yellow solid, m.p. 280–290°. Both samples were shown to be slightly impure 2-(4-nitrophenyl)-4-amino-6-nitroquinazoline by comparison of infrared spectra with the spectrum of an authentic sample[8] m.p. 303–304°, and by subsequent recrystallization to give pure material. Cooling of the water extract above yielded 0.1 g. of 2-amino-5-nitrobenzonitrile, m.p. 204–206°, identical with an authentic sample.[12]

PRINCETON, N. J.

(12) H. Ph. Baudet, *Rec. trav. chim.*, **43**, 707 (1924).

[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY, THE ORTHO RESEARCH FOUNDATION]

Piperidylquinolizidines Derived from Sparteine

HENRY BADER[1a]

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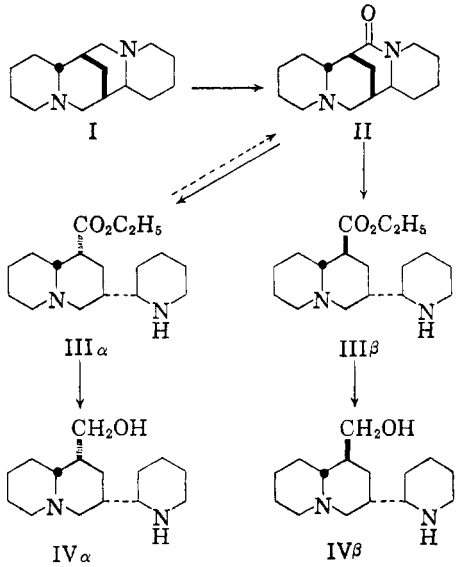
Through the hydrolytic cleavage of *l*-oxysparteine 1α- and 1β-carbethoxy-3α-(2′-piperidyl)quinolizidine (IIIα and IIIβ) were obtained, and from these were derived various other 1-substituted 3α-(2′-piperidyl)quinolizidines. Several different approaches to the synthesis of the 1-unsubstituted 3α-(*N*-methyl-2′-piperidyl)quinolizidine (XI) are described; one of these, utilizing a Curtius degradation, proved successful.

The known oxytocic properties of sparteine (I) prompted an investigation of simpler piperidylquinolizidines which can be derived from it through an opening of its ring C.



This class of compounds, very little known when the present work was initiated, has in the meantime received attention from several workers,[4–6,9,19] most of whom have used fully synthetic routes. The alternative approach followed in this work, namely using *l*-sparteine as the starting material, had the advantage of being able to produce individual steroisomers rather than diastereoisomeric pairs. The preparation of the starting material, *l*-oxysparteine (II), in satisfactory yield required some modification of the conditions hitherto mentioned in the literature. Although Schöpf[1b] claimed a 95% yield of the crystalline lactam after one-half minute of oxidation of sparteine with potassium ferricyanide, in our hands these conditions produced only 15% of oxysparteine. Clemo, Morgan, and Raper[2] obtained a 35% yield after five hours of reaction at room temperature. In our experience the best yield (60%) was obtained after three hours at 55–60°.

l-Oxysparteine was hydrolyzed with concentrated hydrochloric acid at 180° during twenty-four hours, following Orechoff's procedure for the hydrolysis of its *d*-isomer, oxypachycarpine.[3] The resulting amino acid was converted into its ethyl ester, which was separated by chromatography into the two isomeric esters IIIα and IIIβ. Regardless of the reaction time, there was always an appreciable amount of oxysparteine recovered. This proved to be attributable, not to incomplete hydrolysis, but to reformation of the original amide from the less stable of the two isomeric amino esters. In fact, the ester which was obtained in lower yield (10–13%) could be completely reconverted into oxysparteine by slow distillation at 130°, and even a very rapid distillation produced an appreciable amount of the lactam. Merely standing at room temperature for one month was sufficient to induce an 18–20% conversion of this isomer into oxysparteine, as judged by the alteration in its infrared spectrum. The other isomer showed no tendency to recyclise. This difference between the two isomers can only be ascribed to a difference in the orientation of the carbethoxy group, which in the unstable isomer must be *cis* to the piperidyl substituent, as it is in oxysparteine. The carbethoxy group of this isomer is therefore α-oriented (IIIα).

The other isomer, obtained in 35–65% yield, could be distilled or stored indefinitely without undergoing conversion to oxysparteine. Its carbethoxy group is therefore *trans* to the piperidyl substituent, or β-oriented (IIIβ). Its formation is,

(1a) Present address: American Cyanamid Company, Bound Brook, N. J.

(1b) C. Schöpf, *Ann.*, **465**, 132 (1928).

(2) G. R. Clemo, W. McG. Morgan, and R. Raper, *J. Chem. Soc.*, 1025 (1936).

(3) A. P. Orechoff, M. I. Kabatchnik, and T. J. Kefely, *Compt. rend. USSR*, **31**, 335 (1941).

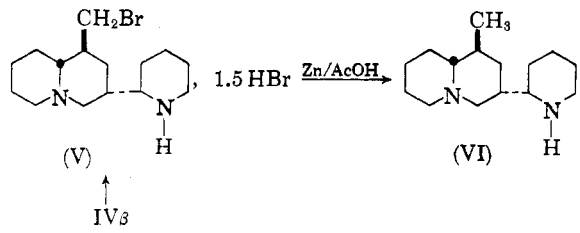
of course, not unexpected, since the COOR thereby attains the more stable equatorial conformation.[4]

The esters III were reduced with lithium aluminum hydride to the corresponding hydroxymethylderivatives (IVα) and (IVβ). These compounds were recently reported by Galinovsky and his collaborators,[5] who used the same reaction sequence described in the present paper, but omitted the separation of the isomeric ethyl esters subjecting the crude distillate of III directly to lithium aluminum hydride reduction. Undoubtedly because of the presence of reformed oxysparteine in this distillate, they were unable to obtain satisfactory analyses for the mixture of esters or their derivatives. The physical constants recorded for their specimens of IV do not agree with our findings (Table I); we can suggest no explanation for these discrepancies.[6]

TABLE I

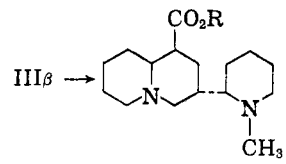
	Present Work	Galinovsky *et al.*[5]
	M.p. 105–105.5°	M.p. 163–164°
	B.p. 143° (bath)/0.004 mm.	—
IVα	$[\alpha]_D^{24}$ 0°	$[\alpha]_D^{18}$ −7.46°
	Dihydrochloride, m.p. 247–248°, $[\alpha]_D^{24}$ + 1.9°	—
	Dipicrate, m.p. 112–113°	—
	M.p. 32°	Oil
	B.p. 140° (bath)/0.001 mm.	B.p. 130–140°/0.02 mm.
IVβ	$[\alpha]_D^{24}$ +19.5°	$[\alpha]_D^{24}$ + 20.6°
	Dihydrochloride m.p. 275–277°	—
	Dipicrate m.p. 96–98°	M.p. 212–213°

To produce a non-oxygenated "opened-ring analog" of sparteine, the carbinol (IVβ) was converted *via* the bromide (V) into the 5-methyl derivative (VI).

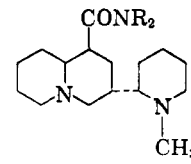


Although the bromide V was stable in the form of its sesquihydrobromide, on liberating the free base an ether-soluble oil was obtained which slowly changed into an ether-insoluble solid. The infrared spectrum of this solid was quite different from that of sparteine hydrobromide. From the stereochemistry one can expect only a polymeric hydrobromide. This agrees with the finding of Galinovsky (*loc. cit.*), who obtained high-boiling polymeric material by treatment of the salt with alkali.

For the sake of further pharmacologic study of piperidylquinolizidines, it seemed desirable to prepare the amides (IX) and (X) and the diethylaminoethyl ester (VIII).



VII. R=C_2H_5
VIII. R=$CH_2CH_2N(C_2H_5)_2$

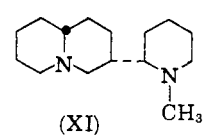


IX. R=H
X. R=C_2H_5

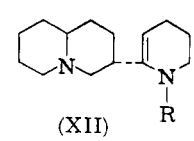
The ester (IIIβ) failed to react with ethanolic ammonia, which recalls the failure of Schöpf[7] to prepare lupininamide; base-catalyzed transesterification of IIIβ with diethylaminoethanol was also unsuccessful. In view of Schöpf's successful preparation of isolupininamide *via* the acid chloride,[7] the acid chloride dihydrochloride of the acid IIIβ was treated with ammonia, but only polyamides or oxysparteine were obtained. These failures are no doubt attributable to interference by the free NH of the piperidyl group.

The ester IIIβ was, therefore, *N*-methylated with formic acid–formaldehyde mixture to VII, which was saponified to the acid and converted to the acid chloride dihydrochloride. From this the ester VIII and the amides IX and X could be obtained without incident.

Attention was now turned to the structure XI, which was at one time suggested as that of a naturally occurring alkaloid, pusilline,[8] and which has subsequently been synthesized by five different



(XI)



(XII)

(4) Very recently, F. Bohlmann, E. Winterfeldt, and D. Schumann [*Chem. Ber.* **93**, 1948 (1960)] described isomeric methyl esters obtained in a very similar manner by hydrolysis of oxysparteine, using a double proportion of hydrochloric acid, and operating at 245° instead of 180°. Surprisingly, they found less reformed oxysparteine (9%), and besides the two isomers corresponding to IIIβ (21.8%) and IIIα (5.4%), obtained as the main product (32.8%) an ester which could be ring closed to 10-oxo-β-isosparteine. The latter was the major product above 220°, while at 200° 50% of the isomer corresponding to IIIα was formed. The conformation of 1,3-disubstituted quinolizidines was discussed by Galinovsky[5] and Bohlman.[6]

(5) F. Galinovsky, J. Derkosch, H. Nesvadba, P. Meindl, and Kh. Orgler, *Monatsh.*, **88**, 967 (1957).

(6) F. Bohlmann, W. Weise, H. Sander, H-G. Hanke, and E. Winterfeldt, *Chem. Ber.*, **90**, 653 (1957), reported the IVα racemate.

(7) C. Schöpf, *Ann.*, **465**, 104 (1928).

(8) L. Marion and S. W. Fenton, *J. Org. Chem.*, **13**, 780 (1948).

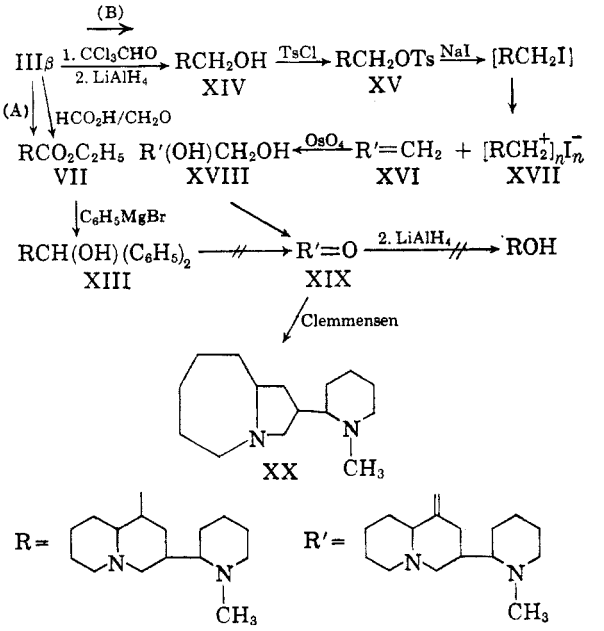
teams of workers,[9] all of whom obtained, however, either isomeric mixtures or racemates of unknown stereochemistry. Although pusilline is now known to be *l*-β-isosparteine,[10] the synthesis of structure XI in a well established stereochemical configuration is still of interest, particularly in view of the Russian work[11] on alkaloids occurring in the plant *Piptanthus nanus*. Piptanthine, piptamine, isopiptanthine and *N*-methylpiptanthine were all claimed to be isomers of structures XII (R = H and R = CH_3). The existence of these structures in nature indicates that piperidylquinolizidines VI and XI are biogenetically, as well as formally, related to sparteine alkaloids.

The simplest approach to XI would consist in the decarboxylation of the parent acid of III or VII. Reviews of the literature of the Hunsdiecker degradation[12] show only one application to a nonaromatic nitrogen heterocyclic compound, 2-bromoquinuclidine,[13] but details of the preparation of its silver salt are not given. In our case, we found that this salt could not be obtained. When the potassium salt obtained from the ester III was treated with silver nitrate, only silver oxide was produced. The same result was obtained even when the *N*-acetyl derivative of the acid of III was used; the quinolizidine system is obviously a stronger base than silver oxide. Rice's modification of the Hunsdiecker reaction,[14] consisting of direct treatment of the acid chloride dihydrochloride with an excess of silver oxide in carbon tetrachloride, was also unsuccessful.

Two multistep routes were therefore considered for degradation of the ester IIIβ to the ketone XIX, as shown in the following chart.

The first of these (A) began with a Barbier-Wieland degradation of the *N*-methyl ester VII. The diphenylcarbinol XIII was readily prepared, but its dehydration with acetic anhydride gave an olefin which could not be readily purified. Oxidation of the crude olefin gave a mixture containing some ketonic material, as shown by infrared spectrum, but in such poor yield that the scheme was dropped in favor of the alternative approach (B).

In this, ester IIIβ was formylated with chloral in chloroform, and the crude product was reduced with lithium aluminum hydride to the *N*-methyl carbinol XIV (92% yield from IIIβ). The tosylate XV of the carbinol reacted instantaneously with sodium iodide in acetone to form the unstable iodide, which, as anticipated, spontaneously eliminated hydrogen iodide to form the desired exomethylene compound (XVI) together with a polymeric quaternary iodide (XVII). (As in the case of the bromide V discussed above, the *trans* orientation of the 1,3-substituents on the quinolizidine ring does not allow ring closure to sparteine or to its isomers, and quaternization has to take place intermolecularly). The methylene compound was



obtained in 38–48% yield, while 50–60% of material polymerized to the quaternary salt. Attempts were made to alter the conditions of the reaction so as to favor the formation of the olefin. Replacing acetone by a solvent of lower dielectric constant, a 1:1 mixture of ethyl acetate and chloroform (ϵ 5.4), failed to suppress the quaternization. Eventually, it was found that the yield of olefin could be increased to 70% when the treatment with sodium iodide was followed with that of sodium *tert*-butoxide in *tert*-butyl alcohol.

The olefin was hydroxylated with osmium tetroxide, and the resulting glycol XVIII was cleaved with periodic acid to the desired 3α-(*N*-methyl-2′-piperidyl)-1-quinolizidone (XIX).

(9)(a) S. Ohki, Y. Noike, and K. Yamakawa, *Pharm. Bull. (Japan)*, **1**, 391 (1953), *Chem. Abstr.*, **49**, 10947i (1955). (b) K. Winterfeld, G. Wald, and M. Rink, *Ann.*, **588**, 125 (1954). (c) G. R. Clemo, B. W. Fox, and R. Raper, *J. Chem. Soc.*, 2693 (1954). (d) P. Knoth, *Monatsh.*, **86**, 210 (1955). (e) K. Winterfeld and K. Flick, *Arch. Pharm.*, **292**, 200 (1959).

(10) R. Greenhalgh and L. Marion, *Can. J. Chem.*, **34**, 456 (1956).

(11) R. A. Konovalova, B. S. Diskina, and M. S. Rabinovich, *J. Gen. Chem. (U.S.S.R.)*, **21**, 773 (1951); *Chem. Abstr.*, **45**, 9548e (1951); *Compt. rend. Acad. Sci. U.S.S.R.*, **78**, 705 (1951); *Chem. Abstr.*, **47**, 3860b (1953); B. S. Diskina and R. A. Konovalova, *Compt. rend. Acad. Sci. U.S.S.R.*, **81**, 1069 (1951), *Chem.Abstr.* **47**, 4889b (1953); N. F. Proskurnina, *J. Gen. Chem. (U.S.S.R.)*, **27**, 3160 (1957); *Chem. Abstr.*, **52**, 8164d (1958). N. J. Leonard in *The Alkaloids* (edited by R. H. F. Manske, Academic Press, New York, 1960, Vol. VII, p. 306) pointed out that the double bond in XII must be in the quinolizidine rather than in the piperidine ring.

(12) J. Kleinberg, *Chem. Rev.*, **40**, 381 (1947); R. G. Johnson and R. K. Ingham, *Chem. Rev.*, **56**, 219 (1956); C. V. Wilson in *Org. Reactions*, **9**, 332 (1957).

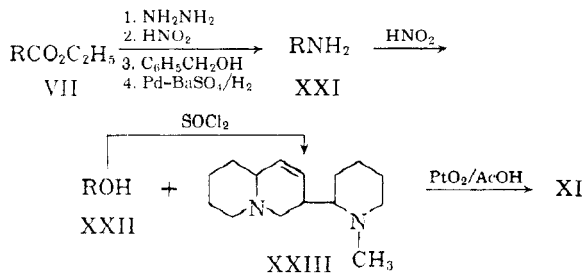
(13) M. V. Rubtsov and M. I. Dorokhova, *Compt. rend. Acad. Sci. U.S.S.R.*, **88**, 843 (1953); *Chem. Abstr.*, **48**, 3975d (1954).

(14) F. A. H. Rice, *J. Am. Chem. Soc.*, **78**, 3173 (1956).

This amino ketone was quite unstable. It was very susceptible to air oxidation and could not be distilled without extensive polymerization (90% of the material decomposed during an attempted distillation). It is not surprising, therefore, that under the drastic conditions of Wolff–Kishner reduction only 30% of a mixture of products could be recovered. The ethylene thioketal of XIX also was prepared, in an incompletely purified state, but could not be completely desulphurized with Raney nickel. An attempted reduction of XIX with lithium aluminum hydride failed to give a reasonable yield of a pure carbinol XX.

Finally, the ketone XIX was subjected to Clemmensen reduction, which produced in 40% yield a base isomeric with the desired quinolizidine (XI). It is clear, however, from the work of Prelog and Leonard and their co-workers[15] that the product of this reduction would not be XI but the isomeric 9-*N* - methylpiperidyl - 1 - aza - bicyclo[5.3.0]decane (XX), because of the generally observed ring contraction of ketone-bearing rings in the Clemmensen reductions of 1-ketoquinolizidines. Thus, neither route A nor route B succeeded in producing the desired XI.

The synthesis of this compound was finally achieved by still another approach, *viz.*, Curtius degradation of the esters VIIα and VIIβ according to the following scheme:

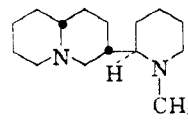


Neither the hydrazides nor the benzylurethanes were isolated, but both amines (XXIα and XXIβ) were obtained pure. These amines should retain the configuration of the original esters,[16] and their behavior on nitrous acid deamination was consistent with this presumption. The β-isomer produced mostly the carbinol, as would be expected from an equatorial amino group,[17] while the axially-substituted α-compound gave a mixture of carbinol and olefin.

The carbinol could be smoothly dehydrated to the olefin XXIII with thionyl chloride. The position of the double bond in formula is based on its ultraviolet absorption with a maximum at 217 mμ, (the alternative enamine would have had an absorption maximum in the 225–230-mμ region[18]).

Reduction of the olefin over Adams' catalyst in acetic acid yielded, after chromatographic separation, a new 3-(*N*-methylpiperidyl)quinolizidine (XI), which was characterized by a dipicrate, dimethiodide and was optically active. It also exhibited the expected "*trans*-quinolizidine" band in the infrared.[19]

One can expect eight optical isomers of XI, or four pairs of racemates. In the previous syntheses,[9] six or seven different racemates were reported, as can be judged from the melting points of the corresponding dipicrates (for tabulations of all the derivatives hitherto reported, see ref. 9e), which means that at least two of them have incorrect structures. The product of the present synthesis should unambiguously possess the same steric arrangement as the starting *l*-sparteine.



The pharmacological properties of the compounds prepared in this paper were investigated, but did not prove to be of outstanding interest.

EXPERIMENTAL[20]

l-Oxysparteine.[21] The directions given by Schöpf[1] were modified for optimum yield of the product. A solution of 100 g. of *l*-sparteine sulfate pentahydrate in 100 ml. of water was added under stirring to a solution of 64 g. of sodium hydroxide in 400 ml. of water, followed by a solution of 400 g. of potassium ferricyanide in 750 ml. of water preheated to 90°. The temperature of the mixture rose to 58°; it was maintained at this temperature for a total of 3 hr. After cooling to room temperature, it was extracted with ether (4 × 1000 ml.); the extract was dried over magnesium sulfate, concentrated, and fractionated through a 5-ft. Vigreux column yielding (*i*) a fraction consisting mostly of sparteine, b.p. 116°–130° (0.1 mm), n_D^{25} 1.5313 (5.0 g.; 9.1% recovery) and (*ii*) oxysparteine, b.p. 142° (0.1 mm) (35.2 g.; 59.9%) as a viscous oil which solidified on standing. After one recrystallization from pentane it melted at 87.5–88°.

1-Carbethoxy-3α-2′-(piperidyl)quinolizidines (IIIα, IIIβ). Two Carius tubes, each containing 15 g. of oxysparteine and 60 ml. of concd. hydrochloric acid, were kept at 180° for 24 hr. The contents of the tubes were filtered, washing with 60 ml. of water; the filtrate was made strongly alkaline with 150 ml. of 40% sodium hydroxide and extracted with benzene (4 × 250 ml.). The benzene extract yielded on evaporation 7.7 g. of recovered oxysparteine. The aqueous solution was reacidified with concentrated hydrochloric acid, evaporated to dryness *in vacuo*, and the residue dried by azeotropic distillation of absolute alcohol-toluene mixture followed by 1 hr. of

(15) V. Prelog and R. Seiwerth, *Ber.*, **72B**, 1638 (1939); N. J. Leonard and W. C. Wildman, *J. Am. Chem. Soc.*, **71**, 3089 (1949); N. J. Leonard and W. V. Ruyle, *J. Am. Chem. Soc.*, **71**, 3094 (1949).

(16) *Cf.* W. Klyne, *Progress in Stereochemistry* (Academic Press, New York, 1954, p. 196).

(17) *Cf.* A. Streitweiser, Jr., and C. E. Coverdale, *J. Am. Chem. Soc.*, **81**, 4275 (1959).

(18) N. J. Leonard and D. M. Locke, *J. Am. Chem. Soc.*, **77**, 437 (1955).

(19) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); **92**, 1798 (1959).

(20) Infrared spectra were taken with a Baird double-beam automatic recording spectrophotometer as liquid film, or in case of solids, in potassium chloride wafers.

(21) With Norman Spiere.

vacuum drying at 100° (15 mm). The resulting solid was redissolved in 550 ml. of absolute alcohol; the solution was saturated with hydrogen chloride at 0°, then heated under reflux for 1 hr., and finally evaporated to dryness under reduced pressure. The residue was redissolved in 70 ml. of water, 300 ml. of ether was added, and then 10% sodium hydroxide solution was progreesively added with shaking of the two layers to *p*H 10–11. The aqueous layer was extracted with three more portions of ether; the organic layers, after drying and concentration, gave 25.0 g. of a clear oil, which was distilled [b.p. 147–154° (0.35 mm.); 22.8 g.]. Chromatography on 1000 g. of Alcoa F-20 alumina, deactivated with 5% of water, gave three fractions: (*i*) pentane containing up to 3% of ether eluted 16.0 g. (45.3%) of the ester IIIβ; (*ii*) 5% of ether gave a further 3.3 g. of oxysparteine (bringing the total recovery of oxysparteine to 36.6%); (*iii*) ether eluted 4.45 g. (12.6%) of the ester IIIα.

Ester IIIβ boiled at 127° (0.2 mm.), n_D^{20} 1.5045, $[\alpha]_D^{20}$ + 16.0° (*c* 1.0, ethanol); infrared absorption: N—H 3.02 (sharp), C=O 5.81 μ, "*trans*-quinolizidine band"[19] at 3.55 and 3.60 μ.

Anal. Calcd. for $C_{17}H_{30}N_2O_2$: C, 69.34; H, 10.27; N, 9.52. Found: C, 69.39; H, 10.46; N, 9.72.

The *dihydrochloride* crystallized from acetone in microcrystals, m.p. 259°, $[\alpha]_D^{20}$ + 10° (*c* 0.33, ethanol).

Anal. Calcd. for $C_{17}H_{32}Cl_2N_2O_2$: Cl, 19.31. Found: Cl, 18.99.

Ester IIIα decomposed to oxysparteine on attempted distillation. However, the best chromatographic fraction, after vacuum concentration at 0.001 mm. for 24 hr. at room temperature, gave correct analytical figures. The resulting oil had $[\alpha]_D^{20}$ + 7.7° (*c* 0.26, ethanol). The infrared spectrum showed a broad N—H peak at 3.07 μ and a C=O peak at 5.83 μ, and no "*trans*-quinolizidine band."

Anal. Calcd. for $C_{17}H_{30}N_2O_2$: C, 69.34; H, 10.27. Found: C, 69.00; H, 10.34.

The amount of cyclization of this ester to oxysparteine could be easily estimated on the basis of the intensities of infrared bands at 5.81 μ (ester carbonyl peak) and at 6 1 μ (amide carbonyl peak).

1α-Hydroxymethyl-3α-(2'-piperidyl)quinolizidine (IVα). A solution of 2.45 g. of the ester IIIα and 0.4 g. of lithium aluminum hydride in 120 ml. of ether was heated under reflux for 8 hr., then decomposed with 0.8 ml. of water. After filtration, washing with methylene dichloride, the filtrate was concentrated; the residue, in pentane, was adsorbed on an alumina column. Elution with pentane containing up to 20% of ether removed small amounts of sparteine (formed by reduction of oxysparteine) and oxysparteine (formed by ring closure of some of the ester); on further elution with ether there was obtained 1.35 g. (79.4%) of the alcohol, b.p. 143° (bath temp.; 0.003 mm.), which crystallized from acetone-pentane in large hexagonal prisms, and from acetone alone in rosettes of colorless needles, m.p. 105–105.5°, $[\alpha]_D^{24}$ 0° (*c* 2.5, ethanol).

Anal. Calcd. for $C_{15}H_{28}N_2O$: C, 71.38; H, 11.18; N, 11.10. Found: C, 71.22; H, 11.00; N, 10.81.

The *dihydrochloride*, prepared in ethanol-ether mixture, was recrystallized from isopropyl alcohol–benzene: m.p. 247–248°, $[\alpha]_D^{24}$ + 1.9° (*c* 1.0, ethanol).

Anal. Calcd. for $C_{15}H_{30}Cl_2N_2O$: C, 55.38; H, 9.30; Cl, 21.80. Found: C, 55.01; H, 9.24; Cl, 21.40.

The *dipicrate* was formed in acetone solution and crystallized from isopropanol as pale yellow microcrystals, m.p. 112–113°.

Anal. Calcd. for $C_{27}H_{34}N_8O_{15}$: C, 45.63; H, 4.82. Found: C, 45.79; H, 5.06.

1β-Hydroxymethyl-3α-(2'-piperidyl)quinolizidine (IVβ). A solution of 2.0 g. of the ester IIIβ and 0.3 g. of lithium aluminum hydride in 30 ml. of ether was stirred for 2.5 hr. at room temperature, then decomposed with 0.7 ml. of water. Filtration, concentration, and distillation gave 1.5 g. (87.4%) of the alcohol, b.p. 140° (bath temp., 0.001 mm.), which on crystallization from pentane at −70° gave 1.35 g. of colorless crystals melting at 32°, $[\alpha]_D^{24}$ + 19.5° (*c* 1.5, ethanol).

Anal. Calcd. for $C_{15}H_{28}N_2O$: C, 71.38; H, 11.18; N, 11.10. Found: C, 71.05; H, 10.86; N, 10.81.

The *dihydrochloride*, prepared in dry ether and crystallized from isopropyl alcohol, melted at 275–277°.

Anal. Calcd. for $C_{15}H_{30}Cl_2N_2O$: C, 55.38; H, 9.30. Found: C, 54.93; H, 9.42.

The *dipicrate* was formed in acetone solution and crystallized from isopropyl alcohol in pale yellow microcrystals, m.p. 96–98°.

Anal. Calcd. for $C_{27}H_{34}N_8O_{15}$: C, 45.63; H, 4.82. Found: C, 45.77; H, 5.09.

1β-Bromomethyl-3α-(2'-piperidyl)quinolizidine sesquihydrobromide (V). A solution of 0.250 g. of IVβ in 10 ml. of 48% aqueous hydrogen bromide was heated under reflux for a period of 2 hr., then filtered and evaporated to dryness. Crystallization of the residue from isopropyl alcohol-acetone mixture gave 0.230 g. of the product, m.p. 293–295°. Addition of ether furnished a second crop which brought the total yield to 0.436 g. (100%).

Anal. Calcd. for $C_{15}H_{27}BrN_2$, $1^1/_2$ HBr: C, 41.25; H, 6.57; N, 6.41. Found: C, 41.48; H, 6.93; N, 6.17.

1β-Methyl-3α-(2'-piperidyl)quinolizidine (VI). A solution of 2.1 g. of the crude bromide salt V in 40 ml. of absolute ethanol and 60 ml. of acetic acid was heated under reflux with 4 g. of zinc dust for 5 hr. The residual metal was filtered and washed with hot methanol and hot water, and the filtrate was evaporated to dryness *in vacuo*. The residue was redissolved in 125 ml. of water and the solution made strongly alkaline. The resulting suspension was extracted four times with a total of 700 ml. of ether, the extracts were dried, the solvent removed through a 2-ft. bubble-cup column, and the residue fractionated through a short Vigreux column yielding the base VI (0.639 g.; 85.3%) as a colorless oil, b.p. 79° (0.1 mm.), n_D^{20} 1.5100, $[\alpha]_D^{28}$ + 17.2° (*c* 1.0, ethanol); infrared absorption: "*trans*-quinolizidine band" at 3.58 and 3.62 μ.

Anal. Calcd. for $C_{15}H_{28}N_2$: C, 76.21; H, 11.94; N, 11.85. Found: C, 76.01; H, 11.70; N, 11.59.

The *dihydrochloride*, prepared in ethereal hydrogen chloride and recrystallized from isopropyl alcohol-benzene, charred at 310° after first softening and resolidifying at 267°; $[\alpha]_D^{27.5}$ + 11.6° (*c* 1.0, ethanol).

Anal. Calcd. for $C_{15}H_{30}Cl_2N_2$: C, 58.24; H, 9.78; Cl, 22.93. Found: C, 57.99; H, 10.00; Cl, 22.53.

1-Carbethoxy-3α-(N-methyl-2'-piperidyl)quinolizidines. (a) VIIβ. Eight milliliters of 98% formic acid was added slowly to 16.1 g. of the ester (IIIβ) at 0°, followed by 5.6 ml. of 37% formalin. The solution was heated under reflux for 12 hr., then transferred to a separatory funnel with 100 ml. of methylene dichloride, and 10 ml. of water and made alkaline by the portionwise addition with intermittent shaking, of 10% sodium hydroxide solution. The extracts were dried, concentrated, distilled, yielding 11.2 g. (66.4%) of the *N*-methylated ester VIIβ, b.p. 152° (0.4 mm.), n_D^{20} 1.5035, $[\alpha]^{23°}$—5.0° (*c* 4.0, ethanol). Infrared absorption: C=O 5.78 μ; "*trans*-quinolizidine band" at 3.55 and 3.60 μ.

Anal. Calcd. for $C_{18}H_{32}N_2O_2$: C, 70.09; H, 10.46. Found: C, 70.22; H, 10.38.

(b) VIα *and* VIIβ. Hydrolysis of 23.7 g. of oxysparteine was carried out, as described above for preparations of IIIα and IIIβ. To the crude mixture of ethyl esters and oxysparteine 20.6 ml. of 98% formic acid and 13.0 ml. of 37% formalin were added and the mixture was treated as under (a). The crude residue (16.8 g.) was chromatographed as described for III. Elution with pentane containing 1–1.5% ether yielded 5.0 g. (17.1%) of VIIβ, identical with the material described under (a); with 1.5–2.5% ether there was obtained 4.8 g. (16.25%) of VIIα. Continued elution with 3–100% ether furnished 5.1 g. (21.6%) of recovered oxysparteine.

Ester VIIα boiled at 135° (0.2 mm.), n_D^{25} 1.5070, $[\alpha]_D^{22}$

$-5.02°$ (*c* 3.0, ethanol); infrared absorption: C=O 5.78 μ; instead of "*trans*-band", single peak at 3.6 μ.

Anal. Calcd. for $C_{18}H_{32}N_2O_2$: C, 70.09; H, 10.46; N, 9.08. Found: C, 69.98; H, 10.30; N, 8.75.

1β-Carbamyl-3α-(N-methyl-2'-piperidyl)quinolizidine (IX). (a) A solution of 7.0 g. (0.0227 mole) of ester VIIβ, 1.9 g. of sodium hydroxide, 20 ml. of methanol, and 7 ml. of water was heated under reflux for 5 hr., then evaporated to dryness, the residue acidified with hydrochloric acid and again evaporated to dryness. The residue was dried azeotropically with benzene and then kept at 100° (15 mm.) for 1 hr. Twenty-five milliliters of thionyl chloride was then added, and the mixture was refluxed for 45 min., then cooled, and dry ether was added. After trituration, the solid mass was washed with ether by decantation and dried *in vacuo*. The crude solid (15.2 g.) was used as such, for the reactions described below, with the assumption that it contained 0.0227 mole of the acid chloride.

(b) The crude acid chloride (5.8 g.) was added in portions to 50 ml. of concd. ammonium hydroxide and the solution was kept for 3 days at room temperature. Sodium hydroxide was added and the solution was extracted with methylene dichloride. The extracts were dried, evaporated to dryness and the residue was reextracted with benzene. Addition of ethereal hydrogen chloride precipitated a colorless solid which was purified by reprecipitation from isopropyl alcohol–ether mixture. The amide salt melted at 278° after softening at 265°. It was dissolved in water and reconverted to the base in the usual manner, yielding the amide IX (0.738 g; 24.4%), b.p. 250° (0.001 mm.), m.p. 71–74°.

Anal. Calcd. for $C_{16}H_{29}ON_3$: C, 68.77; H, 10.46. Found: C, 68.89; H, 10.44.

The *dihydrochloride monohydrate* was prepared by addition of ethereal hydrogen chloride to the benzene solution of the base and reprecipitated from isopropyl alcohol–ether mixture, as a solid, m.p. 288–290°.

Anal. Calcd. for $C_{16}H_{31}Cl_2N_3O \cdot 1H_2O$: C, 51.90; 8.98; Cl, 19.15. Found: C, 52.08; H, 9.26; Cl, 19.76.

1β-Diethylcarbamyl-3α-(N-methyl-2'-piperidyl)quinolizidine dihydrochloride (X).[21] To a stirred suspension of 5.3 g. of crude acid chloride (from IX (a)) in a 50 ml. of benzene, 45 ml. of diethylamine was slowly added, and the mixture kept for 20 hr. at room temperature. Sodium hydroxide solution was added, and the mixture was extracted with benzene. The residue obtained upon removal of solvent could not be distilled without decomposition. It was adsorbed on a column of Alcoa F-20 alumina deactivated with 5% of water, and eluted with pentane containing increasing proportions of ether. Fractions eluted with 10–20% ethereal pentane, which exhibited C=O amide peak in infrared, were combined and decolorized with charcoal. Addition of ethereal hydrogen chloride precipitated a solid which was twice recrystallized from 21:3:8 isopropyl alcohol-acetone–ether mixture, yielding 1.03 g. (28.1%) of the dihydrochloride, m.p. 277–278°.

Anal. Calcd. for $C_{20}H_{39}Cl_2N_3O$: C, 58.83; H, 9.62. Found: C, 58.69; H, 9.47.

1β-Carboxy-3α-(N-methyl-2'-piperidyl)quinolizidine diethylaminoethyl ester (VIII).[21] A mixture of 4.1 g. of the crude acid chloride (from IX (a)) and 35 ml. of diethylaminoethanol was kept at 100° for 3 hr. Water (100 ml.) was added, the solution was made alkaline with sodium hydroxide and extracted with methylene dichloride. The organic extract was dried over magnesium sulfate, the solvent and excess reagent were removed *in vacuo* and the residue was extracted with pentane. The concentrate from the pentane extract was fractionally distilled. The ester (0.887 g.; 37.7%) had b.p. 145° (0.001 mm.), n_D^{21} 1.5023.

Anal. Calcd. for $C_{22}H_{41}N_3O_2$: C, 69.61; H, 10.89. Found: C, 69.87; H, 10.76.

The *trihydrochloride hemihydrate* was prepared in isopropyl alcohol and isolated by addition of ether. It was extremely hygroscopic, melted at 55°, evolved gas at 135° then resolidified and remelted at *ca.* 170°.

Anal. Calcd. for $C_{22}H_{44}Cl_3N_3O_2 \cdot {}^1/_2\ H_2O$: C, 53.07; H, 9.11; Cl, 21.36. Found: C, 52.76; H, 8.96; Cl, 21.16.

1β-Diphenylhydroxymethyl-3α-(N-methyl-2'-piperidyl)-quinolizidine (XIII). A solution of 1.65 g. of ester VIIβ in 10 ml. of ether was added to phenylmagnesium bromide (from 2.35 g. bromobenzene and 0.27 g. magnesium) in 30 ml. of ether, and the mixture was stirred and refluxed for 2.5 hr. After decomposing with 2.5 ml. of 30% ammonium acetate solution and making alkaline, the resulting slurry was extracted with ether. The solid residue from concentration of the ether extract was crystallized from pentane, yielding 1.40 g. (62.5%) of the carbinol, m.p. 186.5°.

Anal. Calcd. for $C_{28}H_{38}N_2O$: C, 80.33; H, 9.15. Found: C, 80.27; H, 9.15.

1β-Hydroxymethyl-3α-(N-methyl-2'-piperidyl)quinolizidine (XIV). Chloral (4.4 ml.) was added to a solution of 13.1 g. of ester IIIβ in 50 ml. of chloroform. After keeping for 20 hr. at room temp. the solution was refluxed for 1 hr. and the solvent removed *in vacuo*. The residue was dissolved in 150 ml. of dry toluene and the solution was added to a refluxing solution of 5.1 g. of lithium aluminum hydride in 200 ml. of ether. The mixture was stirred and heated under reflux (liquid phase temp. 55°) for 8 hr., then decomposed with 9 ml. of water at $-30°$. After filtration and removal of solvent distillation of the residue yielded 10.9 g. (91.9%) of the carbinol as a very viscous colorless oil, b.p. 147° (0.2 mm.), n_D^{25} 1.5229 $[\alpha]_D^{25}$ $-7.9°$ (*c* 2.5, ethanol), which crystallized from pentane at $-70°$ as a solid melting at 7.5–8.0°.

Anal. Calcd. for $C_{16}H_{30}N_2O$: C, 72.13; H, 11.35. Found: C, 72.02; H, 11.29.

p-Toluenesulfonate of XIV (XV) A solution of 8.4 g. of XIV in 100 ml. of dry pyridine was cooled to $-15°$, and 6.6 g. of tosyl chloride was added. The mixture was swirled by hand until homogeneous, and kept for 5 hr. at $-5°$. Water was added (10 ml. in small portions, then 100 ml. all at once) and the solution was extracted with chloroform (7 × 100 ml.). Evaporation of the solvent yielded 12.7 g. (95.9%) of brittle resin, which was not purified further.

1-Methylene-3α-(N-methyl-2'-piperidyl)quinolizidine (XVI). A solution of 2.9 g. of sodium iodide in 60 ml. of *tert*-butyl alcohol was added to a solution of 5.7 g. of the tosylate (XV) in 30 ml. of *tert*-butyl alcohol, causing an immediate precipitate. After 45 min. at 20° a solution of sodium *tert*-butoxide (from 0.4 g. of sodium hydride in 50 ml. of *tert*-butyl alcohol) was added and the mixture refluxed under an atmosphere of nitrogen for 1.5 hr. The solvent was distilled, at first under atmospheric pressure and finally under vacuum, and 100 ml. of water was added to the residue. The solution was extracted five times with pentane, the extract evaporated to dryness, the residue taken up in a small amount of pentane and filtered from the quaternary salt (XVII). The pentane solution gave 2.37 g. (70.4%) of clear oil, b.p. 75° (0.25 mm.), n_D^{23} 1.5184, $[\alpha]_D^{23}$ $-44.6°$ (*c* 4.0, ethanol); infrared absorption: methylene bands at 6.08 and 11.2 μ.

Anal. Calcd. for $C_{16}H_{28}N_2$: C, 77.36; H, 11.36. Found: C, 77.75; H, 11.54.

The quaternary salt (XVII), purified by reprecipitation from acetone–ether, melted at 214–215°.

Anal. Calcd. for $(C_{16}H_{29}IN_2)_n$: C, 51.06; H, 7.77. Found: C, 51.49; H, 7.83.

1-Hydroxy-1-hydroxymethyl-3α-(N-methyl-2'-piperidyl)-quinolizidine (XVIII). To a stirred solution of 2.7 g. of the olefin XVI in 3 ml. of pyridine and 30 ml. of ether, a solution of 3.0 g. of osmic acid in 300 ml. of ether was added at $-30°$ over 10 min. The resulting solution was kept at 0° for 17 hr., the precipitated solid was filtered, washed with ether, and redissolved in 1 l. of chloroform. This solution was stirred for 6 hr. at 20° with a solution of 55 g. of mannitol and 40 g. of sodium hydroxide in 500 ml. of water, by which time the organic layer had become almost colorless. Removal of solvent from the organic phase and distillation of the residue produced 2.1 g. (68.5%) of the glycol as a very viscous, colorless oil, b.p. 121° (0.001 mm.), which set to an amorphous

solid, m.p. 48°; $[\alpha]_D^{24}$ −21.7° (*c* 2.5, ethanol). It was water soluble.

Anal. Calcd. for $C_{16}H_{30}N_2O_2$: C, 68.04; H, 10.71. Found: C, 68.28; H, 10.86.

3α-(N-Methyl-2'-piperidyl)-quinolizid-1-one (XIX). Solutions of 1.8 g. of the glycol XVIII in 20 ml. of methanol and 6.4 g. of periodic acid in 100 ml. of water were mixed at 20° and kept at 24 hr. Seventy milliliters of solvent was then distilled off under reduced pressure, the residue was made alkaline, saturated with solid potassium carbonate, and extracted five times with chloroform. The extracts yielded 1.85 g. of an oil, estimated on the basis of infrared absorption to contain 73% of the ketone—*i.e.* 1.35 g. (85.0%). Distillation gave 0.5 g. (31.3%) of pure ketone, b.p. 55–57° (0.2 mm.), n_D^{20} 1.5190, $[\alpha]_D^{24}$ −10.8° (*c* 3.0, ethanol); infrared absorption: C=O 5.85 μ.

Anal. Calcd. for $C_{15}H_{26}N_2O$: C, 71.95; H, 10.47. Found: C, 72.36; H, 10.54.

9-N-Methylpiperidyl-1-aza-bicyclo[5.3.0]decane (XX). Five grams of granular zinc, 0.5 g. of mercuric chloride, 7 ml. of water, and 0.5 ml. of concd. hydrochloric acid were shaken together for 5 min., the solution was decanted, and a solution of 0.5 g. of the ketone XIX in 10 ml. of concd. hydrochloric acid was added to the amalgamated zinc. The mixture was refluxed for 17 hr., after which the solid was filtered and washed with small amounts of water. The filtrate was made alkaline with 50% sodium hydroxide, and both the precipitated solid and the solution were extracted several times with methylene dichloride. After drying, solvent was removed first through a 1-ft. bubble-cup column under atmospheric pressure, then *in vacuo*. The residue was extracted with pentane, the solvent was removed and the residual oil distilled giving 0.189 g. (40.0%) of the base, b.p. 117° (bath, 0.15 mm.), n_D^{22} 1.5088, $[\alpha]_D^{24}$ −21.1° (*c* 1.0, ethanol).

Anal. Calcd. for $C_{15}H_{28}N_2$: C, 76.21; H, 11.94; N, 11.85. Found: C, 75.95; H, 11.67; N, 11.39.

The *dipicrate* was prepared in hot ether, and crystallized by Soxhlet extraction with ether, as a greenish yellow solid, m.p. 102.5–103.5°.

Anal. Calcd. for $C_{27}H_{34}N_8O_{14}$: C, 46.68; H, 4.93. Found: C, 46.66; H, 5.30.

The *dimethiodide* crystallized from an acetone solution of the base and methyl iodide; after one recrystallization from ethanol-ether it melted at 250–251°.

Anal. Calcd. for $C_{17}H_{34}I_2N_2$: C, 39.24; H, 6.59. Found: C, 39.13; H, 6.85.

The dihydrochloride and the dihydrobromide were very hygroscopic and light sensitive.

1β-Amino-3α-(N-methyl-2'-piperidyl)quinolizidine (XXIβ). A solution of 3.85 g. of ester VIIβ in 30 ml. of *n*-butyl alcohol was refluxed for 72 hr. with hydrazine (1.5-g. portions of 95% hydrazine added at 0, 24, and 48 hr.), by which time all the ester had disappeared (as judged by C=O bands in the infrared spectrum). The excess reagent and solvent were removed *in vacuo* and the residual glassy hydrazide (3.8 g.; C=O broad band at 6.05 μ) was dissolved in 100 ml. of 0.25*N* aqueous hydrochloric acid. To this solution under stirring, 12.5 ml. of 1*N* solution of sodium nitrite was added all at once at 0°, followed with 50 ml. of 0.25*N* hydrochloric acid, added over 4 min. After a further 5 min., 100 ml. of ether was added and then 160 ml. of 1*N* sodium bicarbonate solution. The aqueous layer was separated, twice more extracted with ether, and to the dried extracts 2 ml. of benzyl alcohol and 20 ml. of xylene were added. After removal of ether, the xylene solution was heated under reflux for 1 hr., then extracted with 10% hydrochloric acid. The aqueous extracts were made strongly alkaline, reextracted with methylene dichloride, and the organic solvent removed. The residue was extracted with ether from which 2.4 g. (50% based on VIIβ) of crude benzylurethane were obtained as a pale oil. Infrared absorption: NH 2.95 μ (wide), C=O 5.80 μ (wide). The crude urethane was hydrolyzed by 1.5 hr. of reflux in ethanolic hydrochloric acid according to Barkdoll and Ross,[22] and after evaporation to dryness, the free base (0.84 g.) was liberated with alkali, dissolved in pentane, and chromatographed on alumina. Elution with pentane containing up to 50% of ether removed various by-products. Further elution with ether (500 ml.) and then methanol (250 ml.) gave 0.384 g. of the crude amine, which on distillation yielded 0.283 g. (9.0% based on ester VIIβ) of a viscous, colorless oil, b.p. 103° (0.2 mm.), n_D^{23} 1.5198, $[\alpha]_D^{22}$ −12.0° (*c* 1.5, ethanol); infrared absorption: N–H 2.99, 3.03 μ; "*trans*-quinolizidine" band at 3.58 and 3.63 μ.

Anal. Calcd. for $C_{15}H_{29}N_3$: C, 71.66; H, 11.63. Found: C, 71.95; H, 11.60.

1α-Amino-3α-(N-methyl-2'-piperidyl)quinolizidine (XXIα). In a similar way, 2.6 g. of ester VIIα was converted *via* hydrazide and azide into the crude benzylurethane (1.65 g.; 50%). A solution of the latter in 40 ml. of methanol and 12 ml. of 10% hydrochloric acid was shaken under hydrogen at atmospheric pressure in presence of 0.5 g. of 10% palladium on barium sulfate catalyst, until absorption ceased. The catalyst was filtered, the solution evaporated to dryness, the residue made alkaline, and the base extracted several times with methylene dichloride. After removal of the solvent the oily residue (0.77 g.) was redissolved in 5 ml. of ether and chromatographed on alumina. Elution with pentane-ether mixtures, then with ether (700 ml.) and methylene dichloride (200 ml.) removed various by-products. Further elution with methanol (300 ml.) furnished 0.355 g. of crude amine, which on distillation yielded 0.277 g. (13.0% based on ester VIIα) of colorless viscous oil, b.p. 153° (bath temp., 0.6 mm.), $n_D^{25.5}$ 1.5203, $[\alpha]_D^{23}$ −42.1° (*c* 1.2, ethanol); infrared absorption: N–H 2.96, 3.04 μ; instead of "*trans*-quinolizidine-band" single peak at 3.60 μ.

Anal. Calcd. for $C_{15}H_{29}N_3$: C, 71.66; H, 11.63. Found: C, 71.90; H, 11.51.

1β-Hydroxy-3α-(N-methyl-2'-piperidyl)quinolizidine (XXII). To a solution of 0.300 g. of amine XXIβ in 2.6 ml. of 1.852*N* hydrochloric acid at 0° was added, dropwise, 1.2 ml. of 1*N* sodium nitrite solution. After 15 min. at room temperature the solution was heated at 90° for 2 hr., then made alkaline and extracted twice with pentane. After drying and removal of solvent the residue (0.260 g.; 86.6%) was distilled as a golden yellow viscous oil, b.p. 90–100° (bath, 0.002 mm.), $n_D^{22.5}$ 1.5185.

Anal. Calcd. for $C_{15}H_{28}N_2O$: C, 71.38; H, 11.18. Found: C, 71.55; H, 11.08.

Δ¹-Dehydro-3α-(N-methyl-2'-piperidyl)quinolizidine (XXIII). A solution of 0.200 g. of the carbinol XXII in 1 ml. of thionyl chloride was heated under reflux for 1 hr. and the excess reagent was removed under vacuum. The residue was dissolved in water, the resulting solution was made alkaline, and extracted with methylene dichloride. The extract was evaporated to dryness, the residue was reëxtracted with hot pentane, which yielded 0.105 g. (50%) of clear oil. Distillation, which resulted in a loss of half the material, gave a pale yellow oil, b.p. 137–140° (bath, 0.15 mm.); ultraviolet absorption in ether: λ_{max} 217 mμ (*cf.* ref. 18); infrared absorption: *cis*-CH=CH 13.25 μ (medium); instead of "*trans*-quinolizidine" band, a single peak at 3.61 μ.

Anal. Calcd. for $C_{15}H_{26}N_2$: C, 76.86; H, 11.18. Found: C, 76.64; H, 10.82.

Treatment of amine XXIα *with nitrous acid.* Under the conditions described above for XXIβ, a mixture of carbinol XXII and olefin XXIII resulted, as estimated by infrared spectrum and by hydrogenation of the crude mixture.

3α-(N-Methyl-2'-piperidyl)quinolizidine (XI). The seven-step sequence starting from 15.6 g. of oxysparteine, carried out as described above, but omitting all separation of intermediates, gave 0.613 g. (4.06% on oxysparteine) of chromatographed and distilled mixture of amines XXIα and XXIβ. This on nitrous acid treatment gave 0.546 g. of a mixture of alcohol XXII and olefin XXIII, which was dis-

(22) A. E. Barkdoll and W. F. Ross, *J. Am. Chem. Soc.*, **66**, 951 (1944).

solved in 10 ml. of glacial acetic acid and shaken under hydrogen at atmospheric pressure in presence of 10 ml. of Adams' platinum oxide catalyst for 2 hr., when absorption ceased. The catalyst was filtered off, the solution evaporated to dryness, treated with alkali, and extracted with methylene dichloride. After removal of the solvent, the residual oil was dissolved in 2 ml. of ether and absorbed on a 30-g. column of Woelm alumina (basic, grade 1). The following fractions were eluted: (*i*) 100 ml. of pentane gave 23 mg. of forerun; (*ii*) 400 ml. of pentane with 5% ether gave 175 mg. of the crude base XI; (*iii*) pentane containing increasing amounts of ether, then ether, and finally methanol gave 340 mg. of crude carbinol XXII.

The crude base gave on distillation an almost colorless, viscous oil, b.p. 113° (bath, 0.15 mm.), n_D^{22} 1.5095, $[\alpha]_D^{24}$ −37.2° (*c* 0.8, ethanol). Infrared absorption showed the "*trans*-quinolizidine band" at 3.57 and 3.61 μ.

Anal. Calcd. for $C_{15}H_{28}N_2$: C, 76.21; H, 11.94; N, 11.85. Found: C, 76.71; H, 11.71; N, 11.63.

The *dipicrate* was prepared in ethanol-acetone mixture and recrystallized from boiling water: m.p. 112–113° with shrinking at 108.5°.

Anal. Calcd. for $C_{27}H_{34}N_8O_{14}$: C, 46.68; H, 4.93. Found: C, 46.43; H, 5.07.

The *dimethiodide* was formed at room temperature in acetone solution, then recrystallized from ethanol as clusters of prisms, m.p. 284–286°.

Anal. Calcd. for $C_{17}H_{34}I_2N_2$: C, 39.24; H, 6.59; I, 48.78. Found: C, 39.54; H, 6.87; I, 48.82.

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[CONTRIBUTION FROM THE RESEARCH DIVISION, WYANDOTTE CHEMICALS CORP.]

Synthesis of Substituted Pyrazines. I. 2-Substituted 3-Methylpyrazines[1,2]

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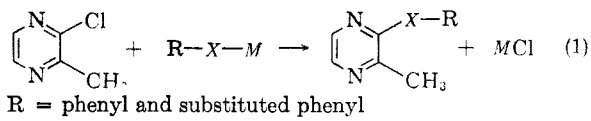
A variety of 2-substituted 3-methylpyrazines, where the substituents are certain phenoxy, thiophenoxy, anilino, and silyl radicals, was obtained in high yields with nucleophilic displacement reactions upon 2-chloro-3-methylpyrazine by the appropriate sodium phenoxide, sodium thiophenoxide, and aniline reagents, and by a magnesium coupling reaction with a chlorosilane, respectively. The action of sodium amide in liquid ammonia upon 2-chloro-3-methylpyrazine produced a dimeric coupling product, 2-chloro-3-(3-methyl-2-pyrazylmethyl)pyrazine. The reaction of sodium diphenylamine with 2-chloro-3-methylpyrazine gave various products depending on the conditions of the reaction.

As part of an extensive program for the preparation of various substituted pyrazines, the synthesis of certain 2-substituted-3-methylpyrazines has been investigated. The general route adopted for the synthesis of these compounds involved reactions by different reagents on the chlorine site of 2-chloro-3-methylpyrazine.[3]

The simple compound, chloropyrazine, has previously been reported to be susceptible to nucleophilic displacement reactions by hydroxyl, alkoxy, and amino groups[4] to give the corresponding hydroxy, ethoxy, and aminopyrazines. Similarly, the related compound, 2-chloro-3-methylpyrazine, has recently been found to undergo reactions with certain aliphatic amines and alcohols.[3] These reactions appeared to be relatively straightforward, with no unexpected complications or difficulties reported. In our investigation, involving a wide scope of nucleophilic displacement reagents, we have confirmed the reactivity of the chlorine in the latter compound. However, it was found that the reaction was not always simple, in that where strongly basic reagents were used competing reactions between the methyl and the chlorine site occurred, giving rise to more complex products.

It is the purpose of this paper to provide a preliminary definition of the scope of displacement and condensation reactions of 2-chloro-3-methylpyrazine, and to lay a foundation for the further inquiry into other derivatives of this highly interesting system. It was of specific interest in the present study to determine whether different and bulkier nucleophilic reagents would react at the chlorine site adjacent to the methyl group. To this end, a variety of aromatic nucleophilic displacement reagents were interacted with 2-chloro-3-methylpyrazine to give high yields of the desired products (see Table I). The general equation (1) illustrates these reactions.



R = phenyl and substituted phenyl

X = O, S, N, N, and Si (CH3)2

M = H, Na and Cl (with Mg)

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(2) This investigation was conducted under contract with Materials Central, Wright Air Development Division, Dayton, Ohio.

(3) H. Gainer, M. Kokorudz, and W. K. Langdon, *J. Org. Chem.*, 26, 2360 (1961).

(4) A. E. Erickson and P. E. Spoerri, *J. Am. Chem. Soc.*, 68, 853 (1946).