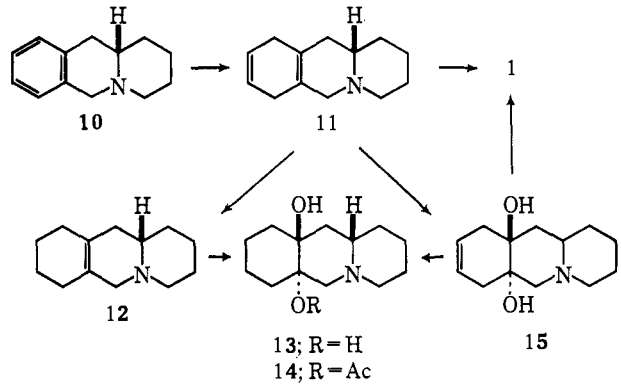
3, $R^1 = R^2 = R^3 = Ac$; $R^4 = H$
4, $R^1 = R^2 = Ac$; $R^3 = R^4 = H$
5, $R^1 = H$; $R^2 = R^3 = R^4 = Ac$
6, $R^1 = R^2 = H$; $R^3 = R^4 = Ac$
7, $R^1 = R^2 = R^3 = H$; $R^4 = OCOC_2H_5$
8, $R^1 = R^2 = R^3 = Ac$; $R^4 = OCOC_2H_5$
9, $R^1 = R^2 = R^3 = R^4 = Ac$

with the inertness toward similar treatment of tertiary hydroxyl groups in structurally related steroidal 1,3-diaxial diols.[14] The latter observation supports the view that the acylation of the C-6a hydroxyl group may be facilitated by the nearby tertiary nitrogen atom, and may, therefore, be an instance of intramolecular bifunctional catalysis of esterification.

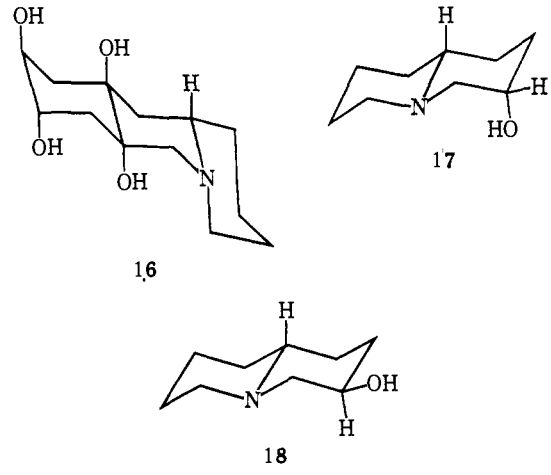
Because of the potential significance of the acylation of perhydrobenzo[*b*]quinolizine polyol derivatives as unique nonenzymatic examples of intramolecular bifunctional catalysis of ester formation, detailed and systematic studies of the stereochemistry of the compounds were undertaken. The results of the stereochemical studies constitute the subject of the sequel.

The key compound, tetrol **1**, was synthesized by Birch reduction of **10** to the diene **11**, followed by hydroxylation of **11** with hydrogen peroxide in formic acid.[12] Alternatively, hydroxylation of diene **11** with 1 molar equiv of hydrogen peroxide in formic acid yielded the unsaturated glycol **15**, and hydroxylation of **15** yielded **1**. The *trans* configuration was assigned to the A/B ring juncture on the grounds that the precursors in the synthetic route to **1** showed characteristic Bohlmann bands in the 3.5–3.7-μ region,[12,15] and that no epimerization at C-11a would be expected during the hydroxylation reaction. Although the tetrol **1** could exist in two conformations differing only in the configuration about the ring nitrogen (*i.e.*, **2** or **16**), the *trans* conformer **2** is strongly favored on the basis of the results of several recent studies of the relative

(14) *Cf.*, *e.g.*, P. A. Plattner, A. Furst, F. Koller, and W. Lang, *Helv. Chim. Acta*, **31**, 1455 (1948).
(15) F. Bohlmann, *Ber.*, **91**, 2157 (1958).



10 **11** **12** **13**; R = H **14**; R = Ac **15**



16 **17**

18

stability of *trans*- and *cis*-quinolizidine derivatives.[16–23]

The doubly *trans*-diaxial configuration of the tetrol system of **1**, suggested earlier[12] on the basis of its synthesis by performic acid hydroxylation and its periodic acid consumption (1.15 molar equiv), has been confirmed by potentiometric, spectroscopic, and chemical evidence. Potentiometric titrations in 80% Methyl Cellosolve indicate that the tertiary diol **13** and tetrol **1** are more basic than their diene precursor **11** (Table I). It has been shown previously that hydrogen bonding of a tertiary nitrogen to hydroxyl results in increased basicity.[24,25] Furthermore, studies of hydroxyquinolizidines have shown that intramolecular hydrogen bonding of hydroxyl to nitrogen leads to an increase in pK_a of 1.3–1.5 units.[26,27] Thus, *e.g.*, the axial 3-hydroxyquinolizidine **17** showed a pK_a of 9.87, whereas the pK_a of the equatorial isomer **18** was 8.60. The pK_a' values of **13** and **1** support the view that the

(16) S. F. Mason, K. Schofield, and R. J. Wells, *Proc. Chem. Soc.*, 337 (1963).
(17) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).
(18) R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc.*, 257 (1964).
(19) K. Brown, A. R. Katritzky, and A. J. Waring, *ibid.*, 257 (1964).
(20) N. L. Allinger and J. C. Tai, *J. Am. Chem. Soc.*, **87**, 1227 (1965).
(21) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowsky, *ibid.*, **87**, 1232 (1965).
(22) C. D. Johnson, R. A. Y. Jones, A. R. Katritzky, C. R. Palmer, K. Schofield, and R. J. Wells, *J. Chem. Soc.*, 6797 (1965).
(23) H. A. Aaron, *Chem. Ind.* (London), 1338 (1965).
(24) H. Rapoport and S. Masamune, *J. Am. Chem. Soc.*, 77, 4330 (1955).
(25) D. E. Ayer, G. Buchi, P. Reynolds-Warnhoff, and D. M. White, *ibid.*, **80**, 6146 (1958).
(26) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).
(27) C. P. Rader, R. L. Young, Jr., and H. S. Aaron, *ibid.*, **30**, 1536 (1965).

Table I. Nmr Correlations[a]

		Acetates				Carbinol protons				C-6 protons			
	pK_a'[b]	C-6a	C-8	C-9	C-10a	C-8	W_H	C-9	W_H	Eq	J	Ax	J
6a,8,9,10a-Tetrol **1**	8.14					5.92	9	6.19	10	7.32	11	7.85	11
6a,8,9,10a-Tetrol 6a,8,9-triacetate **3**	6.50	7.97	7.99	7.91		4.93[f]	7			6.72	11	7.65	11
6a,8,9,10a-Tetrol 6a,8-diacetate **4**	6.67	7.97	8.00			5.00	7	6.01	5	6.67	12	7.62	12
6a,8,9,10a-Tetrol 8,9,10a-triacetate **5**	6.67		7.99	7.93	7.96		4.92–5.06[e]			7.42	12	7.75	12
6a,8,9,10a-Tetrol 9,10a-diacetate **6**	7.05			7.97	8.02	6.22	8	4.93	9	7.42	11	7.75	11
10a-Ethyl carbonate **7**	7.17						6.02[e]			7.35	11	7.70	11
6a,8,9-Triacetate 10a-ethyl carbonate **8**	5.34	8.00	8.02	7.95				5.00[f]	7	6.62	13	7.63	13
6a,8,9,10a-Tetrol 6a,8,9,-10a-tetraacetate **9**	5.64	7.94	7.99	7.93	7.96			4.98[f]	8	6.60	12	7.72	12
Diene **11**	7.40												
6a,10a-Diol **13**	8.42									7.47	11	7.87	11
3α-(ax)-Hydroxyquinolizidine **17**	9.87[c]					6.26	6.5[d]						
3β-(eq)-Hydroxyquinolizidine **18**	8.60[c]					6.38	19[d]						
9,10a-Carbonate **19**	6.49					5.90	10	5.38	8	7.40	12	7.67	12
9,10a-Carbonate 6a, 8-diacetate **20**	5.16	7.95	7.91			4.72	9	5.31	7	6.50	13	7.67	13
9,10a-Carbonate 6a-monoacetate **21**	5.61	7.95				5.75	8	5.42	8	6.53	13	7.73	13
9,10a-Carbonate 8-monoacetate **22**	6.40		7.90			4.87	10	5.39	9	7.32	12	7.77	12
9,10a-Carbonate 8-ethyl carbonate **23**	6.30					4.95	10	5.33	9	7.30	12	7.73	12
9,10a-Carbonate 6a-acetate 8-ethyl carbonate **24**	5.27	7.94				4.95	10	5.33	10	6.53	13	7.72	13
8β-(eq)-Ol **34**	7.87					6.43	22						
8β-(eq)-Ol acetate **35**	7.52		7.99			5.25	22						
6a,8,10a-Triol **36**	8.43					6.02	7			7.45	11	7.82	11
6a,8,10a-Triol 6a,8-diacetate **37**	6.98	7.94	8.01			4.84	9			6.58	12	7.73	12
6a,8,10a-Triol 6a-monoacetate **38**	7.39	7.97				5.90	11			6.58	12	7.75	12
8α-(ax)- Ol **39**	8.02					5.93	9						
8α-(ax)-Ol acetate **40**	7.71		8.00			4.91	7						

[a] In deuteriochloroform unless otherwise specified; chemical shifts expressed in τ, W_H = band width at one-half the peak height in cps, J = cps. [b] 80% by volume Methyl Cellosolve (see Experimental Section) unless otherwise specified. [c] In water. [d] In carbon tetrachloride; C-3 carbinol proton. [e] Broad, fused signal (2 H). [f] Both carbinol protons apparently have identical chemical shifts.

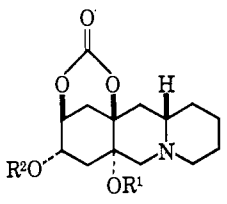
C-6a hydroxyl in each is hydrogen bonded to the nitrogen atom and is, therefore, α oriented.

The nmr data summarized in Table I support assignment of axial conformation to the hydroxyl groups at C-8 and C-9 in **1**. Thus, the signals for the two protons on hydroxyl-bearing carbons show half-widths nearly identical with the equatorial carbinol proton of the C-8 axial alcohol **39**. It has been found earlier that an axial carbinol proton (equatorial alcohol) usually resonates at a higher field and shows a larger half-width (W_H = 20–22 cps) than an equatorial proton (W_H = 7–10 cps).[28,29] The axial carbinol proton of **18** shows a signal at τ 6.38 (W_H = 19 cps) while the equatorial proton of **17** shows a signal at τ 6.26 (W_H = 6.5 cps).[26] As the data in Table I indicate, the carbinol protons in tetrol **1** exhibit signals at τ 5.92 (W_H = 9 cps) and 6.19 (W_H = 10 cps), in good accord with assignment of axial configuration to the two secondary alcohol groups.

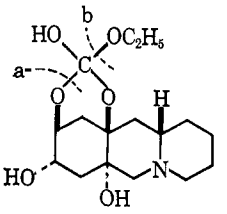
Attempts at conversion of tetrol **1** to an acetonide derivative were unsuccessful. However, treatment of **1** with phosgene in pyridine yielded the 9,10a-carbonate **19**. An alternative route to **19** proceeded *via* the ethyl tetrol carbonate **7**. Treatment of **1** with ethyl chloroformate in tetrahydrofuran yielded the hydrochloride salt of **7**, and careful basification of the hydrochloride salt in the cold with simultaneous extraction with chloroform gave **7**. When the hydrochloride salt was treated with base at room temperature, the 9,10a-carbonate **19** was obtained. Acetylation of **19** yielded the 9,10a-carbonate 6a,8-diacetate **20**, the anticipated product based on acetylation of tetrol **1** to the 6a,8,9-triacetate **3**.

The aforementioned selective acylation with ethyl chloroformate of the tertiary C-10a hydroxyl group is noteworthy. The assignment of structure **7** for the ethyl tetrol carbonate is based largely on its nmr spectral characteristics. The nmr spectrum indicates the presence of one ethyl group, and shaking the deuteriochloroform solution of **7** with deuterium oxide resulted in exchange of three protons. Earlier studies have shown that acylation of a secondary alcohol by carbonate formation results in a downfield shift of the carbinol proton.[29,30] The two carbinol protons of **7**, however, resonate in the τ 6.02 region, very near to

(28) E. W. Garbisch, Jr., *J. Org. Chem.* 27, 4249 (1962).
(29) R. U. Lemieux, R. K. Kullnig, W. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, 80, 6098 (1958).
(30) J. N. Schoolery and M. T. Rogers, *ibid.*, 80, 5121 (1958).



19; $R^1 = R^2 = H$
20; $R^1 = R^2 = Ac$
21; $R^1 = Ac$; $R^2 = H$
22; $R^1 = H$; $R^2 = Ac$
23; $R^1 = H$; $R^2 = OCOC_2H_5$
24; $R^1 = Ac$; $R^2 = OCOC_2H_5$



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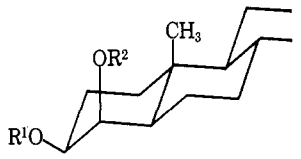
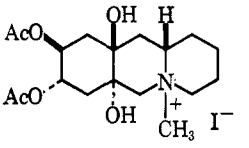


26, $R^1 = Ac$; $R^2 = H$
27, $R^1 = H$; $R^2 = Ac$



28

those of tetrol **1**, at τ 5.92 and 6.19. In contrast, the C-9 proton of cyclic carbonate **19** resonates at τ 5.38 (W_H = 8 cps), whereas the C-8 proton signal is at τ 5.90 (W_H = 10 cps). Acylation of the C-8 hydroxyl in **19** with ethyl chloroformate in pyridine yielded the 9,10a-carbonate 8-ethyl carbonate **23**, which shows a signal for the C-8 carbinol proton at τ 4.95 (W_H = 10 cps). Finally, acetylation of **7** yielded the 6a,8,9-triacetoxy-10a-ethyl carbonate **8**. The infrared spectrum of **8** indicates the absence of hydroxyl, and the nmr spectrum shows three acetate methyl signals and C-8 and C-9 carbinol proton signals with predicted shifts (see Table I). The ethyl carbonate moiety is apparently more highly hindered in the fully acetylated derivative **8** than in the precursorial ethyl tetrol carbonate **7**. The nmr spectrum of **7** shows the usual pattern for an ethoxy group: quartet at τ 5.87 (J = 7 cps) and triplet at 8.72 (J = 7 cps). The nmr spectrum of **8** shows a triplet at τ 8.77 (J = 7 cps) and a complicated methylene multiplet at 5.84. It appears that the rotation of the methylene carbon in **8** may be hindered, resulting in nonequivalence of the methylene protons of the ethyl group.[31]

Attempted acylation of the tertiary diol **13** with ethyl chloroformate under a variety of conditions was unsuccessful. The latter observation lends support to the view that the secondary alcohol at C-9 plays a role in the acylation of the C-10a tertiary hydroxyl. A possible route might proceed by prior acylation at C-9 followed by formation of the orthoester intermediate **25**. Cleavage of the intermediate in a neutral medium would then proceed *via* route "a," to yield the 10a-ethyl carbonate **7**, whereas cleavage under alkaline conditions would proceed *via* route "b," to yield the 9,10a-cyclic carbonate **19**. At first sight, the postulated migration of an acyl group from C-9 to C-10a would appear to involve moving to a higher energy state. However, ample analogy exists for intramolecular migration of an acyl group to the more highly hindered hydroxyl group of a diol system. Thus, the 3-acetate of cholestane-3β,4β-diol (**26**) is isomerized to the 4-acetate **27** by treatment with basic alumina for 10 hr.[32] Treatment of either of the diol monoacetates with sodium borohydride in 2-propanol[32] (or with aqueous pyridine[33]) resulted in formation of substantially the same equilibrated mixture, containing *ca.* 20–30% of **26** and *ca.* 70–80% of **27**. It was proposed that either the size of the oxygen atom in the acyloxy group may be effectively diminished by the electron-attracting properties of the carbonyl group,[32] or the effective size of the *solvated* hydroxyl group may be greater than that of the acyl group.[33] Similar rationalizations may be advanced for formation of the 10a-ethyl carbonate **7** by prior acylation at C-9 and migration *via* **25**.

When tetrol **1** was acetylated by treatment in acetic anhydride with perchloric acid, followed immediately by termination of the reaction with excess methanol, the 8,9,10a-triacetate **5** was obtained. When the same acetylation reaction was allowed to proceed for 12 hr before termination with methanol, the 6a,8,9,10a-tetraacetate **9** resulted. Tetraacetate **9** could also be obtained by perchloric acid catalyzed acetylation of the 6a,8,9-triacetate **3**, or by acetic anhydride–pyridine acetylation of the 8,9,10a-triacetate **5** at elevated temperature. However, attempted acetic anhydride–pyridine acetylation of the 6a,8,9-triacetate **3**, under the same conditions, was unsuccessful. Comparison of the nmr spectra of the isomeric triacetates **3** and **5** revealed an interesting, and potentially useful, difference. Acetylation at C-6a apparently results in a downfield shift of the signal for the equatorial proton. There are signals for five protons in the τ 7.5–8.0 region, assignable to the five protons on carbons adjacent to the nitrogen. The low-field signals can be assigned to the C-4 and C-6 equatorial protons, and the upfield signals to the C-4, C-6, and C-11a axial protons.[34,35] Of the five protons, the two at C-6 are isolated from the rest, and would be expected to appear as a pair of doublets. Such a pair is found in the nmr spectrum of tetrol **1** at τ 7.32 (J = 11 cps) for the equatorial proton, and at τ 7.85 (J = 11 cps) for the axial proton. Following acetylation to **3**, the signals were found to have shifted to τ 6.72 (J = 11 cps) and 7.65 (J = 11 cps), respectively. Double resonance experiments showed that the protons exhibiting doublets at τ 6.72 and 7.65 are coupled.[36] As the data in Table I indicate, all compounds which bear an acetate at C-6a exhibit a downfield shift in the signal for the equatorial proton.

Steric hindrance to the nitrogen in the 6a,8,9-triacetate **3** was indicated by the slow rate of methiodide formation. Whereas methiodide formation from the tetrol **1** was complete in 48 hr, completion of methiodide formation from **3** required 6 days. Furthermore, acetylation of tetrol methiodide yielded the 8,9-diacetate methiodide **28**. The failure to form a 6a,8,9-triacetate may be attributable to both steric bulk of the methiodide and the change in the electronic character of the nitrogen.

(31) S. M. Kupchan, S. Kubota, E. Fujita, S. Kobayashi, J. H. Block, and S. A. Telang, *J. Am. Chem. Soc.*, **88**, 4212 (1966).

(32) S. M. Kupchan, P. Slade, R. J. Young, and G. W. A. Milne, *Tetrahedron*, **18**, 499 (1962).

(33) S. J. Angyal and G. J. H. Melrose, *J. Chem. Soc.*, 6494 (1965).

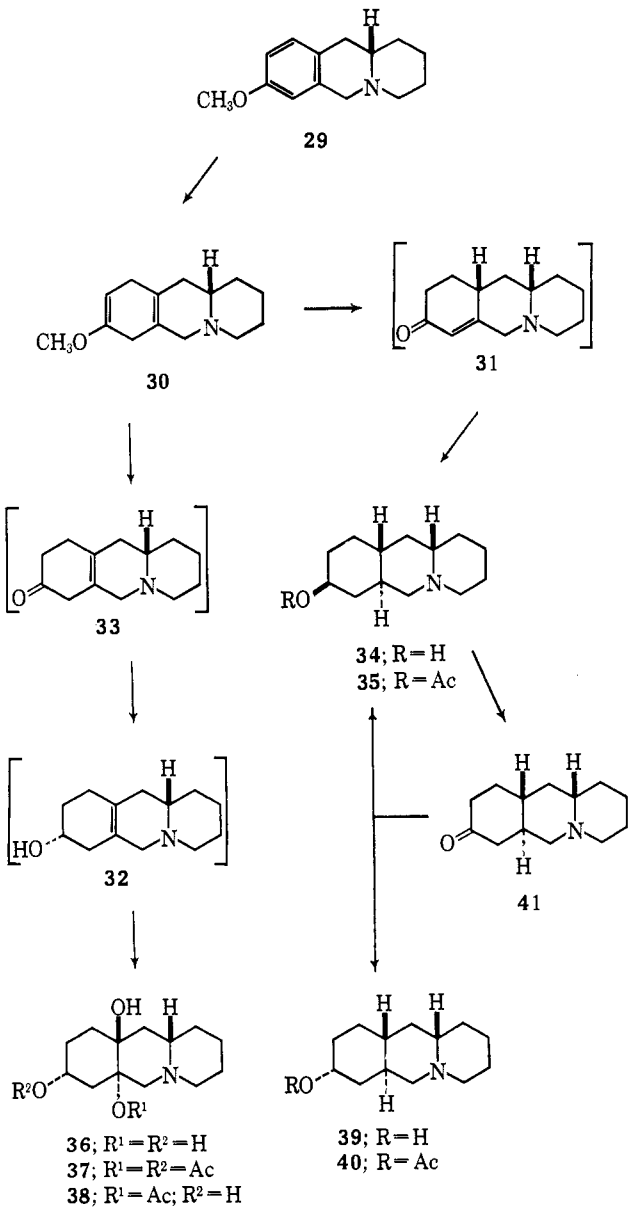
(34) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Letters*, 2553 (1964).

(35) F. Bohlmann, D. Schumann, and C. Arndt, *ibid.*, 2705 (1965).

(36) We thank Dr. Ross Pitcher of Varian Associates for the double resonance experiments.

The C-9 acetate of **3** bears a 1,3-diaxial relationship to the C-10a hydroxyl group, and the C-8 acetate of **5** bears the same relationship to the C-6a hydroxyl group. Accordingly, it was expected that the acetate esters would undergo selective and rapid methanolysis.[5-10] In fact, allowing a 9:1 methanol–water solution of **3** to stand at room temperature smoothly yielded the tetrol 6a,8-diacetate **4**. Treatment of **4** with phosgene afforded the cyclic carbonate 6a,8-diacetate **20**, which had been prepared earlier *via* an alternate route. Room temperature methanolysis of **5** yielded the 9,10a-diacetate **6**, which was acetylated with acetic anhydride in pyridine at room temperature to the tetrol tetraacetate **9**.

Corroborative evidence for the foregoing interpretations of the reactions and stereochemistry of derivatives of tetrol **1** was obtained from studies of triol **36** and the epimeric monohydroxy compounds **34** and **39**. The



enol ether **30**, available by Birch reduction of **29**,[12] was hydrolyzed with oxalic acid in methanol to yield the β,γ-unsaturated ketone **33**. Attempts at peracid oxidation of **33** yielded intractable mixtures of products. Hydrogenation of **33** with 5% ruthenium on carbon in ethanol (a procedure known to favor production of axial alcohols in related systems[37]) yielded a pale oil with spectral properties in accord with structure **32**. Direct hydroxylation with hydrogen peroxide in excess formic acid gave **36**. The nmr spectrum of **36** shows a signal for a single carbinol proton at τ 6.02 (W_H = 7 cps), indicative of the presence of an axial secondary alcohol at C-8. Triol **36** consumed only 0.25 molar equiv of periodic acid in 20 hr, in accord with assignment of *trans* configuration to the ditertiary glycol.

When enol ether **30** was hydrolyzed with mineral acid according to the procedure described earlier, the product was largely the α,β-unsaturated ketone **31**.[12] Lithium and ammonia reduction of **31** afforded an oily product, which, on the basis of thin layer chromatographic analysis, consisted largely of the equatorial alcohol **34** (*vide infra*). Chromic acid oxidation of **34** gave a ketone isomeric with the *cis* B/C ketone obtained earlier by an alternate route.[12] By analogy to the stereochemical course of lithium–ammonia reduction of related systems,[38] the new ketone was assigned the *trans* B/C ketone structure **41**. Reduction of **41** with lithium aluminum hydride in ether gave the equatorial alcohol **34**. The same alcohol was produced by reduction with sodium borohydride or catalytic hydrogenation with platinum in ethanol. Hydrogenation of **41** in 50% acetic acid with a platinum catalyst yielded two alcohols in approximately equal amounts. The first isomer eluted from basic alumina was the same as that obtained by the chemical reductions and was formulated as the β-equatorial isomer **34**.[39a] In accord with this assignment, the nmr spectrum of **34** shows a signal for an axial carbinol proton at τ 6.43 (W_H = 22 cps). Acetylation of **34** to **35** was accompanied by the expected downfield shift of the C-8 proton to τ 5.25 (W_H = 22 cps). The more polar alcohol, formed by catalytic reduction in an acidic medium,[39a] was assigned the α-axial configuration **39**. The nmr spectrum of **39** shows a signal for an equatorial carbinol proton at τ 5.93 (W_H = 9 cps), and the spectrum of its acetate **40** shows a signal for the C-8 proton at τ 4.91 (W_H = 7 cps). In further accord with expectation,[39b] the infrared spectrum of the equatorial alcohol **34** shows C–O stretching at lower wavelength (9.75 μ) than that of the axial alcohol **39** (10.00 μ).

It appears likely that the facile acylation of the C-6a tertiary hydroxyl group is an instance of intramolecular catalysis of direct esterification. The alternative pathway, *via* prior acetylation at C-8 followed by transesterification to C-6a, is rendered unlikely by the observations which follow. (1) Treatment of triol **36** at room temperature with 1 molar equiv of acetic anhydride in pyridine–benzene yielded the 6a-monoacetate **38**. The nmr spectrum shows signals for the acetate methyl at τ 7.97, the C-8 carbinol proton (unchanged) at τ 5.90, and the C-6 equatorial proton (shifted downfield) at τ 6.58 (J = 12 cps). In accord with this structural assignment, the pK_a' of **38** was found to be 7.39, some 1.04 units lower than that of triol **36**.

(37) C. P. Rader, G. E. Wicks, R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **29**, 2252 (1964).

(38) *Cf.* G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 176 (1964).

(39) *Cf.* E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965: (a) pp 115–120; (b) p 143.

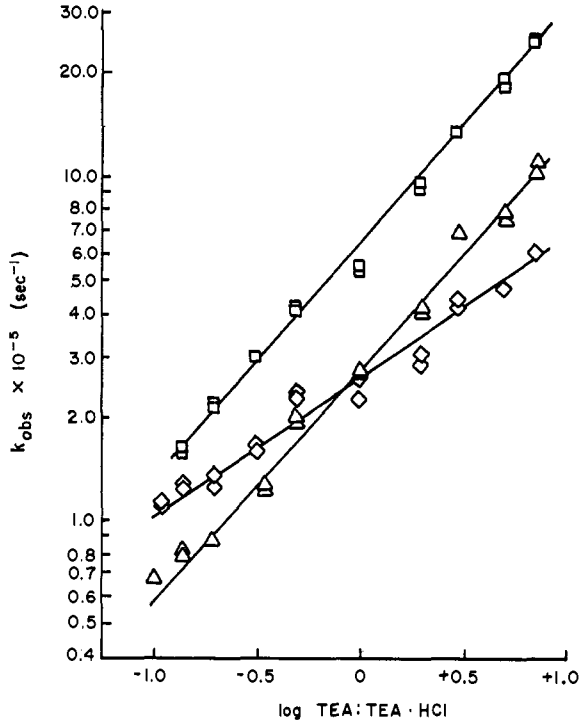


Figure 1. Logarithmic plot of the rate of methanolysis of 6a,8,9-triacetate **3**, Δ; 8,9,10a-triacetate **5**, ◇; and 9,10a-carbonate 8-monoacetate **22**, □, against logarithm of buffer ratio in 1.2 *M* triethylamine–triethylammonium chloride buffers at 25° and ionic strength 1.2 (solvent system, 9:1 methanol–water).

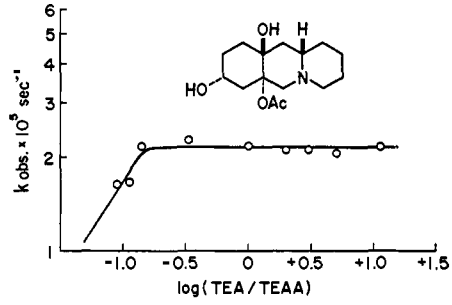


Figure 2. Logarithmic plot of the rate of methanolysis of triol monoacetate **38** (0.014 *M*) against logarithm of buffer ratio in 0.12 *M* triethylamine–triethylammonium acetate buffers at 25° and ionic strength 0.09 (solvent system, 9:1 methanol–water).

In a similar manner, acylation of the 9,10a-carbonate **19** with 1 molar equiv of acetic anhydride in pyridine yielded the 6a-monoacetate **21**. The nmr spectrum of **21** shows signals for the C-8 carbinol proton (unchanged) at τ 5.75 (W_H = 8 cps) and the C-6 equatorial proton (shifted downfield) at τ 6.53 (J = 13 cps). Treatment of **21** with excess acetic anhydride in pyridine at room temperature gave the 6a,8-diacetate **20**. (2) Treatment of the 9,10a-carbonate **19** with acetic anhydride in perchloric acid in the cold, followed immediately by termination of the reaction with excess methanol, yielded the 8-monoacetate **22**. The nmr spectrum of **22** shows signals for the C-6 equatorial proton (unchanged) at τ 7.32 (J = 12 cps) and C-8 carbinol proton (shifted downfield) at 4.87 (W_H = 10 cps). It was not possible to acetylate **22** further with excess acetic anhydride in pyridine, even at elevated temperature. Similarly, acetylation of the cyclic

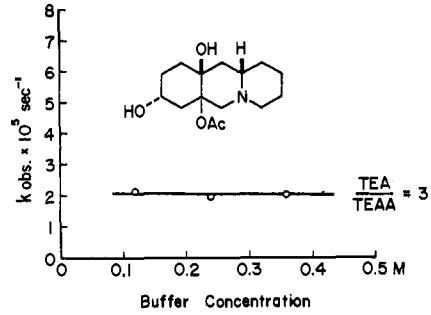


Figure 3. Plot of the observed pseudo-first-order rate constant (k_{obsd}) for solvolysis at 25° (μ = 0.09 *M*) of triol monoacetate **38** *vs.* concentration of triethylamine–triethylammonium acetate at constant buffer ratio (3:1).

carbonate **19** with excess acetic anhydride in pyridine yielded a two-component mixture, shown by tlc to be a mixture of the 6a,8-diacetate **20** and the 8-monoacetate **22**. (3) The 8,9,10a-triacetate **5** and the 9,10a-carbonate 8-ethyl carbonate **23** were recovered essentially unchanged after attempted acetylation at room temperature. Acetylation to the respective 6a-acetate esters (**9** and **24**) could be accomplished only by prolonged heating at elevated temperature. (4) Migration of acetate in the opposite direction, *i.e.*, from C-6a to C-8, has been observed in studies of cyclic carbonate 8-monoacetate **21** and triol monoacetate **38** (*vide infra*).

Direct study of the kinetics of intramolecular catalysis of acylation reactions is difficult, because of the nature of the reagents involved. On the other hand, deacylation reactions lend themselves more readily to kinetic investigation, and a preliminary study of the solvolysis of several perhydrobenzo[*b*]quinolizine polyol acetates consequently was undertaken. In the rate studies, acetate esters were methanolyzed (unless otherwise noted) in solutions prepared by dissolving each compound and the appropriate buffer in 9:1 methanol–water. The rate of production of methyl acetate, the solvolysis product, was determined by direct gas chromatographic analysis of the reaction mixture, as described earlier.[10]

The buffer ratio–rate profile using 1.2 *M* triethylamine–triethylammonium chloride (Figure 1) indicated the *intermolecular* basic catalysis of the pseudo-first-order solvolysis of **3**, **5**, and **22**.[10] On the other hand, intramolecular basic catalysis of the solvolysis of the triol monoacetate **38** was indicated by the experimentally determined buffer ratio–initial rate profile (Figure 2). In the horizontal portion of the curve, the ring nitrogen is essentially nonprotonated and serves as an intramolecular base for the normally base-catalyzed solvolysis of 1,3-diaxial hydroxy acetates.[10] As the buffer is made more acidic, the rate drops off, decreasing approximately in proportion to the protonation of the ring nitrogen. In the "intramolecular base-catalyzed" region, that is, the horizontal portion of the curve, there is no apparent change in rate with variation of the buffer concentration. Thus, with a triethylamine (TEA)–triethylammonium acetate (TEAA) ratio of 3 (Figure 3), the participation of the external base appears to be nearly negligible in effect when compared with the effect of internal tertiary amine.

From the relative rates of solvolysis of the respective acetate esters (Table II), it is evident that the rate of the

doubly assisted methanolysis of the C-6a acetate ester **38** was 580 times faster than that of the axial 8-acetate **39**. Since secondary alcohol esters are normally hydrolyzed 17 times faster than tertiary alcohol esters,[40] the approximate rate enhancement was 10,000-fold over that expected for **38**. On the other hand, the rate of solvolysis of the 6a,10a-diol 6a-monoacetate **14** was 59 times faster than that of the axial 8-monoacetate **39**. Hence, an intramolecular role as a basic catalyst can be attributed to the nitrogen. However, the rate of methanolysis of **14** was one-tenth that of the 6a,8,10a-triol 6a-monoacetate **38**, in support of the view that the solvolysis of the acetate ester **38** is facilitated by the hydroxyl at C-8 (in a *cis*-1,3 juxtaposition) in addition to the intramolecular catalysis by ring nitrogen.

Table II. Rates of Ester Solvolysis at 1:3 Triethylamine–Triethylammonium Acetate Buffer (0.12 *M*) and Ionic Strength 0.09 *M* at

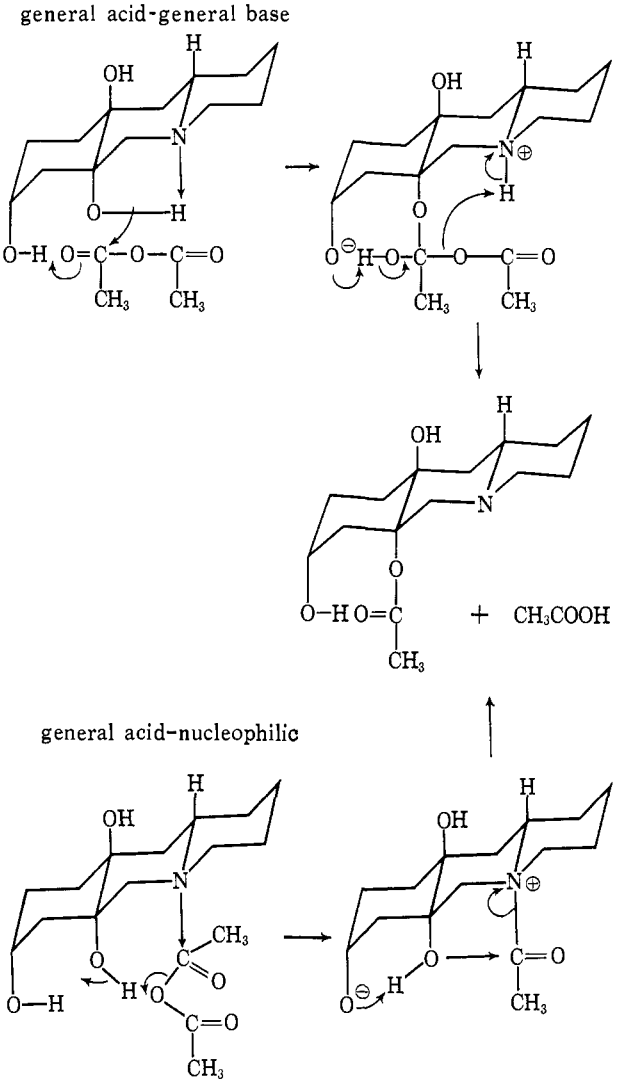
Compound	k_{obsd}, sec^{-1}	Relative rates
8α-(ax)-Ol acetate **40**[a]	3.91×10^{-8}	1
8β-(eq)-Ol acetate **35**[a]	6.74×10^{-8}	1.7
6a,8,10a-Triol 6a,8-diacetate **37**	2.34×10^{-7}	6
6a,10a-Diol 6a-monoacetate **14**	2.30×10^{-6}	59
9,10a-Carbonate 6a-monoacetate **21**	9.08×10^{-6}	232
6a,8,9,10a-Tetrol 6a,8,9-triacetate **3**	1.28×10^{-5}	330
6a,8,9,10a-Tetrol 8,9,10a-triacetate **5**	1.97×10^{-5}	500
6a,8,10a-Triol 6a-monoacetate **38**	2.28×10^{-5}	580
Cevadine D-orthoacetate diacetate[a,b]	2.5×10^{-5}	640
9,10a-Carbonate 8-monoacetate **22**	2.94×10^{-5}	750
Cevadine diacetate[a,b]	7.5×10^{-5}	1900

[a] Data obtained in solutions in which chloroform constituted 10% of the total volume. [b] Reference 1.

There was a departure from strictly pseudo-first-order kinetics after the solvolysis of **38** and **21** had proceeded to some extent, and the pseudo-first-order rate constants discussed were calculated from the slopes of the initial portions of the kinetic plots. After 4 hr, the rate of solvolysis of **38** began to decrease. To evaluate the hypothesis that the decrease in rate might be attributed, in part, to transesterification of the acetate to C-8, the reaction in 9:1 CD_3OD–D_2O was studied by nmr spectrometry. As noted above, acylation of a secondary alcohol results in a downfield shift in the secondary carbinol proton signal. The nmr spectrum of a solution of **38** in CD_3OD–D_2O showed a single acetate peak and a broad multiplet for the C-8 carbinol proton at *ca.* τ 6.0. After 4 hr, the nmr spectrum showed two acetate signals and two broad multiplets at *ca.* τ 6.0 (C-8 proton of alcohol) and *ca.* τ 5.0 (C-8 proton of acetate) in a 1:1 ratio. After 22 hr, the nmr spectrum showed one acetate methyl peak and a single broad multiplet at *ca.* τ 6.0. The results are in accord with the view that the solvolysis of **38** is accompanied by a slow transesterification to C-8, and the 8-monoacetate in the triol series methanolyzes at a slower rate than the 6a-monoacetate **38**. In contrast, the 9,10a-carbonate 6a-monoacetate **21** showed a slow initial rate (*ca.* half that of **38**), which began to increase after 3 hr. The presence of 9,10a-carbonate 8-monoacetate **22** was detected by tlc, and the concentration of **22** increased with time with the less basic buffer ratios. With more basic buffer ratios, very little of **22** appeared, presumably because the compound was methanolyzed as rapidly as it formed. To secure acetate **22** on a preparative scale, **21** was treated in 9:1 *t*-butyl alcohol–water with triethylamine. After 5 days, the migration was complete and no detectable solvolysis had occurred. Hence, the solvolysis of **21** is accompanied by transesterification to C-8, and the 8-monoacetate methanolyzes at a faster rate than the 6a-monoacetate **21**. The view that introduction of the 9,10a-carbonate moiety into the tetrol structure causes profound stereoelectronic changes is supported by examination of the pK_a' measurements in Table I. Thus, whereas tetrol **1** has a pK_a' of 8.14, the 9,10a-carbonate **18** has a pK_a' of 6.49. Apparently, introduction of an acyl group at C-10a alone is sufficient to cause a base-weakening effect, for 10a-ethyl tetrol carbonate has a pK_a' of 7.17. The 10a-ethyl tetrol carbonate 6a,8,9-triacetate **8** shows a pK_a' of 5.34, 1.16 units less than that of the tetrol 6a,8,9-triacetate **3**.

The ease of direct acylation of the tertiary hydroxyl group at C-6a in **1**, **19**, and **36** appears to be attributable to facilitation by the C-8 secondary hydroxyl group and the nearby tertiary nitrogen atom. Two alternative mechanisms for the bifunctional intramolecular catalysis are illustrated in Scheme I, involving general acid–general base catalysis or general acid–nucleophilic

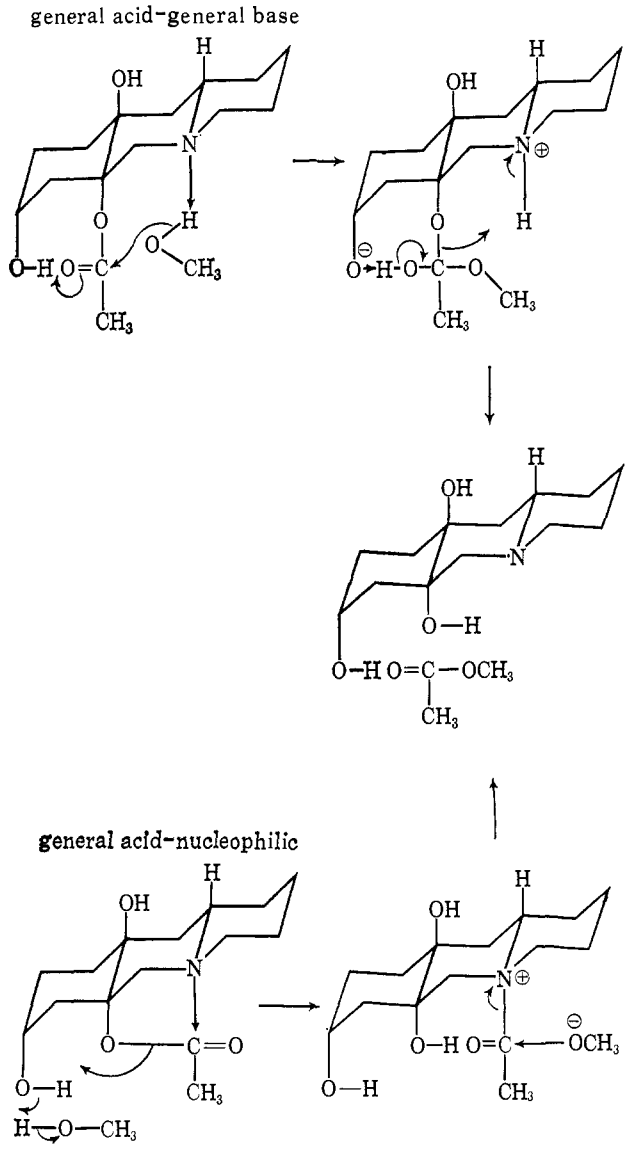
Scheme I



(40) *Cf.* J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p 275.

catalysis. In a similar manner, the initial facile solvolysis of the C-6a acetate **38** may proceed by the alternative bifunctionally catalyzed reactions illustrated in Scheme II. Studies aimed at further elucidation of

Scheme II



the mechanisms of the respective reactions are in progress.

Considerable evidence has been accumulated during the past few years to indicate that esters are catalytically hydrolyzed by esteratic enzymes through a double displacement reaction involving an acylated enzyme intermediate. The formation of acyl-enzyme takes place after formation of an enzyme–substrate complex, and undoubtedly involves intracomplex participation of specific catalytic groups.[41,42] The deacylation step apparently involves intramolecular catalysis by the same enzymatic components.[43-45] The facile acylations and deacylations among perhydrobenzo[*b*]quinolizine polyol derivatives appear to involve unusual intramolecular bifunctional catalyses and may have considerable significance as appropriate models for esteratic enzyme action.

(41) H. Gutfreund and J. M. Sturtevant, *Biochem. J.*, **63**, 656 (1956).
(42) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).
(43) M. L. Bender, G. R. Schonbaum, G. A. Hamilton, and B. Zerner, *J. Am. Chem. Soc.*, **83**, 1255 (1961).
(44) R. M. Krupka and K. J. Laidler, *ibid.*, **83**, 1458 (1961).
(45) M. L. Bender and F. J. Kézdy, *ibid.*, **86**, 3704 (1964).

Experimental Section

Melting points were determined on a Fisher-Johns hot stage and have been corrected. Ultraviolet absorption spectra were determined in 95% ethanol on a Beckman DK-2A ratio recording spectrophotometer. Infrared spectra were determined on Beckman IR-5A and Perkin-Elmer Model 421 recording spectrophotometers in chloroform unless otherwise specified. Nuclear magnetic resonance spectra were determined on a Varian Associates A-60 recording spectrometer at 60 Mc in deuteriochloroform unless otherwise stated. The double resonance studies were performed on a Varian Associates HA-100 recording spectrometer at 100 Mc. Chemical shifts have been recorded in τ values downfield from the internal standard tetramethylsilane. Microanalyses were performed by J. F. Alicino, Metuchen, N. J., and Spang Microanalytical Laboratory, Ann Arbor, Mich. 48106. Skellysolve B refers to a petroleum ether fraction boiling at 60–68° and Skellysolve C to a fraction boiling at 90–100°. Thin layer chromatograms were run on Brinkmann silica gel G in 9:1 CH_3OH–$CHCl_3$ or 3:7 CH_3OH–$CHCl_3$.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol Hydrochloride (1·HCl). An ether solution of hydrogen chloride was added to a solution of tetrol **1**[12] (1 g) in ethyl acetate (150 ml) until no further precipitate formed. The mixture was filtered, yielding solid material which was recrystallized from ethanol–ethyl acetate to yield 0.995 g, mp 284–285° dec. The infrared spectrum in Nujol shows hydroxyl bands at 2.99 and 3.11 μ.

Anal. Calcd for $C_{13}H_{24}ClNO_4$: C, 53.14; H, 8.23; Cl, 12.07; N, 4.77. Found: C, 53.19; H, 8.27; Cl, 12.06; N, 4.81.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 6a,8,9-Triacetate (3). A solution of pyridine (10 ml, previously dried over potassium hydroxide), acetic anhydride (4 ml, 0.04 mole equiv), and tetrol **1** (0.5 g, 0.0019 mole equiv) was allowed to stand overnight. The mixture was cooled in an ice bath, made basic with 7 *N* ammonium hydroxide, and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The pyridine in the residue was removed by codistillation with benzene under reduced pressure. The solid residue (0.686 g) was recrystallized from ethyl acetate–Skellysolve B to yield 0.507 g (mp 184–185°) of white crystalline material. The infrared spectrum shows a hydroxyl band at 2.81 and a strong broad carbonyl band at 5.75 μ. The infrared spectrum in Nujol shows three carbonyl peaks, at 5.74, 5.80, and 5.90 μ. The nmr spectrum shows the loss of one proton upon shaking with D_2O.

Anal. Calcd for $C_{19}H_{29}NO_7$: C, 59.51; H, 7.62; N, 3.65; neut equiv, 383.4; acetyl, 33.7. Found: C, 59.55; H, 7.62; N, 3.71; neut equiv, 373; acetyl, 32.9.

Methiodide Salt. Conversion to the methiodide salt required 6 days for completion. Two forms of the salt were obtained: (1) anhydrous, mp 197–199° (*Anal.* Calcd for $C_{20}H_{32}INO_7$: C, 45.73; H, 6.14; I, 24.16; N, 2.66. Found: C, 45.94; H, 6.26; I, 24.24; N, 2.78); (2) hydrated mp 160°, resolidified at 170–180° and remelted at 222–223° (*Anal.* Calcd for $C_{20}H_{32}INO_7 \cdot H_2O$: C, 44.21; H, 6.31; I, 23.34; N, 2.58. Found: C, 44.35; H, 6.39; I, 23.44; N, 2.58).

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 6a,8-Diacetate (4). A solution of 6a,8,9-triacetate **3** (0.100 g) in aqueous methanol (9:1 CH_3OH–H_2O) was allowed to stand for 24 hr. The solvent was removed, leaving a water-contaminated residue. This was dissolved in chloroform, treated with anhydrous magnesium sulfate, and filtered. Evaporation of the chloroform yielded 0.072 g of residue, mp 164–165°. Recrystallization from benzene–Skellysolve B yielded an analytical sample, mp 174–175°. The infrared spectrum showed bands for hydroxyl at 2.89 and carbonyl at 5.75 μ. The infrared spectrum in Nujol shows a single carbonyl band at 5.75 μ. The nmr spectrum shows the loss of two protons upon shaking with D_2O.

Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.82; H, 7.99; N, 4.10. Found: C, 59.63; H, 7.87; N, 4.08.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 8,9,10a-Triacetate (5). A mixture of tetrol hydrochloride **1**·HCl (0.250 g) and acetic anhydride (2 ml) was cooled in an ice–salt bath, and 60% perchloric acid (0.2 ml) was added, followed immediately by methanol (2 ml) which decomposed the excess acetic anhydride. The mixture was made basic

with concentrated ammonium hydroxide and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The gummy residue solidified upon treatment with Skellysolve B. The yield was 0.3 g. The thin layer chromatogram (3:7 CH_3OH–$CHCl_3$) showed the presence of some tetraacetate **9**. Material from several runs was combined and recrystallized from Skellysolve B, yielding one-spot material with mp 137–138°. The infrared spectrum shows a bonded hydroxyl band at 2.91 and a strong broad carbonyl band at 5.70 μ. The infrared spectrum in Nujol shows a single carbonyl absorption at 5.75 μ rather than the resolved carbonyl shown by the 6a,8,9-triacetate **3**. The nmr spectrum shows the loss of one proton upon shaking with D_2O.

Anal. Calcd for $C_{19}H_{29}NO_7$: C, 59.51; H, 7.62; N, 3.65. Found: C, 59.54; H, 7.64; N, 3.65.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 9,10a-Diacetate (6). The 8,9,10a-triacetate **5** (0.100 g) was dissolved in aqueous methanol (25 ml, 9:1 CH_3OH–H_2O) and allowed to stand for 24 hr. The solution was diluted with benzene and evaporated under reduced pressure. Two additional treatments with methanol and benzene removed the remaining water, yielding a gum which solidified upon addition of Skellysolve B. The crude product (0.073 g, mp 158°) was recrystallized twice from Skellysolve B to yield 0.046 g, mp 164–165°. The infrared spectrum shows bands for bonded hydroxyl at 2.90 and carbonyl at 5.78 μ. The nmr spectrum shows the loss of two protons upon shaking with D_2O.

Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.87; H, 7.85; N, 4.35.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 10a-Ethyl Carbonate Hydrochloride (7·HCl). A solution of tetrol **1** (2.0 g, 0.0078 mole equiv), tetrahydrofuran (800 ml), and ethyl chloroformate (80 ml, 0.8 mole equiv) was stirred for several hours and then allowed to stand overnight. The mixture was filtered, yielding 0.987 g of material characterized as tetrol hydrochloride (**1**·HCl) by the melting point (285° dec) and infrared spectrum. The filtrate was evaporated to dryness under a stream of nitrogen on a steam bath. The residue was washed with ethyl acetate and recrystallized three times from ethanol–ethyl acetate, to yield 1.436 g of crystalline material (mp 189–190° dec). The infrared spectrum in Nujol shows hydroxyl bands at 2.97 and 3.09 and a carbonyl band at 5.79 μ.

Anal. Calcd for $C_{16}H_{28}ClNO_6$: C, 52.53; H, 7.71; N, 3.83; Cl, 9.69. Found: C, 52.67; H, 7.75; N, 3.80; Cl, 9.25.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 10a-Ethyl Carbonate (7). Ethyl tetrol carbonate hydrochloride 7·HCl (0.749 g) was dissolved in water (5–10 ml) and cooled in an ice bath. Chloroform (10 ml) was added, and the mixture was stirred rapidly. Ammonium hydroxide (7 *N*) was added to pH 10. The cold mixture was immediately extracted with chloroform (three 10-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. Addition of Skellysolve B solidified the viscous residue, yielding 0.462 g (mp 140–142° dec) of material whose thin layer chromatogram indicated presence of some tetrol **1**. Recrystallization from ethyl acetate yielded 0.278 g of one-spot material with mp 163–166° dec. The nmr spectrum showed significant signals at τ 5.87 q (J = 7 cps, 2 H) and 8.72 t (J = 7 cps, 3 H), and loss of three protons in the 5.8 region upon shaking with D_2O. The infrared spectrum shows a sharp but weak band for nonbonded hydroxyl at 2.79 μ, a broad band for bonded hydroxyl at 2.91 μ, and strong bands at 5.74 and 7.96 μ for carbonate.

Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.55; H, 7.95; N, 3.92.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 6a,8,9-Triacetate 10a-Ethyl Carbonate (8). A solution of pyridine (5 ml, previously dried over potassium hydroxide), ethyl tetrol carbonate **7** (0.100 g, 0.0003 mole equiv), and acetic anhydride (0.62 ml, 0.006 mole equiv) was allowed to stand overnight. The mixture was cooled in an ice bath, made basic with 7 *N* ammonium hydroxide solution, and extracted with chloroform (three 10-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was treated three times with benzene to remove the pyridine as an azeotrope, to yield a semisolid material which solidified upon addition of Skellysolve B. The impure product (0.110 g) was dissolved in boiling Skellysolve B and filtered, leaving behind a considerable amount of oily insoluble material. The filtrate was concentrated, to yield 0.050 g (mp 154–155°) of crystalline material. Concentration of the mother liquors yielded an additional 0.019 g (mp 152–153°). The infrared spectrum shows the absence of hydroxyl absorption and strong carbonyl absorption at 5.75 μ. The nmr spectrum shows a triplet at τ 8.77 (J = 7 cps) and a complicated quartet at τ 5.84.

Anal. Calcd for $C_{22}H_{33}NO_9$: C, 58.01; H, 7.30; N, 3.08. Found: C, 58.23; H, 7.35; N, 3.19.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 6a,8,9,10a-Tetraacetate (9). A. By Acetylation of 3 with Acetic Anhydride in Perchloric Acid. To a solution of acetic anhydride (3 ml) and 6a,8,9-triacetate **3** (0.050 g) in an ice–salt bath was added 60% perchloric acid (0.1 ml). The mixture was allowed to stand overnight in the freezing compartment of the refrigerator. The reaction mixture was placed in an ice–salt bath, decomposed with methanol (3 ml), made basic with concentrated ammonium hydroxide, and extracted with chloroform (three 10-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure, yielding 0.050 g. Recrystallization from Skellysolve B yielded 0.035 g of crystals (mp 185–186°) with infrared spectrum identical with a sample produced by the same procedure from the 8,9,10a-triacetate **5**. The infrared spectrum shows no hydroxyl band, *trans*-quinolizine bands at 3.55 and 3.61, and a strong broad carbonyl band at 5.74 μ. The infrared spectrum in Nujol fails to show a resolved carbonyl band, but shows a strong band at 5.76 μ.

Anal. Calcd for $C_{21}H_{31}NO_8$: C, 59.28; H, 7.34; N, 3.29. Found: C, 59.25; H, 7.40; N, 3.32.

B. By Acetylation of 5 with Acetic Anhydride in Pyridine. A solution of pyridine (1 ml, previously dried over potassium hydroxide), 8,9,10a-triacetate **5** (0.025 g), and acetic anhydride (0.1 ml) was heated on a steam bath for 16 hr, cooled in an ice bath, made basic with 7 *N* ammonium hydroxide, and extracted with chloroform (three 10-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Treatment of the residue with benzene and distillation under reduced pressure removed the pyridine as an azeotrope, yielding 0.019 g. Recrystallization from Skellysolve B, with decolorizing treatment with Norit, yielded 0.006 g (mp 183–184°) of crystalline material with infrared spectrum identical with an authentic sample of **9**, and the mixture melting point with an authentic sample was not depressed.

C. By Acetylation of the 9,10a-Diacetate 6. A solution of pyridine (2 ml, previously dried over potassium hydroxide), 9,10a-diacetate **6** (0.037 g, 0.00011 mole equiv), and acetic anhydride (0.2 ml 0.0022 mole equiv) was allowed to stand overnight. The mixture was cooled in an ice bath, made basic with 7 *N* ammonium hydroxide, and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Treatment of the residue with benzene and distillation under reduced pressure removed the pyridine as an azeotrope, yielding semisolid material which solidified in Skellysolve B. Recrystallization from Skellysolve B gave 0.023 g (mp 185–186°) of tetraacetate **9** with infrared spectrum identical with the spectra of all previous samples.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,10a-diol 6a-Monoacetate (14). A solution of pyridine (5 ml, previously dried over potassium hydroxide), acetic anhydride (0.8 ml, 0.01 mole equiv), and diol **13** (0.225 g, 0.001 mole equiv) was heated on a steam bath for 6 hr and allowed to stand overnight. The mixture was cooled in an ice bath, made basic with 7 *N* ammonium hydroxide, and extracted with chloroform (three 10-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The pyridine in the residue was removed by codistillation with benzene, yielding 0.240 g of viscous residue which solidified in the refrigerator but melted at room temperature. Thin layer chromatography showed two spots, one of which was starting material. Preparative thick layer chromatography in 3:7 CH_3OH–$CHCl_3$ yielded approximately 0.060 g of one-spot material which could not be crystallized. The infrared spectrum showed bands for free hydroxyl at 2.80, bonded hydroxyl at 2.92, and carbonyl at 5.80 μ. The nmr spectrum showed the loss of one proton upon shaking with D_2O. The diol monoacetate was characterized as its hydrochloride salt by dissolving in ethyl acetate, adding an ether solution of hydrochloric acid, and evaporating to dryness, yielding 0.058 g. This was recrystallized from ethanol–ethyl acetate–ether to yield 0.050 g, mp 250–251° dec. The infrared spectrum in Nujol shows the presence of water (band at 3.15 μ).

Anal. Calcd for $C_{15}H_{26}ClNO_3 \cdot {}^1/_3H_2O$: C, 58.14; H, 8.67; N, 4.52. Found: C, 58.65; H, 8.75; N, 4.51.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 9,10a-Carbonate (19). A. From Ethyl Tetrol Carbonate Hydrochloride 7·HCl. Ethyl tetrol carbonate hydrochloride 7·HCl (1.435 g) was dissolved in a small amount of distilled water, made basic with 7 *N* ammonium hydroxide, allowed to stand about 5 min, and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Addition of Skellysolve B solidified the gummy residue, yielding 0.808 g. Thin layer chromatography showed the presence of tetrol **1**, starting material, ethyl tetrol carbonate **7**, and desired cyclic carbonate. The mixture was recrystallized twice from methanol and once from ethyl acetate to yield 0.334 g (mp 181–182° dec). The infrared spectrum shows a hydrogen-bonded hydroxyl band at 2.90 and a carbonyl band at 5.75 μ. The infrared spectrum in Nujol indicates the presence of at least two crystal forms. In one, the hydroxyl absorption is at 2.88 and 2.97 μ and the carbonyl absorption at 5.78 μ. In the other crystal form, the hydroxyl group absorbs at 2.99 and carbonyl group at 5.69 μ. The nmr spectrum shows the loss of two protons upon shaking with D_2O.

Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.22; H, 7.66; N, 4.89.

The hydrochloride salt of **19**, recrystallized from chloroform–ethyl acetate, showed mp 270–275° dec.

Anal. Calcd for $C_{14}H_{22}ClNO_5$: C, 52.58; H, 6.93; Cl, 11.09; N, 4.38. Found: C, 52.36; H, 6.75; Cl, 11.00; N, 4.32.

B. By Reaction of Phosgene with Tetrol 1. A solution of pyridine (20 ml, previously dried over potassium hydroxide), tetrol **1** (0.5 g, 0.0019 mole equiv), and chloroform (30 ml) was cooled in an ice–salt bath, and phosgene in benzene (12.5%, 40 ml, 0.05 mole equiv) was added dropwise with stirring. The mixture became thick and took on a yellowish-white opaque color. It was cooled, stirred for 1 hr, and then allowed to stand overnight. As the mixture warmed up, the precipitate dissolved, forming a red, cloudy solution. The next day the solution had become black with a dirty yellow solid on the sides. The mixture was cooled in an ice bath. Upon addition of chipped ice, there was effervescence and the yellow solid dissolved. The mixture was made basic with 7 *N* ammonium hydroxide and extracted with chloroform. The chloroform extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Treatment of the residue with benzene and distillation under reduced pressure removed the pyridine as an azeotrope, yielding 0.283 g of crude material. This was treated twice with boiling Skellysolve C and filtered. The filtrate was concentrated under reduced pressure and the residue recrystallized from ethyl acetate to yield 0.156 g (mp 176–177° dec). The infrared spectrum was identical with that of the cyclic carbonate produced from ethyl tetrol carbonate **7**.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 9,10a-Carbonate 6a,8-Diacetate (20). A. From 6a,8-Diacetate 4. To a solution of pyridine (2 ml, previously dried over potassium hydroxide), chloroform (3 ml), and 6a,8-diacetate **4** (0.05 g, 0.00015 mole equiv) cooled in an ice–salt bath was slowly added phosgene in benzene (12.5%, 3 ml, 0.005 mole equiv). The reaction mixture was allowed to stand overnight at room temperature. The flask was then cooled in an ice bath and ice was added. The cold mixture was made basic with 7 *N* ammonium hydroxide and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Treatment of the residue with benzene and distillation under reduced pressure removed the pyridine as an azeotrope. Addition of Skellysolve B caused solidification of the oily residue to yield 0.046 g of one-spot material. Treatment with Norit in Skellysolve B removed the yellow color. Recrystallization from Skellysolve B yielded 0.022 g of crystalline material (mp 173–174°). The infrared spectrum shows no hydroxyl absorption, *trans*-quinolizidine absorption at 3.52 and 3.58, and strong broad carbonyl absorption at 5.68 μ.

Anal. Calcd for $C_{15}H_{23}NO_7$: C, 58.84; H, 6.86; N, 3.81. Found: C, 59.02; H, 6.96; N, 3.83.

B. By Acetylation of 9,10a-Cyclic Carbonate 19. A solution of pyridine (7 ml, previously dried over potassium hydroxide), 9,10a-cyclic carbonate **19** (0.100 g, 0.00034 mole equiv), and acetic anhydride (0.7 ml, 0.0068 mole equiv) was allowed to stand overnight. The solution was cooled in an ice bath, made basic with 7 *N* ammonium hydroxide, and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was treated with benzene and distilled under reduced pressure, removing the pyridine as an azeotrope. Skellysolve B was added to induce crystallization to yield 0.131 g of two-spot material. Using two different thin layer solvent systems (9:1 CH_3OH–$CHCl_3$ and 3:7 CH_3OH–$CHCl_3$), the material with the higher R_f was shown to be the desired diacetate **20** and the material with lower R_f, the cyclic carbonate 8-monoacetate **22**. Fractional crystallization from Skellysolve B yielded clean material corresponding to the spot with the higher R_f. Its infrared spectrum was identical with that of an authentic sample of cyclic carbonate diacetate **20**, and its melting point was not depressed by admixture with an authentic sample.

C. By Acetylation of the 9,10a-Cyclic Carbonate 6a-Monoacetate 21. A solution of pyridine (2 ml, previously dried over potassium hydroxide), cyclic carbonate 6a-monoacetate **21** (0.033 g, 0.0001 mole equiv), and acetic anhydride (0.2 ml, 0.002 mole equiv) was allowed to stand overnight. The mixture was cooled in an ice bath, made basic with 7 *N* ammonium hydroxide, and extracted with chloroform (three 10-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Treatment of the residue with benzene and distillation under reduced pressure removed the pyridine as an azeotrope to yield semicrystalline product which solidified upon addition of Skellysolve B. The crude material (0.033 g) was recrystallized from Skellysolve B to yield 0.021 g of crystalline material whose melting point (173–174°) was not depressed upon admixture with an authentic sample of **20**. Its infrared spectrum was identical with that of the authentic sample.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 9,10a-Carbonate 6a-Monoacetate (21). Cyclic carbonate **19** (0.274 g, 0.00097 mole equiv) was dissolved with heating in benzene (30 ml) and pyridine (2 ml, previously dried over potassium hydroxide). After cooling to room temperature, acetic anhydride (0.18 ml, 0.0019 mole equiv) was added. The mixture was stirred for several hours and allowed to stand overnight. The precipitate (presumably starting material) that formed early in the reaction had redissolved by morning. The reaction mixture was concentrated under reduced pressure, cooled in an ice bath, made basic with 7 *N* ammonium hydroxide, and extracted with chloroform (three 10-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and removed under reduced pressure. The residue was treated with benzene and distilled under reduced pressure, removing the pyridine as an azeotrope. Treatment of the viscous residue with Skellysolve B caused solidification, yielding 0.269 g (mp 179–180° dec). Thin layer chromatography showed no starting material and only traces of cyclic carbonate diacetate **20**. Recrystallization from benzene–Skellysolve B yielded 0.219 g of crystalline material (mp 195–196°). The infrared spectrum shows bands for bonded hydroxyl at 2.90 and carbonyl at 5.74 μ. The infrared spectrum in Nujol shows a hydroxyl band at 2.91 and carbonyl bands at 5.68 and 5.84 μ. The nmr spectrum shows the loss of one proton upon shaking with D_2O.

Anal. Calcd for $C_{16}H_{23}NO_6$: C, 59.06; H, 7.13; N, 4.31. Found: C, 58.96; H, 7.20; N, 4.33.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 9,10a-Carbonate 8-Monoacetate (22). A. By Acetylation with Acetic Anhydride in Perchloric Acid. To a solution of acetic anhydride (1 ml) and cyclic carbonate **19** (0.050 g) cooled in an ice–salt bath was added 60% perchloric acid (0.1 ml). This was immediately followed by methanol (*ca.* 2 ml). Concentrated ammonium hydroxide was added until the reaction mixture was basic. The cold basic mixture was extracted with chloroform (three 10-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and removed under reduced pressure. Addition of Skellysolve B caused solidification of the gummy residue, to yield 0.064 g of crude material whose thin layer chromatogram showed traces of cyclic carbonate diacetate **20**. Two recrystallizations from Skellysolve B and one from benzene–Skellysolve B yielded 0.019 g of analytical sample. This sample melted at 158 and 167°, and showed indication of two crystal forms. When recrystallized from Skellysolve B alone, the melting point usually covered the range of 158–162°. The infrared spectrum shows a bonded hydroxyl band at 2.91 and a strong broad carbonyl band at 5.73 μ. The infrared spectrum in Nujol shows carbonyl bands at 5.66 and 5.74 μ. The nmr spectrum shows the loss of one proton upon shaking with D_2O.

Anal. Calcd for $C_{16}H_{23}NO_6$: C, 59.06; H, 7.13; N, 4.31. Found: C, 59.19; H, 7.07; N, 4.26.

B. By Transesterification of the Acetate from the C-6a to the C-8 Position. A solution of aqueous *t*-butyl alcohol (5 ml, 9:1 *t*-BuOH–H_2O) which was 0.12 *M* in triethylamine and cyclic car-

bonate 6a-monoacetate **21** (0.025 g) was allowed to stand for 5 days at room temperature. Thin layer chromatography showed that after 24 hr, the reaction was about 25% complete, after 48 hr about 50%, after 72 hr about 80%, after 96 hr almost complete, and 120 hr essentially complete, with a faint spot corresponding to the solvolysis product **19**. The mixture was diluted with benzene and enough acetone to hold the water in solution and then concentrated under reduced pressure. Addition of Skellysolve B to the gummy residue yielded solid material which was recrystallized from Skellysolve B, to yield 0.020 g of material with mp 157–158°. The melting point was not depressed upon admixture of an authentic sample of cyclic carbonate 8-monoacetate **22**. The infrared spectrum was identical with that of the authentic sample.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 9,10a-Carbonate 8-Ethyl Carbonate (23). To a solution of pyridine (5 ml, previously dried over potassium hydroxide) and cyclic carbonate **19** (0.050 g, 0.0002 mole equiv) was added dropwise ethyl chloroformate (1 ml, 0.01 mole equiv). The mixture was allowed to stand for 6 hr at room temperature. The initially formed precipitate dissolved in a few hours. The reaction mixture was cooled in an ice bath, made basic with 7 *N* ammonium hydroxide, and extracted with chloroform (three 15-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Treatment of the residue with benzene and distillation under reduced pressure removed the pyridine as an azeotrope and left a solid residue (0.058 g). The residue was dissolved in ethyl acetate, decolorized with Norit, and recrystallized from benzene–Skellysolve B, yielding 0.015 g (mp 187–188° dec). The infrared spectrum shows bands for bonded hydroxyl at 2.91 and strong broad carbonyl at 5.71 μ. The nmr spectrum exhibits a quartet at τ 5.78 (J = 7 cps) and a triplet at 8.70 (J = 7 cps).

Anal. Calcd for $C_{17}H_{25}O_7N$: C, 57.45; H, 7.09; N, 3.94. Found: C, 57.63; H, 7.12; N, 3.94.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 9,10a-Carbonate 6a-Monoacetate 8-Ethyl Carbonate (24). A solution of pyridine (2.5 ml, previously dried over potassium hydroxide), ethyl tetrol carbonate cyclic carbonate **23** (0.117 g, 0.00033 mole equiv), and acetic anhydride (0.3 ml, 0.03 mole equiv) was heated on a steam bath for 8 hr, and allowed to stand overnight. The mixture was cooled in an ice bath, made basic with 7 *N* ammonium hydroxide, and extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Treatment of the residue with benzene and distillation under reduced pressure removed the pyridine as an azeotrope, to yield 0.121 g of crude, but one-spot material. Decolorization with Norit in Skellysolve B, followed by recrystallization from Skellysolve B, yielded 0.088 g of product (mp 140–141°). The infrared spectrum shows no hydroxyl band and a strong carbonyl band at 5.70 μ. The nmr spectrum shows a quartet at τ 5.78 (J = 7 cps) and a triplet at 8.70 (J = 7 cps).

Anal. Calcd for $C_{19}H_{27}NO_8$: C, 57.42; H, 6.85; N, 3.52. Found: C, 57.31; H, 6.94; N, 3.69.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 8,9-Diacetate Methiodide (28). A solution of pyridine (5 ml, previously dried over potassium hydroxide), acetic anhydride (0.5 ml, 0.005 mole equiv), and tetrol methiodide[12] (0.100 g, 0.00025 mole equiv) was allowed to stand for 2 days. The acetylated methiodide was precipitated with anhydrous ether and filtered, yielding 0.117 g (mp 259–260°). Two recrystallizations from ethanol–ethyl acetate yielded 0.100 g with mp 242–243°, but, when placed on the melting point block preheated to 230°, the compound melted at 255–260°. The infrared spectrum in Nujol shows hydroxyl bands at 2.82 and 2.98 and a carbonyl band at 5.78 μ. There was no change in the spectrum before and after recrystallizations. The nmr spectrum in trifluoroacetic acid (TMS internal standard) shows an acetate signal at τ 7.70, corresponding to six protons.

Anal. Calcd for $C_{18}H_{30}INO_6$: C, 44.73; H, 6.25; I, 26.26; N, 2.90. Found: C, 44.63; H, 6.21; I, 26.41; N, 2.87.

Mineral Acid Hydrolysis of 1,3,4,6,7,10,11,11a-Octahydro-2*H*-benzo[*b*]quinolizin-8-ol Methyl Ether (30). A solution of 1,3,4,6,7,-10,11,11a-octahydro-2*H*-benzo[*b*]quinolizin-8-ol methyl ether (**30**, 6.70 g, mp 57–60.5°) in 10% hydrochloric acid (84 ml) was stirred at room temperature for 11 hr. The solution was cooled in an ice bath and made basic (pH 10–11) with 50% sodium hydroxide solution. It was then extracted with ether (three 150-ml portions), and the combined ether extracts were washed once with water and dried over anhydrous sodium sulfate. The solution was filtered and the filtrate concentrated under reduced pressure to yield a brown oil. The oil was dried in a vacuum desiccator for 2 hr. The product, a mixture of 1,3,4,6,7,8,9,10,11,11a-decahydro-2*H*-benzo[*b*]-quinolizin-8-one (**33**) and 1,3,4,6,8,9,10,10a,11,11a-decahydro-2*H*-benzo[*b*]quinolizin-8-one (**31**) weighed 5.80 g. It exhibited $\lambda_{max}^{CHCl_3}$ 3.57, 3.64 (*trans*-quinolizidine); 5.85 (β,γ-unsaturated ketone C=O); 6.20 μ (α,β-unsaturated ketone C=C). The ultraviolet spectrum showed λ_{max}^{EtOH} 223 mμ (ϵ 7400). The product was directly reduced with lithium and ammonia.

Lithium and Ammonia Reduction of 1,3,4,6,8,9,10,10a,11,11a-Decahydro-2*H*-benzo[*b*]quinolizin-8-one (31). To approximately 500 ml of ammonia condensed in a 1 l., three-necked flask in a Dry Ice–acetone bath, 10.5 g of lithium metal chunks (Fisher Scientific) was added. An intense blue color was produced. To this solution, 9.11 g of a mixture of 1,3,4,6,7,8,9,10,11,11a-decahydro-2*H*-benzo[*b*]quinolizin-8-one (**33**) and 1,3,4,6,8,9,10,10a,11,11a-decahydro-2*H*-benzo[*b*]quinolizin-8-one (**31**) (obtained from the hydrochloric acid hydrolysis of **30**) in ~100 ml of ether was added dropwise over a period of 15 min. The reaction was allowed to proceed for 15 min more and then alcohol was added dropwise until the blue color was discharged. The mixture was allowed to stand overnight to allow the liquid ammonia to evaporate. Ammonium hydroxide was added to bring the pH to 10–11 and the mixture was extracted three times with ether. The combined ether extracts were washed once with water and the ether solution was dried over anhydrous sodium sulfate. The ether solution was filtered and the filtrate concentrated to yield 9.00 g of a brown oil; $\lambda_{max}^{CHCl_3}$ 2.75, 2.95 (O–H); 3.57 μ (*trans*-quinolizidine).

Chromic Acid Oxidation of 1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizin-8-ol (34). Chromium trioxide (10 g, J. T. Baker Reagent) in 200 ml of 90% acetic acid was added dropwise, with stirring, to a solution of 10.0 g of 1,3,4,6,6a,7,8,9,-10,10a,11,11a-dodecahydro-2*H*-benzo[*b*]quinolizin-8-ol (**34**) (obtained from the lithium–ammonia reduction of the α,β-unsaturated ketone **31**). Addition of the chromic acid solution took 15 min, and the mixture was then stirred at room temperature for 2 hr. It was cooled in an ice bath and made basic (pH ~ 10) with 50% sodium hydroxide. The mixture was diluted to 2 l. and extracted twice with ether. An emulsion formed which could only be broken by centrifugation. The ether solution was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to yield 5.54 g of a brown oil. The product was chromatographed on 500 g of alumina (Merck). Elution of the column with 2% ethanol in chloroform yielded solid ketone which was sublimed under reduced pressure to yield 1.03 g of light tan crystals, mp 83–90°; $\lambda_{max}^{CHCl_3}$ 3.57, 3.64 (*trans*-quinolizidine); 5.85 μ (C=O). Analytically pure material, mp 87–90°, was obtained by resublimation under reduced pressure.

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 74.95; H, 10.05; N, 6.86.

Lithium Aluminum Hydride Reduction of 1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizin-8-one (41). A solution of 0.035 g of the saturated ketone **41** in 10 ml of ether was added dropwise to 0.035 g of lithium aluminum hydride (Metal Hydrides, Inc.) in 15 ml of ether. The mixture was stirred at reflux temperature on a water bath for 3 hr. Water and 5% hydrochloric acid were added, followed by sodium carbonate solution to pH ~10. The mixture was extracted with ether. The ether extract was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue crystallized from Skellysolve B to yield 0.020 g of crystals, mp 140–144°, of the 8β-(eq)-ol **34**. The product was characterized by mixture melting point, mixture tlc, and infrared spectral comparison with the authentic sample.

Reduction of **41** with sodium borohydride in methanol or hydrogenation with platinum in ethanol also yielded **34**.

Catalytic Hydrogenation of 1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizin-8-one (41) in an Acidic Medium. Platinum oxide (350 mg; Engelhard Industries) in 600 ml of 50% acetic acid was reduced and equilibrated in an atmospheric pressure hydrogenation apparatus. A solution of 0.836 g of the saturated ketone **41** in 100 ml of 50% acetic acid was added and the hydrogenation conducted for 14 hr. The solution was filtered and the filtrate concentrated under reduced pressure to remove most of the acetic acid. The solution was made basic with 20% sodium hydroxide solution to pH 10–11 and extracted three times with ether. The combined ether extracts were washed once with water and dried over anhydrous sodium sulfate. The ether solution was filtered and the filtrate concentrated, to yield 0.770 g of a solid. A column of 100 g of alumina (Merck) was used to chromatograph

the product. Elution of the column with 10% benzene in chloroform yielded 0.133 g of the less polar alcohol **34** which was crystallized from Skellysolve B to yield crystals, mp 145–148°; λ_{max}^{KBr} 3.57, 3.64 (*trans*-quinolizidine); 9.75 μ (C–O); $\lambda_{max}^{CHCl_3}$ 2.75, 2.9–3.2 (O–H); 3.53, 3.60 (*trans*-quinolizidine); 9.80 μ (C–O).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.38; H, 11.47; N, 6.91.

Elution of the column with 1% methanol in chloroform yielded 0.301 g of the more polar alcohol **39** which was crystallized from Skellysolve B to yield crystals, mp 139–140°; λ_{max}^{KBr} 3.57, 3.62 (*trans*-quinolizidine); 10.0 μ (C–O); $\lambda_{max}^{CHCl_3}$ 2.75, 2.95–3.20 (O–H); 3.55, 3.60 (*trans*-quinolizidine); 10.0 μ (C–O).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.71; H, 11.03; N, 6.95.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizin-8-ol Acetates (35 and 40). A solution of 0.020 g of each alcohol (8β-(eq)-ol **34** and 8α-(ax)-ol **39**) in pyridine (0.5 ml) and acetic anhydride (0.01 ml) was heated in a water bath at 80–90° for 3 hr. Each solution was made basic with ammonium hydroxide to pH 9 and extracted three times with chloroform. The combined chloroform extracts were washed once with water and dried over anhydrous sodium sulfate. The chloroform solutions were filtered and the filtrates concentrated under reduced pressure. The residues obtained were dissolved in benzene and concentrated several times to remove the pyridine. The equatorial alcohol **34** yielded 0.024 g of its acetate ester, mp 103–105°. This was dissolved in Skellysolve B, treated with Norit, and filtered. The filtrate gave crystals, mp 104–107°; λ_{max}^{KBr} 3.57, 3.62 (*trans*-quinolizidine); 5.76 (C=O); 8.10 (C–O–C); 9.70 μ (C–O); $\lambda_{max}^{CHCl_3}$ 3.53, 3.60 (*trans*-quinolizidine); 5.80 (C=O); 8.00 (C–O–C); 9.75 μ (C–O).

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.92; H, 10.03; N, 5.53.

The axial alcohol **40** yielded 0.024 g of its acetate ester, mp 77–79°. The ester was dissolved in Skellysolve B, treated with Norit, and filtered. The filtrate gave crystals, mp 77–80°; λ_{max}^{KBr} 3.57, 3.62 (*trans*-quinolizidine); 5.78 (C=O); 8.03, 8.10, 8.20 (C–O–C); 9.85 μ (C–O); $\lambda_{max}^{CHCl_3}$ 3.53, 3.60 (*trans*-quinolizidine); 5.76 (C=O); 7.94 (C–O–C); 9.80 μ (C–O)

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.75; H, 9.95; N, 5.64.

Oxalic Acid Hydrolysis of 1,3,4,6,7,10,11,11a-Octahydro-2*H*-benzo[*b*]quinolizin-8-ol Methyl Ether (30). A solution of 1,3,4,-6,7,10,11,11a-octohydro-2*H*-benzo[*b*]quinolizin-8-ol methyl ether (**30**, 2.50 g) and oxalic acid dihydrate (7.50 g, Baker and Adamson, reagent grade) in methanol (425 ml) and water (75 ml) was allowed to stand at room temperature for 6 hr. The solution was then concentrated to remove the methanol and made basic to pH 9–10 with saturated sodium carbonate solution. Disodium oxalate was usually precipitated but could be readily dissolved upon dilution. The solution was extracted three times with ether and the combined ether extracts were washed once with water and dried over anhydrous sodium sulfate. The ether solution was filtered and the filtrate concentrated to yield 2.28 g of a brown oil. The infrared spectrum in chloroform shows a strong peak at 5.85 μ with a weak shoulder at 6.0 μ. The ultraviolet spectrum shows only end absorption with ϵ 1200 at 224 mμ.

Catalytic Hydrogenation of 1,3,4,6,7,8,9,10,11,11a-Decahydro-2*H*-benzo[*b*]quinolizin-8-one (33) with a Ruthenium Catalyst. Ruthenium on carbon (450 mg, 5%, Engelhard Industries) in absolute ethanol (70 ml) was equilibrated in an atmospheric hydrogenation apparatus. A solution of 1,3,4,6,7,8,9,10,11,11a-decahydro-2*H*-benzo[*b*]quinolizin-8-one (**33**, 2.28 g) in absolute ethanol (70 ml) was added and hydrogenation continued for 6.5 hr. The solution was filtered and the filtrate vacuum evaporated to yield 2.51 g of a light brown oil. The infrared spectrum in carbon tetrachloride shows a broad band at 3.0 μ, peaks at 3.60 and 3.70 μ, and no absorption in the 6-μ region. A peak at 9.60 μ indicates the presence of an equatorial alcohol. The oily product was directly hydroxylated with performic acid to triol **36**.

Reduction of **33** with sodium borohydride in methanol, lithium aluminum hydride in ether, and lithium tri-*t*-butoxyaluminohydride in tetrahydrofuran, or hydrogenation with platinum in ethanol also gave oily products which could be hydroxylated with performic acid to yield triol **36**.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,10a-triol (36). Hydrogen peroxide (30%, 2.8 ml) was added to a solution of 1,3,4,6,7,8,9,10,11,11a-decahydro-2*H*-benzo-[*b*]quinolizine-8-ol (**32**, 2.5 g) in formic acid (88%, 75 ml). The solution was stirred in a 40–50° water bath for 4 hr and allowed to stand at room temperature for 8 hr more. It was cooled in an ice bath, made basic with 50% sodium hydroxide solution, and extracted three times with chloroform. The chloroform solution was washed once with water and dried over anhydrous sodium sulfate. The chloroform was filtered and the filtrate concentrated under reduced pressure to yield 1.81 g of an oil which solidified on the addition of benzene. The product was chromatographed on 120 g of formamide supported on 180 g of acid-washed Celite. Elution of the column with formamide-saturated benzene–chloroform (1:1) yielded a solid which was crystallized from benzene to yield 0.51 g of triol **36**, mp 154–159°. Several recrystallizations from benzene yielded analytically pure material, mp 163–165°; λ_{max}^{KBr} 3.57, 3.64 (*trans*-quinolizidine); 10.0 μ (C–O); $\lambda_{max}^{CHCl_3}$ 2.78, 2.84–3.00 (O–H); 3.57 (*trans*-quinolizidine); 10.0 μ (C–O).

Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.69; H, 9.66; N, 5.72.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,10a-triol 6a,8-Diacetate (37). To a solution of triol **36** (0.046 g) in pyridine (0.3 ml), acetic anhydride (0.3 ml) was added. The solution was allowed to remain at room temperature for 14 hr. Ammonium hydroxide was then added to pH 10. The solution was extracted three times with chloroform and the chloroform extract washed once with water and dried over anhydrous sodium sulfate. The solution was filtered and the filtrate concentrated to yield a residue which was treated with benzene and distilled to remove the pyridine by codistillation. A solid resulted which was crystallized from benzene–Skellysolve B to yield 0.036 g of crystals, mp 170–180° dec. Several recrystallizations yielded analytically pure material, mp 180–182.5° dec; λ_{max}^{KBr} 3.57, 3.62 (*trans*-quinolizidine); 5.78, 5.85 (C=O); 7.78; 7.97, 8.07 μ (C–O–C); $\lambda_{max}^{CHCl_3}$ 2.78, 2.90 (O–H); 3.57–3.64 (*trans*-quinolizidine); 5.76 (C=O); 7.80, 7.95, 8.07 μ (C–O–C).

Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36; N, 4.30. Found: C, 62.82; H, 8.43; N, 4.22.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2*H*-benzo[*b*]quinolizine-6a,8,10a-triol 6a-Monoacetate (38). Dissolution of 0.484 g of triol **36** in 1.2 ml of pyridine and 12 ml of benzene was effected with gentle heating, and 0.2 ml of acetic anhydride was added. The solution was allowed to remain at room temperature for 20 hr. At the end of this time some of the triol had crystallized from the solution. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform, and the chloroform solution was washed twice with a saturated solution of sodium carbonate and dried over anhydrous sodium sulfate. The chloroform solution was filtered and the filtrate concentrated to yield a residue that was repeatedly dried by distillation with benzene, to yield 0.393 g of a solid. The solid was crystallized three times from benzene to yield 0.122 g of crystals, mp 184–187°; λ_{max}^{KBr} 3.57, 3.64 (*trans*-quinolizidine); 5.88 (C=O); 7.78, 8.00, 8.10, (C–O–C); 10.0 μ (C–O); $\lambda_{max}^{CHCl_3}$ 2.78, 2.90–3.00 (O–H); 3.57–3.64 (*trans*-quinolizidine); 5.80 (C=O); 7.8–8.2 (C–O–C); 9.90 μ (C–O).

Anal. Calcd for $C_{13}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.95; H, 8.79; N, 5.12.

Kinetic Measurements. Rates of methanolysis were determined for **3**, **5**, and **22** as 0.010–0.015 *M* solutions of ester in triethylamine–triethylammonium acetate or chloride buffer (1.2 *M*) in methanol–water (9:1) at 25°, unless otherwise indicated. Rates of methanolysis for **38** were determined as 0.014–0.015 *M* solutions of ester in triethylamine–triethylammonium acetate buffer (0.12 *M*) in methanol–water (9:1) at 25°. The ionic strength was maintained at 1.2 *M* for **3**, **5**, and **22** and at 0.09 *M* for **38** by adding the proper amounts of tetramethylammonium chloride. For esters **35** and **40**, the production of methyl acetate, the solvolysis product, was determined as described earlier.[1] For the remaining acetate esters, aliquots were removed every 20–40 min and injected onto a 6 ft long 0.25-in. diameter stainless steel column of 10% diethylene glycol succinate (LAC-728) on 60–80 or 80–100 mesh Diatoport S. The instrument employed was an F & M Scientific Model 700 laboratory chromatograph with flame ionization detector. The column oven was maintained at 60 or 65°, depending on the condition of the column. The flow rate of the nitrogen carrier gas was 50–55 ml/min. The heights of the peaks were measured against two different standards of methyl acetate in 90% methanol–water. About every 4 hr, the column was heated to 190° for 5 min to drive off residual triethylamine. The calculated amount of ester initially present was taken as the concentration at zero time and, therefore, was the initial point on the log of solvolyzable ester remaining *vs.* time plots. It was found that the solvolysis of the two triacetates **3** and **5** followed pseudo-first-order kinetics for the first 4–8 hr; the longer the half-life, the longer before deviations were noted. The

solvolysis of cyclic carbonate 8-monoacetate **22** deviated from pseudo-first-order kinetics after 1–2 hr.

pK_a' Determinations. The pK_a' values were determined by potentiometric titration in 80% Methyl Cellosolve–water (4:1) using a Radiometer pH meter with potassium chloride and glass electrodes or a Beckman expanded-scale pH meter with Beckman glass and potassium chloride electrodes. Approximately 3–6 mg was dissolved in 5–6 ml of 80% Methyl Cellosolve–water, and titrated with 0.01 *N* hydrochloric acid in 80% Methyl Cellosolve–water using an Ultra Buret whose tip was immersed in the solution. The solution was stirred with a magnetic stirring bar and pH′ readings were taken after each addition of acid. Determinations were done in duplicate with the reproducibility checked each day using the tetrol **1** as the standard.

Periodic Acid Titrations. The procedure followed was essentially that of Jackson.[46] Approximately 0.020 g of the substrate was dissolved in 0.54 *M* periodic acid (0.5–1.0 ml) and 2.0 ml of water. The reaction was allowed to proceed for approximately 20 hr. The sample was diluted with water to about 10 ml, and 1.5 g of sodium bicarbonate, 50 ml of 0.1 *N* sodium arsenite solution, and 1.0 ml of 20% potassium iodide solution was added. The solution was kept at room temperature for 10–15 min and then titrated with 0.1067 *N* iodine solution (Table III).

(46) E. L. Jackson, *Org. Reactions*, 2, 341 (1944).

Table III. Periodic Acid Titrations

Compound	Consumption of periodic acid, molar equiv
6a,10a-Diol **13**	0.37
6a,8,9,10a-Tetrol **1**	1.15
6a,8,10a-Triol **36**	0.25

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General Acid Cleavage of Allylmercuric Iodide[1a]

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Abstract: Allylmercuric iodide is cleaved by a wide variety of acids. The Brønsted catalysis law is obeyed by carboxylic acids with high precision, but structurally dissimilar acids show substantial deviations. Bisulfate ion has a catalytic coefficient very similar to that of hydronium ion, explaining the anomalous effectiveness of H_2SO_4 in A-SE2 reactions. The Brønsted α, obtained from carboxylic acids, is 0.67, in excellent agreement with one of the possible α_i's obtained from isotope effects. The thermodynamic acid dissociation constants of chloroacetic, fluoroacetic, and difluoroacetic acids were redetermined to remove uncertainties in the latter two, and values of 1.33×10^{-3}, 1.75×10^{-3}, and 3.5×10^{-2} *M*, respectively, obtained.

A good deal of progress has recently been made in analyzing the relations that may exist among variously defined isotope effects and the Brønsted α for A-SE2 reactions,[2-5] that is, reactions in which proton transfer constitutes an important part of the reaction coordinate. In particular it has been possible to obtain a quantity, α_i, analogous to the Brønsted α, from a consideration of primary and secondary solvent isotope effects attending proton transfer from the aquated proton.[2,4] It is of considerable interest to know how closely α_i approximates α, obtained by a conventional study of molecular acids.[6] In addition it is of interest to know how widely the Brønsted catalysis law[6] is obeyed by reactions of this type, and what sorts of series of acids should be used to evaluate α. On this latter point some disagreement is evident.[7,8]

The present paper reports a study of the cleavage of allylmercuric iodide by acids other than the aquated proton. (Cleavage by the aquated proton has already been described.[2]) As before,[2] the reactions were carried out in the presence of a trace (4×10^{-5} *M*) of I^- to inhibit secondary reactions and small percentages of methanol (1–4%) to facilitate the assembly of reacting solutions. All of the rate constants given in this paper pertain to 25°, and except where otherwise noted, to an ionic strength of 0.2 *M* (maintained by suitable additions of $NaClO_4$). The course of the reactions was monitored by following, spectrophotometrically, the disappearance of the intense 248-mμ peak of allylmercuric iodide.[2]

Results

In all cases the change in optical density with time was accurately given by eq 1.[9] The symbols have their

$$k_1 = [2.303/(t - t_0)] \log [(D_0 - D_\infty)/(D_t - D_\infty)] \quad (1)$$

usual significance.[2] Pseudo-first-order rate constants, k_1, were evaluated graphically. As in previous work, the typical deviations in k_1 values measured repetitively were 3–5%.

(1) (a) Supported, in part, by the National Science Foundation through GP-5088. (b) National Science Foundation Undergraduate Research Participant, Summer, 1965. (c) National Science Foundation Undergraduate Research Participant, Summer, 1966.
(2) M. M. Kreevoy, P. J. Steinwand, and W. V. Kayser, *J. Am. Chem. Soc.*, **88**, 124 (1966).
(3) A. J. Kresge and D. P. Onwood, *ibid.*, **86**, 5014 (1964).
(4) V. Gold and M. A. Kessick, *J. Chem. Soc.*, 6718 (1965).
(5) Earlier references are cited in ref 2–4.
(6) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, England, 1949, Chapter V.
(7) A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **83**, 2877 (1961).
(8) R. J. Thomas and F. A. Long, *ibid.*, **86**, 4770 (1964).
(9) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1961, p 29.