solution was evaporated to give 13 mg. of a liquid which was treated with permanganate and steam distilled as in the preparation of **3**. The product was 8 mg. of a liquid with an infrared spectrum identical with that of **3**.

The ester was converted to the *t*-butylamide as described for **22**, and purified by chromatography over 8 g. of neutral alumina (activity I) which was eluted with hexane–chloroform(2:1). After 180 ml. had passed through the column, 6 mg. of the amide, m.p. 90–105°, was eluted. The infrared spectrum was superimposable on that of **7**. The amide was sublimed and recrystallized from ethanol–water to give white needles, m.p. 127–130°, melting point undepressed upon admixture of the needles with **7** from photolysis in the presence of oxygen.

Nonoxidative Photolysis of Carvonecamphor in Benzene. A solution of 4.0 g. of carvonecamphor in 1050 ml. of benzene mixed with 10 ml. of water was stirred continuously and irradiated for 3 hr. with the Hanovia lamp in a quartz well. The solution was extracted with sodium carbonate solution. Acidification and extraction of the aqueous solution resulted in only a trace of product. The benzene was removed by distillation at reduced pressure, leaving 4.1 g. of a syrupy residue, λ_{max}^{neat} 5.49 and 5.73 μ. To the residue was added 0.8 ml. of bis(2-ethoxyethyl) ether (which has a boiling point nearly that anticipated for an unsaturated aldehyde, $C_{10}H_{14}O$), and the mixture was distilled at 63° (2 mm.). The residue was hydrolyzed to the acid **4**. The distillate showed no 5.49-μ absorption. One milliliter of benzene was added to the distillate and the solution was washed thoroughly with water. The n.m.r. spectrum of the benzene solution showed the product mixture to contain a maximum of 2% of aldehyde, and no trace at all of protons in the region of τ 5.5 to 5.9, or 9.2 to 9.6. A crude 2,4-dinitrophenylhydrazone derivative was prepared, and the n.m.r. spectrum of this derivative likewise indicated the complete absence of methylenecyclobutane and cyclopropane protons.

The Diterpene Alkaloids. A Study of the Isomerization of Iso-Type Diterpene Alkaloid Salts to Normal-Type Salts

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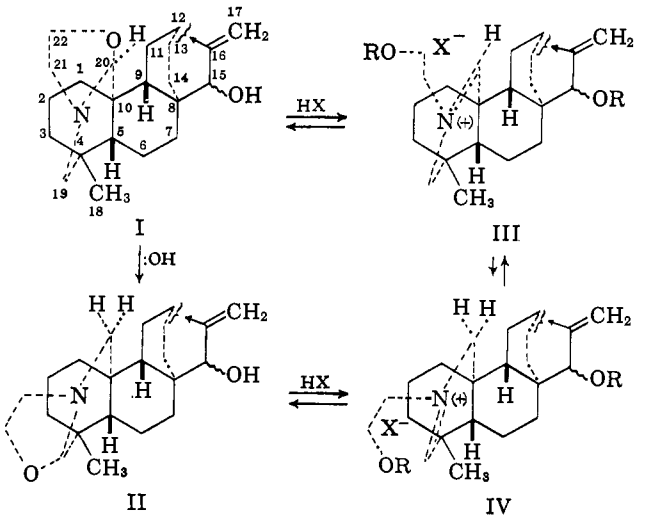
The iso-type diterpene salts are smoothly isomerized to the normal-type salts at reflux temperature in such solvents as DMA, DMF, DEF, DMSO, phenol and high-boiling alcohols. The isomerization follows first-order kinetics and the rate is greater in the proton-donor type solvents than in the nondonor type. The effect of temperature on the rate of isomerization of isoatisinium chloride in DEF, DMSO, methyl carbitol, ethyl carbitol, and 2-butoxyethanol is shown by Arrhenius plots. The energy of activation (E_a), enthalpy of activation ($\Delta H°*$), entropy of activation ($\Delta S°*$), and frequency factor (A) were calculated for isomerization in DEF, DMSO, methyl carbitol, and 2-butoxyethanol. A plot of ln k_1/T vs. $1/T$ demonstrates that the data for the isomerization do not show a true isokinetic relationship. Thermal isomerization of the ternary iminium salts provides a convenient, practical method of reversing the facile normal base → isobase isomerization.

The smooth isomerization of the normal-type diterpene bases (I)[1] such as atisine, veatchine, garryfoline, and cuachichicine to the iso-type bases (II) has been accounted for in terms of the steric interaction between substituents on the tetrahedral C-20 atom of the oxazolidine form and other parts of the molecule.[1a,b,e,2-4] In the normal-type bases it can readily be demonstrated with models that serious repulsive interactions exist between the 20-H and the 13-H and 14-H, when C-20 is tetrahedral. However, in the ternary iminium salt form (III) in which C-20 is trigonal, these interactions are relieved.[2,3,5] The isomerization may, therefore,



(1) Recent review articles on the diterpene alkaloids are: (a) S. W. Pelletier, *Experientia*, 20, 1 (1964); (b) S. W. Pelletier, *Tetrahedron*, **14**, 76 (1961); (c) H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Academie-Verlag, Berlin, 1961, pp. 851–905, 1009–1011; (d) E. S. Stern in "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, pp. 473–503; (e) K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products," Vol. XVI, Springer-Verlag, Vienna, 1958, pp. 26–63.

(2) K. Wiesner and J. A. Edwards, *Experientia*, **11**, 255 (1955).

(3) S. W. Pelletier and W. A. Jacobs, *Chem. Ind.* (London), 1385 (1955).

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(5) D. Dvornik and O. E. Edwards, *Can. J. Chem.*, **35**, 860 (1957).

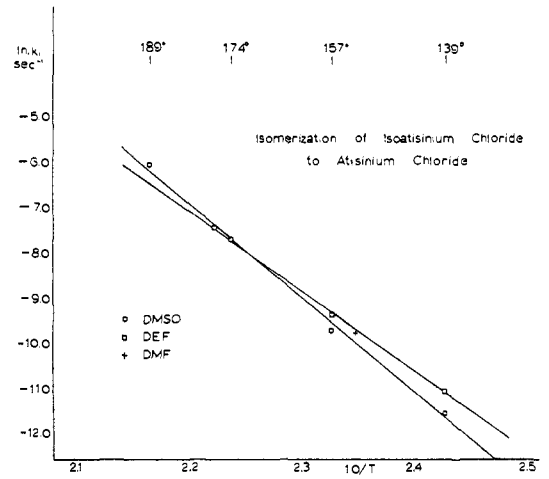

Figure 1. Arrhenius plot of ln k_1 *vs.* $1/T$.

proceed through the ternary iminium salt forms (III → IV) by prototropy. Since steric factors are responsible for the "iso"-bases (II) having a lower free energy than the normal bases, the equilibrium is shifted toward the more favored "iso"-forms (II).[1b,6]

In the case of the salts of the normal and "iso"-bases, a stability the reverse of that described for the free bases would be expected.[2,7] Thus, the normal-type salt with the less bulky trigonal carbon atom in the hindered 20-position (III) should be more stable than the "iso"-salt (IV) which has a tetrahedral carbon at this position. In this connection it has been reported that refluxing isoatisinium diacetate chloride[8] (IV, R = Ac, 12–16 bond) in acetic anhydride–acetic acid gives the corresponding atisinium diacetate chloride (III, R = Ac, 12–16 bond).[9] Since, however, the conversion of atisinium diacetate chloride to atisine by treatment with base risks isomerization[1a,10] back to isoatisine or elimination of the β-acetoxyethyl group by an internal, Hofman-type reaction,[5] the procedure is of little practical utility in reversing the normal to "iso"-base isomerization. It was, therefore, of particular interest to determine whether stability factors were such as to allow a reversal of the isomerization by operation directly on the "iso"-base salts. This paper reports details of the successful isomerization of isoatisinium chloride (IV, R = H, X = Cl, 12–16 bond) to atisinium chloride (III, R = H, X = Cl, 12–16 bond) under a variety of experimental conditions[7] (Table I). The isomerization proceeds smoothly at reflux temperatures in such polar solvents as N,N-dimethyl acetamide (DMA), N,N-dimethylformamide (DMF), N,N-diethylformamide (DEF), phenol, dimethyl sulfoxide (DMSO), the cellosolves, and carbitols. The isomerization even proceeds in water, with 20 hr. of boiling effecting conversion of the iso-salt to atisinium chloride to the extent of 19%. Pure atisinium chloride could be isolated from most of the solvents employed in a yield of about 85%. For preparative purposes (see the Experimental Section) dimethyl sulfoxide is the solvent of choice. Although the rate of isomerization in 2-octanol is almost as great as in DMSO and the boiling temperature is lower, the low solubility of isoatisinium chloride in 2-octanol restricts the preparative utility of this solvent.

Table I

Solvent	—Temp.— °C.	°K.	$10^3/T$	$10^4 k_1$, sec.$^{-1}$	$-\ln k_1$, sec.$^{-1}$
2-Methoxyethanol	121	394	2.538	0.16	11.04
2-Ethoxyethanol	134	407	2.457	0.31	10.37
DMF	153	426	2.347	0.60	9.70
1-Hexanol	156	429	2.331	2.82	8.17
DMA	165	438	2.283	1.56	8.76
2-Octanol	177	450	2.222	21.2	6.15
Phenol	180	453	2.208	13.5	6.60
DMSO	189	462	2.165	25.2	5.98
	174	447	2.237	4.83	7.63
	157	430	2.326	0.634	9.67
	139	412	2.427	0.101	11.49
DEF	177	450	2.222	6.28	7.37
	157	430	2.326	0.927	9.29
	139	412	2.427	0.168	11.0
Methyl carbitol	192	465	2.151	25.2	5.98
	174	447	2.237	5.52	7.49
	157	430	2.326	1.11	9.10
	139	412	2.427	0.237	10.64
Ethyl carbitol	198	471	2.123	31.3	5.76
	174	447	2.237	5.04	7.59
	157	430	2.326	1.258	8.98
	139	412	2.427	0.146	11.14
2-Butoxyethanol	169	442	2.263	2.98	8.11
	157	430	2.326	1.116	9.10
	139	412	2.427	0.162	11.03

This isomerization of the ternary iminium salts of diterpene bases is apparently of general utility for it has been demonstrated that garryinium chloride[11] (IV, R = H, X = Cl, 13–16 bond) is isomerized to veatchinium chloride,[11] (III, R = H, X = Cl, 13–16 bond) in 85% yield by refluxing for 30 min. in dimethyl sulfoxide.[7] Since the normal-type ternary iminium salts can be smoothly converted to the corresponding bases by treatment with cold, aqueous sodium hydroxide, the present work provides a convenient method of reversing the facile normal base → "iso"-base isomerization.

It can be seen from Table I that the rate of isomerization is a function of the boiling point of the solvent selected. The pseudo-first-order rate constant ($k_1 = \ln [C_0/C]/t$) calculated at the reflux temperature of each solvent is shown in Table I. It is also apparent that at a given temperature, the isomerization rate is greater in proton-donor-type solvents such as alcohols than in nonproton-donor solvents such as DMF or DMA. For example, the rate in DMF (b.p. 153°) is 0.60×10^{-4} sec.$^{-1}$ whereas in 1-hexanol (b.p. 156°) it is 2.82×10^{-4} sec.$^{-1}$. Even in the higher boiling DMA (b.p. 165°), the rate (1.56×10^{-4} sec.$^{-1}$) is less than in 1-hexanol. Another interesting comparison is the rate difference between DEF ($k_1 = 6.28 \times 10^{-4}$ sec.$^{-1}$) and 2-octanol ($k_1 = 21.2 \times 10^{-4}$ sec.$^{-1}$), both of which boil at the same temperature. On the other hand, the isomerization rate in DMSO (b.p.

(6) A. J. Solo and S. W. Pelletier, *Proc. Chem. Soc.*, **14** (1961).
(7) S. W. Pelletier and K. Kawazu, *Chem. Ind.* (London), 1879 (1963).
(8) Isoatisinium chloride is the so-called "isoatisine hydrochloride." Since the salts resulting from the addition of HX acids to atisine, veatchine, and related diterpene bases exist as ternary iminium salts rather than simple hydrohalide salts, they will be referred to as atisinium, veatchinium, etc., halides.
(9) O. E. Edwards and T. Singh, *Can. J. Chem.*, **33**, 448 (1955).
(10) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **147**, 567 (1943).
(11) K. Wiesner, S. F. Figdor, M. F. Bartlett, and D. R. Henderson, *Can. J. Chem.*, **30**, 608 (1952).

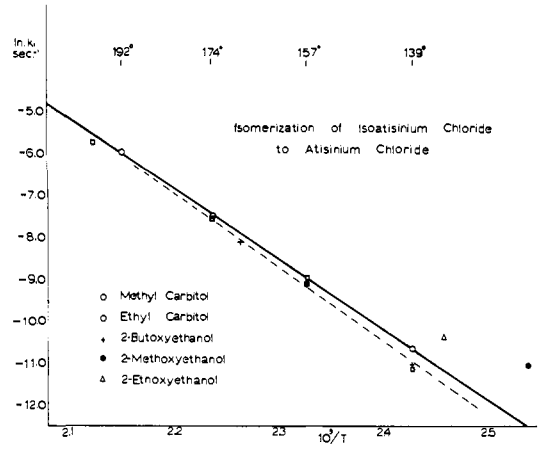

Figure 2. Arrhenius plot of ln k_1 *vs.* $1/T$.

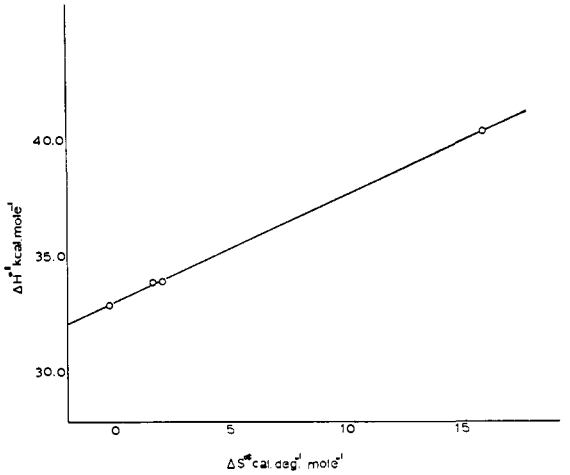

Figure 3. Plot of $\Delta H^{\circ *}$ *vs.* $\Delta S^{\circ *}$ for data of Table II.

189°, $k_1 = 25.2 \times 10^{-4}$ sec.$^{-1}$) is equal to that of methyl carbitol (b.p. 192°).

The effect of temperature on the rate of isomerization in DMSO is revealed by an Arrhenius plot of ln k_1 *vs.* the reciprocal of the absolute temperature, T (Figure 1). A similar treatment of the data for DEF is also shown in Figure 1. The straight line for DEF also accommodates the data obtained for DMF at the reflux temperature. The variation of rate with temperature was also studied in three typical proton-donor solvents; namely, methyl carbitol, ethyl carbitol, and 2-butoxyethanol (Figure 2). The straight line obtained for methyl carbitol also accommodates fairly well the data for ethyl carbitol. The energies of activation (E_a) were calculated for the slopes of the lines obtained using the formula $E_a = -R$ (slope). The frequency factor (A), enthalpy of activation ($\Delta H^{\circ *}$), and the entropy of activation (ΔS^{0*}) were also calculated from the equations $\ln A = \ln k_1 - (\text{slope}/T)$, $\Delta H^{\circ *} = E_a - RT$, and $A = (RT/Nh)e^{\Delta S^{\circ *}/R+1}$, respectively. A summary of these results is provided in Table II.

Table II

Solvent	E_a, kcal. mole^{-1}	$\Delta H^{\circ *}$, kcal. mole^{-1}	A, sec.$^{-1}$	$\Delta S^{\circ *}$ (157°), cal. deg.$^{-1}$ mole^{-1}
DEF	35.0	34.1	5.75×10^{13}	1.7
DMSO	41.5	40.6	7.76×10^{16}	16.0
Methyl carbitol	34.0	33.1	2.19×10^{13}	−0.21
2-Butoxyethanol	35.0	34.1	7.08×10^{13}	2.1

From Table II it is clear that the energy of activation for isomerization decreases as the reaction is conducted in more polar solvents. A similar difference is also observed in the frequency factor, A, which has a value of the order of 10^{16} in DMSO compared with 10^{13} in methyl carbitol.

The effect of polarity of the solvent on the rate of reaction is best seen by reference to the line for 2-butoxyethanol in Figure 2. The data for isomerization in 2-methoxy- and 2-ethoxyethanol at the reflux temperature are also included in the figure. The rate of isomerization in 2-butoxyethanol at 139° is 1.62×10^{-4} sec.$^{-1}$. Although the boiling point of 2-methoxyethanol is 18° lower, the rate in this solvent is about equal (1.6×10^{-4} sec.$^{-1}$) to that in the butyl derivative. Furthermore, the ln k_1 value as calculated from Figure 2 for 2-butoxyethanol at 134° is −11.4. This value is much lower than the corresponding value of −10.37 at 134° for 2-ethoxyethanol. Therefore, at 134°, the isomerization proceeds much faster in ethyl cellosolve than in butylcellosolve. Thus, increase in polarity (decrease of alkyl chain length) in going from butyl to ethyl to methyl cellosolve increases the rate of reaction.

The data of Table II are ideally suited to check the possibility of the existence of an isokinetic relationship. A plot of $\Delta H^{\circ *}$ against $\Delta S^{\circ *}$ at 430°K. for the four solvents listed in Table II gives a straight line (Figure 3) with points deviating only slightly from the line. This isomerization would then qualify as an example of an isokinetic relationship by the standard of Leffler and Grunwald.[12] However, the inadequacy of a $\Delta H^{\circ *}$ *vs.* $\Delta S^{\circ *}$ plot as a demonstration of the existence of isokinetic relationship has recently been discussed.[13,14] These authors have pointed out that $\Delta H^{\circ *}$ and $\Delta S^{\circ *}$ are derived quantities removed from experiment by a number of computation steps and their values are not obtained independently, but are both computed from a single equation. Furthermore, it was shown that, if the observed variation in $\Delta H^{\circ *}$ throughout a given series of reactions were due largely to random errors in the determinations of the rate constant, exactly this linear relationship between $\Delta H^{\circ *}$ and $\Delta S^{\circ *}$ would be observed. These authors further noted the lack of a clearly valid linear $\Delta H^{\circ *}$–ΔS^{*} relationship in the literature.[14] In view of this, log k_1/T was plotted against $1/T$ (Figure 4). If there were a true isokinetic relationship, the four lines on Figure 4 should intersect at one point. It can be readily seen that this is not the case and, therefore, the data for the isomerization of isoatisinium chloride to atisinium chloride do not show a true isokinetic relationship.

(12) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963.
(13) R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, **83**, 3819 (1961).
(14) R. C. Petersen, *J. Org. Chem.*, **29**, 3133 (1964).

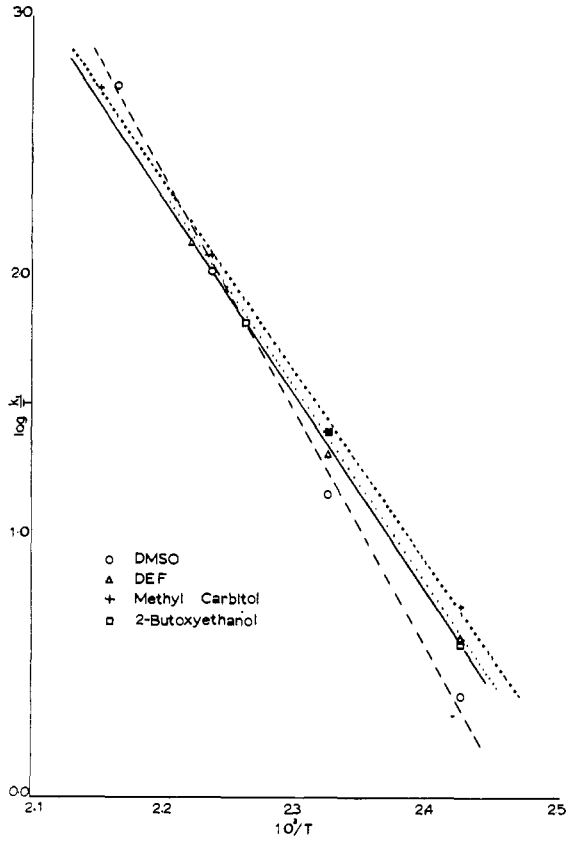

Figure 4. Activation plot of data of compounds in Table II.

Experimental Section

All solvents were carefully distilled prior to use. Some samples of diethylformamide contained considerable amounts of formic acid which caused the reduction of isoatisine to dihydroatisine. The solvent was therefore dried twice over potassium hydroxide and distilled over lime. Melting points are corrected and were taken on a hot stage equipped with a microscope and polarizer. Finely powdered samples were placed on the stage 15° below the melting point and the temperature raised at a rate of about 4°/min.

Isoatisinium Chloride. To a cold solution of 2.1 g. of isoatisine in 30 ml. of acetone was added, with cooling in ice, a solution of 0.6 ml. of concentrated hydrochloric acid in 5 ml. of acetone until the solution was faintly red to litmus. The crystals were collected and washed with ether until free of hydrochloric acid. Recrystallization of the product from methanol–ether gave 1.99 g. of pure isoatisinium chloride, m.p. 312–314° (lit.[10] m.p. 295–299°), $[\alpha]^{21}D$ −7.3° (*c* 2.0, EtOH).

Linearity of Optical Rotation with Composition. Pure samples of atisinium chloride, $[\alpha]D$ +22.4 (EtOH), and isoatisinium chloride, $[\alpha]D$ −7.3° (EtOH), were mixed in three different compositions and the rotations determined in 95% ethanol. An average of ten readings was taken for each composition: % atisinium chloride, 73.95, 49.49, and 26.18; $[\alpha]D$, +14.2, +7.4, and −0.2. A plot of $[\alpha]D$ against per cent of atisinium chloride gave a straight line.

Determination of the Rate of Isomerization. A. At Reflux Temperature of the Solvent. Isoatisinium chloride (30–40 mg.) was dissolved in as small an amount of the indicated solvent as possible. The solution was boiled under reflux in a gentle stream of nitrogen for the indicated time and then the contents was cooled quickly in an ice bath. The solvent was evaporated *in vacuo*, and the residue was dissolved in methanol and concentrated to a very small volume. Addition of a large excess of ether precipitated a mixture of atisinium and isoatisinium chlorides in 84–95% yield. The composition of the mixture was determined as described under B. Table III contains the results used to calculate the rates of isomerization.

B. At Temperatures Lower Than the Reflux Temperature of the Solvent. The apparatus consists of two, concentric, round-bottomed flasks joined at the neck with a ground-glass joint. The larger outer flask which contained the bath liquid was also provided with a side neck fitted with a ground-glass joint for the attachment of a condenser. The inner flask was attached through a gas inlet type joint to a condenser. The bath liquid in the outer flask was chosen so that it boiled at the temperature for which the kinetic data was required, *e.g.*, boiling *p*-dichlorobenzene for a temperature of 174°, boiling bromobenzene for a temperature of 157°, and boiling xylene for a temperature of 139°.

With the outer flask about half-filled with the bath liquid and the inner flask containing the solvent in which the reaction was to be run, the apparatus was assembled and a gentle stream of nitrogen was passed through the reaction flask. The bath liquid was allowed to reflux for about 30 min. to permit the solvent in the inner flask to attain the temperature of the bath liquid. Isoatisinium chloride (40–50 mg.) was quickly introduced, the apparatus was shaken briefly to facilitate solution, and the stop watch was started. The mixture was heated in a gentle stream of nitrogen for the indicated period. The entire apparatus was quickly cooled in ice, and the solution was drawn off from the inner flask and evaporated *in vacuo*. Further work-up was as previously described. A different sample was used for each determination since a procedure utilizing withdrawal of aliquots did not give reproducible results.

The composition of the mixture was calculated from its optical rotation, using the linear relation existing between atisinium chloride, $[\alpha]D$ +22.4° (EtOH), and isoatisinium chloride, $[\alpha]D$ −7.3° (EtOH). The rate constant (k_1) for the isomerization was calculated from the slope of the plot of the log of the concentration of isoatisinium chloride against time. Table III contains the results used to calculate rate constants.

Isomerization of Isoatisinium Chloride to Atisinium Chloride (Preparative Method). A solution of 1.0 g. of isoatisinium chloride, $[\alpha]D$ −7.3°, in 25 ml. of dimethyl sulfoxide was boiled under reflux in a gentle stream of nitrogen for 30 min. The solvent was removed *in vacuo* and the residue was crystallized from methanol–ether to give 938 mg. of crude atisinium chloride, $[\alpha]D$ +21.5° (*c* 2.0, EtOH). The infrared spectrum in Nujol revealed the presence of a small amount of the isoatisine salt. A solution of the above product in 1% sulfuric acid was basified to pH 8.65 with sodium carbonate solution and extracted with benzene to remove the isoatisine. The cold, aqueous

Table III. Percentage of Isoatisinium Chloride in Isomerization Mixture

Solvent	Temp., °C.	5 min.	10 min.	15 min.	30 min.	1 hr.	2 hr.	2.5 hr.	4 hr.	6 hr.	9 hr.	15 hr.	20 hr.	24 hr.
Water	100												81	
2-Methoxyethanol	121							87		71	55		32	
2-Ethoxyethanol	134								64	50	37	24[a]	12	
DMF	153				91	79		58	41	28	14			
1-Hexanol	156			81	63	42,[b] 31	20[c]	9						
DMA	165		94		81	60		22	10					
2-Butoxyethanol	169			75	54	36	12	7						
	157					67	45	27.5[d]						
	139									67.5[e]		38.5[q]		25[r]
DEF	177	82		55	34	11		2						
	157						46	38.5[d]		20[f]				
	139										59.3[g]	35[h]		23.5
2-Octanol	177	44	32	12	10[i]									
Phenol	180	65	46	30	9									
DMSO	189	73,[j] 46	23	11	2									
	174			76	42	17								
	157						65.5		40	25				
	139										71[k]		49	34,[l] 24[m]
Methyl carbitol	192	52,[n] 47	21	11	1									
	174			74	33	12								
	157				86	70		35	19					
	139								70		45	31	18	
Ethyl carbitol	198	75,[j] 38	16	6										
	174			73, 65[i]	42.25	19[p]								
					29.5[o]									
	157						43.5	24.5[d]	16.75					
	139									68.5[e]		43[q]	34	

[a] 12 hr. [b] 45 min. [c] 90 min. [d] 3 hr. [e] 7 hr. [f] 5 hr. [g] 8 hr. [h] 17 hr. [i] 20 min. [j] 2 min. [k] 10 hr. [l] 30 hr. [m] 40 hr. [n] 4 min. [o] 40 min. [p] 50 min. [q] 16 hr. [r] 25 hr.

solution was basified to pH 11.5 with sodium hydroxide solution and quickly extracted with benzene to give 922 mg. of atisine. Conversion to the hydrochloride salt afforded 825 mg. (83%) of pure atisinium chloride, m.p. 316–318°, $[\alpha]_D$ +22.5° (EtOH). The infrared spectrum in Nujol was identical with that of an authentic sample of atisinium chloride.

Isomerization of Isoatisinium Chloride in Dry DMSO. DMSO was dried over calcium hydride, distilled, and dried twice over a molecular sieve. A solution of 30 mg. of isoatisinium chloride in 1.5 ml. of very dry DMSO was refluxed in a gentle stream of dry nitrogen (passed through silica gel and a molecular sieve) for 15 min. Work-up as usual gave 27.2 mg. of crystals, $[\alpha]_D$ +19.3°, showing 90% atisinium chloride content. The result did not differ any from that of experiments in which the isomerization was conducted in ordinary DMSO.

Isomerization of Veatchine To Garryine. A solution of 480 mg. of veatchine,[11,15] m.p. 128–130°, in 20 ml. of methanol was boiled under reflux for 9 hr. Evaporation of the solvent *in vacuo* gave an amorphous solid, m.p. 65–70°. Crystallization from acetone–water (3:2) gave 480 mg. of garryine hydrate,[11] m.p. 73–76°. Recrystallization from acetone furnished 364 mg. of garryine hydrate, m.p. 73–76°.

Anal. Calcd. for $C_{22}H_{33}NO_2 \cdot H_2O$: C, 73.09; H, 9.76. Found: C, 73.06; H, 9.61.

Garryinium Chloride. To a solution of 300 mg. of garryine hydrate in 5 ml. of acetone was added dropwise a cold solution of 1 ml. of concentrated hydrochloric acid in 5 ml. of acetone until the solution was faintly acid to litmus. The crystals were collected and washed free of acid with ether, 293 mg., m.p. 266–270°. Crystallization from methanol–ether afforded 260 mg. of garryinium chloride,[11] m.p. 269.5–272.5°.

Anal. Calcd. for $C_{22}H_{33}NO_2 \cdot HCl$: C, 69.55; H, 9.02. Found: C, 69.65; H, 9.12.

Isomerization of Garryinium Chloride to Veatchinium Chloride. A solution of 29 mg. of garryinium chloride in 0.9 ml. of DMSO was boiled under reflux in a gentle stream of nitrogen for 30 min. Evaporation of the solvent gave a residue which was taken up in methanol. Addition of ether gave 25 mg. of veatchinium chloride,[11,15] m.p. 273–275°, $[\alpha]_D$ −56.5° (*c* 1.4, EtOH). An authentic sample showed $[\alpha]_D$ −55.9°. The infrared spectrum of the product in Nujol was identical with that of an authentic sample of veatchinium chloride.

Conversion of Isoatisinium Chloride to Dihydroatisine. A solution of 259 mg. of isoatisinium chloride in 24 ml. of diethylformamide was boiled under reflux in a current of nitrogen for 10 min. Evaporation of a 3-ml. aliquot *in vacuo* gave 24 mg. of residue which showed no $>C{=}N^{+}<$ absorption in the 1680-cm.$^{-1}$ region of the infrared spectrum. The solution of the product in water was basified and extracted with benzene. Evaporation of the benzene gave a product which crystallized from aqueous acetone, m.p. 162–165°. The infrared spectrum of the product was identical with that of a sample of dihydroatisine.

When isoatisinium chloride was refluxed with DEF which had been previously dried over KOH and distilled over lime, reduction to dihydroatisine did not occur.

(15) S. W. Pelletier and D. M. Locke, *J. Am. Chem. Soc.*, 87, 772 (1965).

Acknowledgment. This work was supported in part by Grant GM 10921 from the National Institutes of Health and by Grant GP-690 from the National Science Foundation. We thank Dr. Francis Johnston for reading the manuscript and making several clarifying suggestions.

The Total Syntheses of *d,l*-Matrine and *d,l*-Leontine[1]

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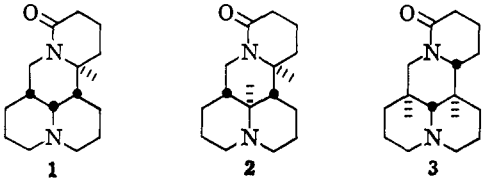
The total syntheses of d,l-matrine and d,l-leontine are described.

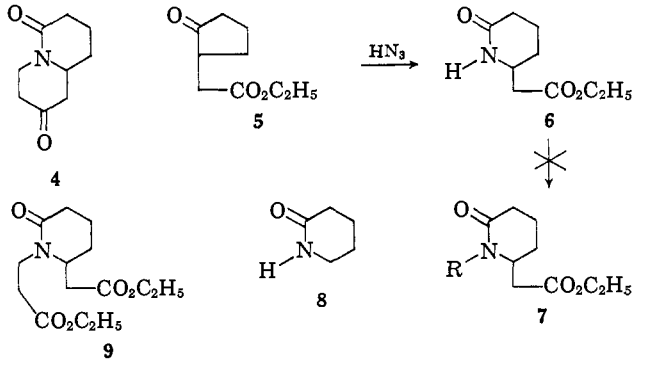
Matrine, the principal alkaloid of *Sophora flavescens* Ait., has been shown[3] to have the structure and relative stereochemistry of **1**. Matrine has been isomerized



1 **2** **3**

with platinum[4] to allomatrine **2**. Leontine, isolated from *Leontice eversmanni* Bge., has been shown[5] to be the optical antipode of allomatrine, and thus has structure **3**. This work reports the application of our quinolizidine synthesis[6] to the total syntheses of *d,l*-matrine (**1**) and *d,l*-leontine (**3**).

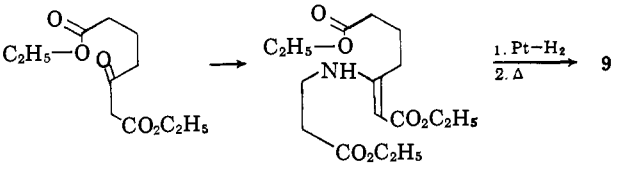
Our earlier work[6,7] had made it apparent that the intermediate needed for this proposed approach would be 8-oxo-2-quinolizidone (**4**), for were we to have this



4 **5** **6** **7** **8** **9**

material available, bis-α,α'-alkylation (*via* the Stork[8] enamine procedure) with acrylonitrile followed by catalytic hydrogenation should afford the gross structure desired. We planned to prepare **4** *via* the diester **9** which should after Dieckmann cyclization, hydrolysis, and decarboxylation, give **4**. Toward this end we attempted the alkylation of **6**, itself prepared as indicated. However, the N-alkylation of **6** could not be effected, even under conditions where **8** alkylates in 95% yield.[9]

We therefore developed an alternate route to the preparation of **9**. Diethyl 3-oxopimelate[10] was condensed with ethyl β-alaninate to yield **10**, which was reduced over Adams catalyst and then warmed on a steam bath to afford **9**.



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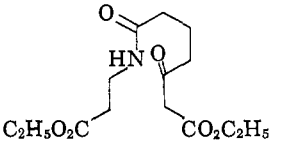
A by-product in the formation of **10** was the amide



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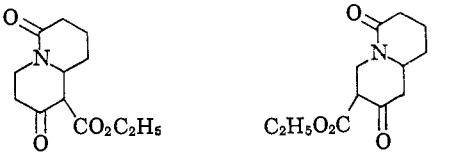
11. Various attempts to utilize this substance in subsequent steps or to discourage its formation were ineffective. However, the lactam diester **9** could be obtained in 78% over-all yield in this sequence.

Dieckmann cyclization of **9** was effected through the agency of sodium hydride in refluxing benzene. Two products are possible from this reaction, **12** and **13**;



12 **13**

however, the reaction apparently proceeds in only one of the two possible directions for the product was

(1) We gratefully acknowledge the support of this work by the National Institutes of Health through Research Grant RG-7902. For a preliminary communication of these results, see L. Mandell, K. P. Singh, J. T. Gresham, and W. J. Freeman, *J. Am. Chem. Soc.*, **85**, 2682 (1963).

(2) This work is taken in part from the Ph.D. Dissertations of K. P. S., 1960, and J. T. G., 1963, and the M.S. Thesis of W. J. F., 1965, at Emory University.

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