*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.

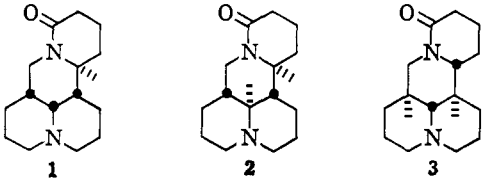
# The Total Syntheses of *d,l*-Matrine and *d,l*-Leontine[1]

**Leon Mandell, K. P. Singh,[2] J. T. Gresham,[2] and W. J. Freeman[2]**

*Contribution from the Department of Chemistry, Emory University, Atlanta, Georgia 30322.* *Received July 28, 1965*

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

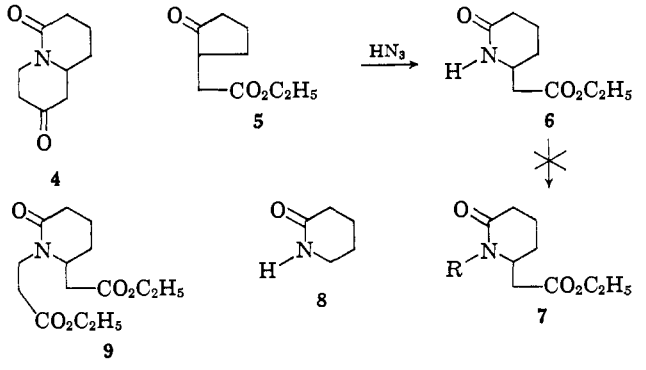
Matrine, the principal alkaloid of *Sophora flavescens* Ait., has been shown[3] to have the structure and relative stereochemistry of **1**. Matrine has been isomerized



**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**).

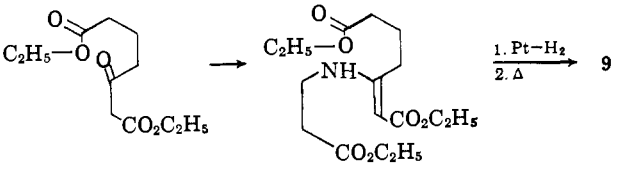
Our earlier work[6,7] had made it apparent that the intermediate needed for this proposed approach would be 8-oxo-2-quinolizidone (**4**), for were we to have this



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

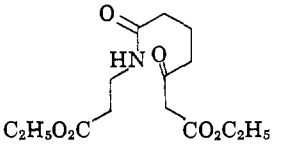
material available, bis-$\alpha,\alpha'$-alkylation (*via* the Stork[8] enamine procedure) with acrylonitrile followed by catalytic hydrogenation should afford the gross structure desired. We planned to prepare **4** *via* the diester **9** which should after Dieckmann cyclization, hydrolysis, and decarboxylation, 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 $\beta$-alaninate to yield **10**, which was reduced over Adams catalyst and then warmed on a steam bath to afford **9**.



**10**

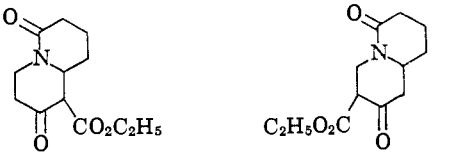
A by-product in the formation of **10** was the amide



**11**

**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.

(3) F. Bohlmann, W. Weise, D. Raktze, and C. Arndt, *Ber.*, **91**, 2167, 2177 (1958); K. Tsuda, *et al.*, *ibid.*, **69**, 429 (1936); *J. Org. Chem.*, **21**, 1481 (1956); E. Ochiai, S. Okuda, and H. Minato, *J. Pharm. Soc. Japan*, **72**, 1481 (1956).

(4) E. Ochiai, S. Okuda, and H. Minato, *ibid.*, **72**, 781 (1956).

(5) F. Rulko and N. F. Prokurnina, *J. Gen. Chem. USSR*, **31**, 308 (1961).

(6) L. Mandell, J. U. Piper, and K. P. Singh, *J. Org. Chem.*, **28**, 3440 (1963).

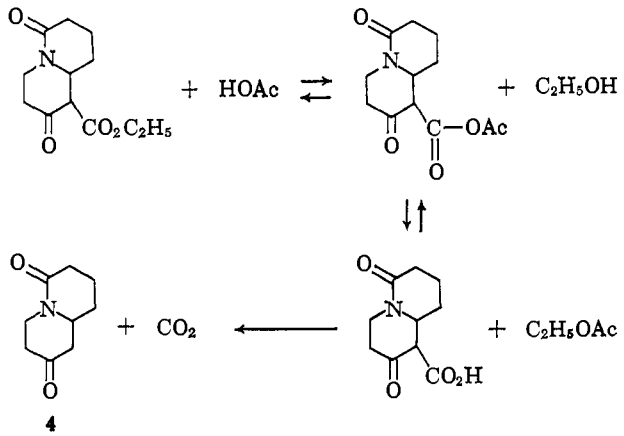
(7) L. Mandell and K. P. Singh, *J. Am. Chem. Soc.*, **83**, 1766 (1961).

(8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R Terrell, *ibid.*, **85**, 207 (1963).

(9) R. Adams and V. V. Jones, *ibid.*, **69**, 1803 (1947).

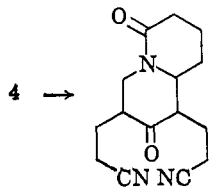
(10) M. Guka and D. Nasipuri, *Org. Syn.*, **42**, 45 (1962).

nicely crystalline. The Dieckmann product was not characterized but was decarboxylated directly. Many different decarboxylation procedures were investigated with little initial success. All of the usual methods seemed to hydrolize the lactam as well as the ester, giving rise to water-soluble products. A new procedure was found which involved refluxing the Dieckmann product in glacial acetic acid for 24 hr. and which provided the desired keto lactam (**4**), in 55% over-all yield from **9**. This reaction was very clean and owes its success to the relatively water-free conditions which thus circumvent the competing lactam hydrolysis. We picture the reaction as follows (illustrated with **12**).



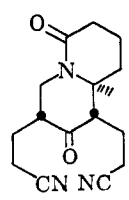
**4**

8-Oxo-2-quinolizidone (**4**) was now bisalkylated with acrylonitrile *via* the Stork[8] enamine synthesis. To effect bisalkylation as completely as possible required a repetitive alkylation procedure in which enamine formation and cyanoethylation were repeated twice before isolation was attempted. This gave a thick material which could not be purified to a single substance but contained (from infrared spectra of the fractionated product) a mixture of mononitriles as well as the expected dinitrile (**14**).

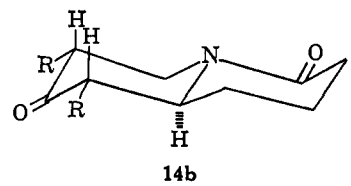


**14**

At this juncture we should consider the relative stereochemistry of the dinitrile **14**. The method of synthesis would leave the three asymmetric centers in this material in the most stable configuration which is as shown in **14a**, for thus the two cyanoethyl groups



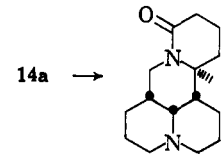
**14a**



**14b**

could both be equatorially disposed with respect to the ring system (**14b**). This assignment assumed the "*trans*-decalin" conformation for the quinolizidone ring fusion for which there is good evidence.[11]

The final step in our work involved the reductive cyclization of **14** to matrine (**1**). This transformation was accomplished by catalytic hydrogenation of **14** with 5% palladium on charcoal in glacial acetic acid solution, at room temperature and 50 p.s.i. hydrogen pressure. The crude reduction mixture was chromatographed on alumina to afford *d,l*-matrine. The *d,l*-matrine was identified by infrared comparison with natural matrine[12] and analysis of its picrate. The mechanism of this reduction and its steric consequences have been discussed previously by us.[6]



Since it had been reported[4] that active hydrogenation catalysts may convert matrine to allomatrine, the optical antipode of leontine, we had hoped that a similar isomerization might be effected during the reductive cyclization by use of a more active catalyst to produce *d,l*-leontine. This expectation was realized when 10% palladium on charcoal was used as catalyst. From chromatography of the product there was isolated *d,l*-leontine as the primary product (in addition to *d,l*-matrine) identified by melting point, infrared comparison, analysis, and melting point of its hydrochloride.

## Experimental Section[13]

*Ethyl 6-Acetate-2-piperidone* (**6**). A stock solution of hydrazoic acid was prepared containing 15–17 g./100 ml. of benzene from sodium azide and sulfuric acid. A mixture of 8.5 g. of ethyl cyclopentanone-2-acetate and 16 ml. of the above hydrazoic acid solution was added dropwise to a stirred cooled (5°) mixture of 10 ml. of concentrated sulfuric acid and 50 ml. of chloroform. The mixture was stirred at this temperature for 1.5 hr. and then poured on ice. The layers were separated and the aqueous layer was extracted with chloroform. The combined nonaqueous solutions were washed with 10% potassium carbonate and dried over sodium sulfate. The solvent was removed and the yellow residue was recrystallized from ligroin to give 7.2 g. of colorless needles, m.p. 48–49°.

*Anal.* Calcd. for $C_9H_{15}NO_3$: C, 58.38; H, 8.1; N, 7.46. Found: C, 58.56; H, 8.2; N, 7.59.

*Ethyl β-Alaninate.* We give the procedure for this preparation as we found the work-up procedure more satisfactory than published procedures. A solution of 108 g. of β-alanine in 400 ml. of absolute ethanol was saturated with hydrogen chloride. The solvent was removed *in vacuo*, fresh ethanol was added, and the procedure was repeated again. We stored the ethyl β-alaninate as its hydrochloride and generated the free ester as needed as follows.

Fifteen grams of ethyl β-alaninate hydrochloride was dissolved in chloroform (filtered to remove mostly un-

(11) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc.*, 218 (1961).

(12) Kindly furnished by Professor K. Tsuda.

(13) Boiling points and melting points are uncorrected. The infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer fitted with a sodium chloride prism. The analyses are by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

reacted β-alanine) and into this solution, cooled in an ice–salt bath, was passed anhydrous ammonia until the ammonium chloride precipitate became curdy. The solution was filtered and the ammonia treatment was repeated until no further precipitation of ammonium chloride occurred. The chloroform was removed *in vacuo* at room temperature and the residue was distilled to yield 5.0 g. of ethyl β-alaninate, b.p. 43–48° (5 mm.).

*Diethyl 6-Acetate-1-β-propionate-2-piperidone* (**9**). Ethyl β-alaninate (62.9 g.) was condensed with 127.8 g. of diethyl β-oxopimelate[10] by refluxing the two in 510 ml. of anhydrous benzene for 12 hr. and azeotroping the water formed. The solvent was removed *in vacuo* and the residue was dissolved in 250 ml. of absolute ethanol containing 6 drops of glacial acetic acid. This solution was hydrogenated using 3.75 g. of Adams catalyst at room temperature and 1750 p.s.i. hydrogen pressure. The platinum catalyst was removed by filtration, the solvent was removed *in vacuo*, and the residue was warmed on a steam bath for 3 hr. to complete lactam formation (followed by infrared spectra). Distillation yielded 125.2 g. of **9**, b.p. 150–160° (0.1 mm.).

*Anal.* Calcd. for $C_{14}H_{23}NO_5$: C, 58.85; H, 8.09; N, 4.92. Found: C, 58.35; H, 8.20; N, 5.02.

*Dieckmann Cyclization of* **9**. The mineral oil was removed from 30 g. of sodium hydride 50% dispersion in mineral oil by washing thoroughly with benzene. This material was suspended in 200 ml. of benzene and to it was added, with cooling, 125.2 g. of **9** in 580 ml. of benzene. The mixture was stirred for 0.75 hr. and then refluxed for 4 hr. The reaction was cooled, 30 ml. of ethanol was added to destroy the excess sodium hydride, and the product was acidified with 500 ml. of 2 *N* sulfuric acid. The layers were separated and the aqueous layer was extracted thoroughly with benzene. The combined benzene layers were dried over sodium sulfate, the solvent was removed *in vacuo*, and the residue was distilled to yield 49.4 g. of product, b.p. 150–160° (0.3 mm.). This material was used in the next step. While standing in a refrigerator the product crystallized. Recrystallization from ethyl acetate afforded material m.p. 94–95°.

*Anal.* Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.19; H, 7.30; N, 5.90.

*8-Oxo-2-quinolizidone* (**4**). The Dieckmann product (49.4 g.) was dissolved in 150 ml. of glacial acetic acid and refluxed for 24 hr. The acetic acid was removed *in vacuo* at steam bath temperature and the residue was distilled to yield 30.9 g. of **4**, b.p. 131–134° (0.05 mm.). While standing in the cold the product crystallized, giving material m.p. 34–5°. DNP had m.p. 215–215.5°.

*Anal.* (of DNP). Calcd. for: $C_{15}H_{17}N_5O_5$: C, 51.87; H, 4.93; N, 20.17. Found: C, 51.65; H, 5.27; N, 20.45.

*Biscyanoethylation of* **4**. The enamine of **4** was prepared by refluxing 15 g. of **4** and 12.5 ml. of pyrrolidine in 100 ml. of benzene with a water separator. After the separation of water had stopped, the solvent was removed *in vacuo* and the residue was refluxed for 22 hr. with 100 ml. of absolute ethanol and 16 g. of acrylonitrile. The ethanol and excess acrylonitrile were removed *in vacuo* and the enamine formation and alkylation were repeated twice more on the residue *via* the procedure given above. Finally, after removing the ethanol and acrylonitrile from the last treatment, the residue was hydrolyzed by stirring for 0.75 hr. in a solution of 8 ml. of glacial acetic acid and 32 ml. of distilled water. The aqueous layer was then extracted thoroughly with chloroform and the chloroform extract was washed successively with 5% hydrochloric acid, 5% sodium bicarbonate, and finally water. The chloroform solution was dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was distilled to yield two fractions, the first 7.05 g., b p. 210–225° (0.70 mm.), and the second 6.48 g., b.p. 230–240° (0.70 mm.). From the relative intensity of the nitrile absorptions (normalized by comparison to the C–H stretch bands) it was decided the first fraction was primarily mononitrile and the second fraction the desired dinitrile, **14**.

The first fraction was subjected again to the alkylation procedure to give an additional 1.21 g. of **14**, with 4.30 g. of what we believe to be monoalkylated compound recovered.

*d,l-Matrine* (**1**). **14** (6 g.) was hydrogenated in 250 ml. of glacial acetic acid using 2 g. of 5% Pd on charcoal as catalyst. The reduction was carried out overnight at room temperature and a hydrogen pressure of 60 p.s.i. The catalyst was filtered, the solvent was removed *in vacuo*, and the residue was chromatographed on 200 g. of alumina. Hexane and ether gave nothing. Methanol (2%) in ether (500 ml.) gave 1.0 g. of material which had an infrared spectrum very nearly identical with natural matrine. This material was rechromatographed on 20 g. of alumina to afford 0.93 g. of *d,l*-matrine, whose infrared spectrum was superimposable on the spectrum of natural matrine. This material was converted to its picrate (92% yield), m.p. 167–169°.

*Anal.* Calcd. for $C_{21}H_{27}N_5O_8$: C, 52.82; H, 5.70; N, 14.67. Found: C, 52.67; H, 5.61; N, 14.62.

*d,l-Leontine* (**3**). The experiment described above was repeated using 7.69 g. of **14** and, in place of 5% Pd on charcoal, 10% Pd on charcoal. It was worked up as before and chromatographed on alumina. From the 2% methanol in ether cuts there was obtained first 115 mg. of *d,l*-matrine, followed by 208 mg. of material which by infrared analysis was shown to be a mixture of *d,l*-matrine and *d,l*-leontine, and finally 770 mg. of *d,l*-leontine, m.p. 85–87° (lit.[5] m.p. 86–87°). The infrared spectrum was identical with that of leontine. Efforts to prepare a crystalline mandelic acid derivative of leontine were futile. This material gave a hydrochloride in good yield, m.p. 215–217° (lit.[5] m.p. 219–220°).

*Anal.* Calcd. for $C_{15}H_{24}NO_2$: C, 72.53; H, 9.74; N, 11.28. Found: C, 72.33; H, 9.71; N, 11.20.