indicated that no other cyclic ether stereoisomeric to **20** and **21** was formed in significant quantity.

Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.93; H, 10.13. Found: C, 71.01; H, 10.25.

Registry No.—**4**, 32925-93-2; **4** dioxime, 34388-66-4; **5**, 32925-94-3; **5** oxime, 34388-96-0; **6**, 32946-04-6; **6** oxime, 34388-98-2; **7a**, 28896-13-1; **8**, 34389-00-9; **9**, 34389-01-0; **10**, 34389-02-1; **18a**, 34407-51-7; **18b**, 34407-52-8; **19**, 33803-58-6; **20**, 34389-03-2; **21**, 34389-04-3.

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Notes

Leguminosae Alkaloids. VIII. Development of an Improved Synthesis of Anagyrine as a Potential Route to Other Lupin Alkaloids[1]

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The newer lupin alkaloids multiflorine (**1**)[2] and nuttalline (**2**)[3] are related to the longer known plant base anagyrine (**3**)[4] by the common stereochemistry of the C/D ring fusion and by similar oxidation states of ring A. A total synthesis of anagyrine was developed by van Tamelen and Baran,[6] which, with suitable modification, appeared as an attractive potential route for synthesis of **1** and **2**. We report now on work which has provided substantial material improvements in the van Tamelen–Baran anagyrine synthesis, enhancing its potential role as a more general sequence.

Our modification of the van Tamelen–Baran synthesis consists of a more direct and more economical means of reaching the intermediate, *r*-(1*R*,3*S*,10*S*)-1-hydroxymethyl-3-(2-pyridyl)quinolizidine[7] (**4**). This key compound is converted to anagyrine *via* quaternization of the bromide **5**, followed by oxidation of the resulting quaternary salt **6**.

The present reaction sequence leading to **4** may be conveniently compared with the earlier one, since both start from α-methylpyridine. van Tamelen and Baran[6] reached **4** with a reaction sequence that required five isolation stages and gave **4** in an overall yield of 2.4%. In addition, that synthesis required the use of α-tripiperideine, a reagent obtained in only moderate yield and with some difficulty from piperidine.[8] The present synthesis is much more advantageous. The amino alcohol **4** is obtained in 23% overall yield from α-methylpyridine with only four isolation stages. The ancillary preparation of α-tripiperideine is not required.

In 1936, Clemo, Morgan, and Raper[9] found that treatment of ethyl (2-pyridyl)acetate (**7**, R = ethyl) with ethyl orthoformate in boiling acetic anhydride gave the quinolizone **8** quite efficiently. While utilization of **8**

(1) Work done at the University of South Carolina.

(2) S. I. Goldberg and R. F. Moates, *J. Org. Chem.*, **32**, 1832 (1967).

(3) S. I. Goldberg and V. M. Balthis, *J. Chem. Soc. D*, 660 (1969).

(4) Naturally occurring anagyrine is levorotatory. Its absolute configuration[5] is actually the mirror image of that shown in structure **3**. (−)-Multiflorine and (+)-nuttalline possess the absolute configurations shown in **1** and **2**, respectively.

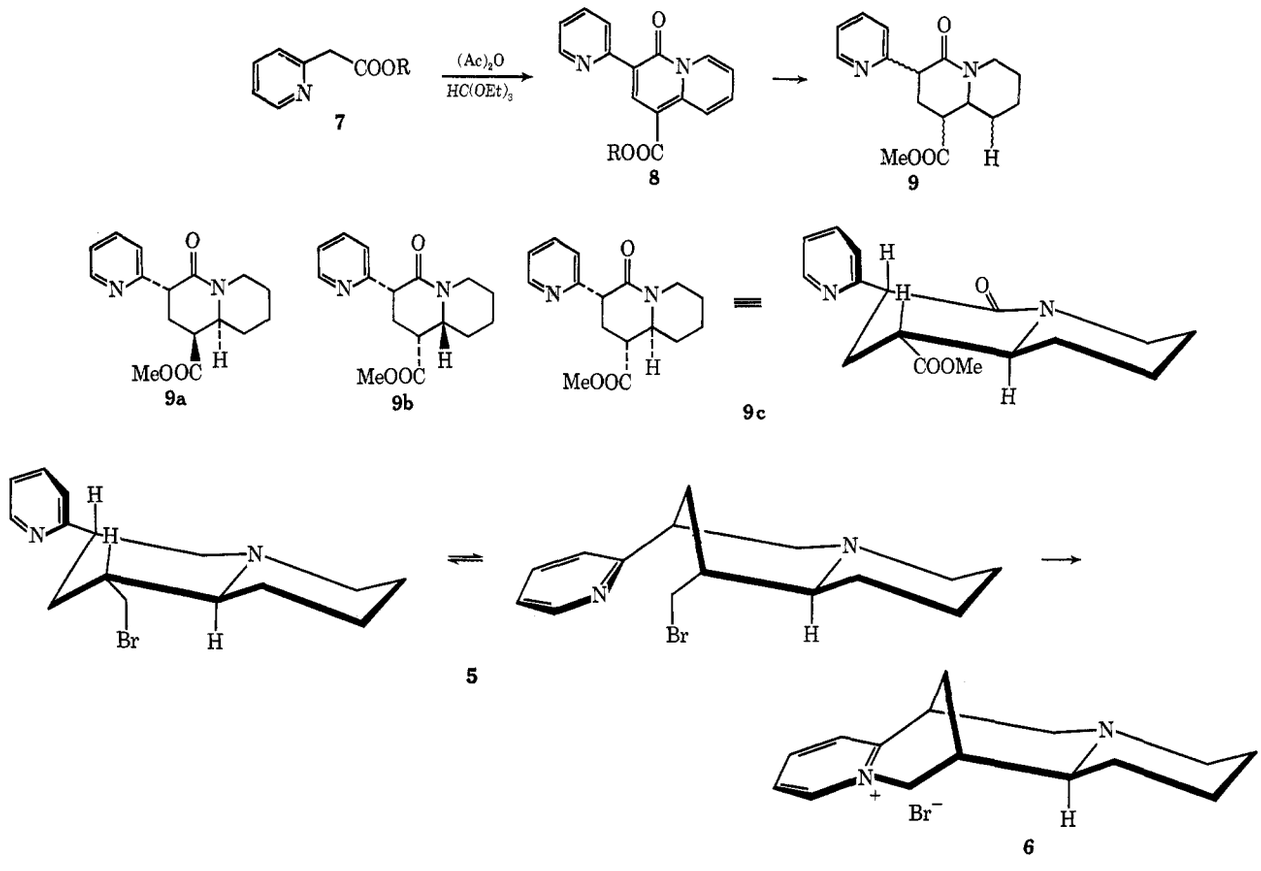
(5) S. Okuda, H. Kataoka, and K. Tsuda, *Chem. Pharm. Bull.*, **13**, 487, 491 (1965).

(6) E. E. van Tamelen and J. S. Baran, *J. Amer. Chem. Soc.*, **80**, 4659 (1958).

(7) IUPAC convention for specification of relative configurations. See Rule E-5. 10.-(G), *J. Org. Chem.*, **35**, 2849 (1970).

(8) C. Schöpf, A. Komzak, F. Brquh, and E. Jacobi, *Justus Liebigs Ann. Chem.*, **559**, 1 (1948).

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



as a precursor of anagyrine is fairly obvious, the recently developed partial hydrogenation procedure of Liu, *et al.*,[10] was needed to make it possible. We have found that the prescribed[8] distillation for isolation of **8** (R = ethyl) is avoided when the compound is prepared as the methyl ester (from **7**, R = methyl[11]), for the latter crystallizes directly out of the dark oily reaction mixture. The methyl ester **8** is efficiently hydrogenated to its octahydro derivative **9**. This compound possesses three chiral centers, so that the hydrogenation product could exist as a mixture of four diastereomers. However, if the hydrogenation proceeded in a stepwise, syn manner, as is frequently the case,[12] only two of the diastereomers (**9a** and **9b**) would result. This was apparently the case, as evidenced by the presence of only two signals at δ 3.63 and 3.67 owing to the methoxyl protons in the nmr spectrum determined from **9**. However, neither **9a** nor **9b** is expected to be the most favored diastereomer of the set. That form is presumably **9c**, the only one that could exist in the trans-fused, chair–chair, all-equatorial form. Indeed, treatment of the mixture **9** with sodium methoxide gave a single isomer in high yield.[13] Retention of the all-cis configuration of **9c** is in fact required for **5** in order to account for the conversion of **5** to **6**. This point has already been discussed by van Tamelen and Baran.[6]

The final step in the present sequence was the routine reduction (lithium aluminum hydride) of **9c** to the desired amino alcohol **4**, followed by conversion of the latter (original van Tamelen and Baran procedure[6]) to anagyrine (**3**).

Experimental Section

General.—Temperatures were uncorrected. The Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., performed the combustion analyses. Infrared (ir) spectra were obtained with a Perkin-Elmer Model 357 grating spectrometer. Nuclear magnetic resonance (nmr) spectra were determined in chloroform-*d* solutions, containing 1–4% (v/v) tetramethylsilane (TMS) internal standard, with a Varian A-60 spectrometer. Chemical shifts were noted under the δ convention in parts per million (ppm) relative to TMS (0 ppm). A Perkin-Elmer Hitachi Model RMU-6 mass spectrometer was used for mass spectra.

1-Carbomethoxy-3-(2-pyridyl)-4-quinolizone (8).—A mixture of methyl (2-pyridyl)acetate (30.2 g, 0.200 mol), triethyl orthoformate (31.6 g, 0.214 mol), and acetic anhydride (38 ml) was heated under reflux for 8 hr. Most of the excess acetic anhydride was removed by distillation at ambient pressure. During distillation of the remaining volatile material at steam bath temperature and reduced pressure (water aspirator) a bright yellow solid formed in the undistilled material. This material was washed twice with small portions of acetone to give 1-carbomethoxy-3-(2-pyridyl)-4-quinolizone (**8**): yield 22.0 g (78.5%); mp 165–168°; ir ($CHCl_3$) 1665, 1640, 1590, 1500 (quinolizone and pyridine), 2960, 2840, 1710, 1240, and 1140 cm^{-1} (carbomethoxy); nmr ($CDCl_3$) δ 9.3, 8.6, 7.7, 7.2 (3 H, 2 H, 2 H, 2 H, multiplets,

(10) H. J. Liu, Z. Valenta, J. S. Wilson, and T. T. J. Yu, *Can. J. Chem.*, **47**, 509 (1969).

(11) R. B. Woodward and E. C. Kornfeld, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 413.

(12) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 16.

(13) While enolization processes are obvious, equilibration of **9b** and **9c** could conceivably take place *via* a pathway involving a β elimination–addition similar to that invoked[6] for another case.[14] β elimination within the enolate formed from **9b** would give a ten-membered ring possessing a negatively charged nitrogen (N-5) which would add to one of two disatereotopic faces of a trans double bond (C-1, C-10) to provide enolate corresponding to **9c**. This notion was tested during the present work by carrying out the equilibration in the presence of (+)-1-methoxy-(2*S*)-methylbutane.[15] The absence of optical activity in the product (**9c**), however, did not allow any conclusions to be drawn.

(14) F. Galinovsky, G. Bianchetti, and O. Vogl, *Monatsh. Chem.*, **84**, 1221 (1953).

(15) S. I. Goldberg and W. S. Bailey, *J. Amer. Chem. Soc.*, **91**, 5685 (1969); *cf. J. Org. Chem.*, **36**, 716 (1971).

quinolizone and pyridine protons), and 3.9 (3 H, singlet methyl protons). The compound obtained in this way was sufficiently pure for use in the next step of the synthesis. A sample was purified for analysis by sublimation at 150° (0.05 mm) as bright yellow, needle-shaped crystals, mp 171–173°.

Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; mol wt, 280. Found: C, 68.54; H, 4.31; mol wt, 280 (mass spectrum).

***r*-(1*R*,3*R*,10*S*)-1-Carbomethoxy-3-(2-pyridyl)-4-quinolizidinone[7] (9c).**—A stirred (magnetic) solution of 1-carbomethoxy-3-(2-pyridyl)-4-quinolizone (8) (25.7 g, 0.0918 mol) in absolute methanol (400 ml), containing a suspension of 10% palladium on charcoal catalyst (9.2 g), was hydrogenated at ambient temperature and pressure. After a volume of hydrogen corresponding to 4 equiv was absorbed (3 days), the solid catalyst was separated from the reaction mixture by filtration of the latter through a Celite bed. Ordinarily the volume of the filtrate was reduced (evaporation) to 150 ml, and the resulting solution was used in the isomer equilibration step (below).

In one instance, however, the filtrate was evaporated to dryness, and the residue was dissolved in the minimum volume of methanol and placed onto a column of alumina (150 g, Woelm, nonalkaline, Activity Grade III) that was previously packed (flow method, *n*-hexane). Development of the column gave one major, diffuse, slightly yellow band, which was eluted with ether. Removal of the ether gave a mass of yellow-colored semisolid material (*ca.* 85% of the original weight) that was examined by means of its nmr spectrum. In addition to the changes expected from hydrogenation of the quinolizone ring in **8**, the presence of only two different signals owing to the methoxyl protons (δ 3.63 and 3.67) was consistent with a mixture of stereoisomeric forms of **9**.

The mixture was converted (equilibrated) to essentially one isomer by dissolving sodium (2.1 g, 0.091 g-atom) in absolute methanol (*ca.* 30 ml), adding the resulting solution to the concentrated methanol filtrate (above), and heating the resulting solution during 2 hr under reflux. After the mixture was cooled and neutralized with acetic acid, the whole was evaporated to leave an oily semisolid. This was chromatographed on alumina (Woelm, nonalkaline, Activity Grade III) as described above. Evaporation of the ether eluant gave *r*-(1*R*,3*R*,10*S*)-1-carbomethoxy-3-(2-pyridyl)-4-quinolizidinone (**9c**): yield 23 g (86%); pale yellow needles; mp 133–136°; ir ($CHCl_3$) 3000, 1600, 1575 (pyridyl), 1635 (lactam carbonyl), 2950, 2865, 1740, 1260, and 1170 cm^{-1} (carbomethoxy); nmr ($CDCl_3$) δ 8.45, 7.55, 7.12 (multiplets, 1 H, 1 H, 2 H, pyridyl protons), 3.65 (singlet, 3 H, methoxyl protons and quinolizidinone protons), 4.78 (broad doublet, 1 H), 3.7 (partially obscured multiplet, 1 H), 2.5 (broad envelope, 4 H), and 1.7 (broad envelope, 7 H).

Recrystallization of the compound from an acetone and hexane mixture gave colorless needles, mp 143–145°.

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; mol wt, 288. Found: C, 66.50; H, 7.03; mol wt, 288 (mass spectrum).

***r*-(1*R*,3*S*,10*S*)-1-Hydroxymethyl-3-(2-pyridyl)quinolizidine (4).[7]**—A solution of **9c** (2.88 g, 0.0100 mol) in tetrahydrofuran (THF) (50 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (1.5 g, 0.039 mol) in THF (50 ml). After the addition was complete, the reaction mixture was boiled gently (reflux) for 2 hr before it was cooled and hydrolyzed by careful successive additions of water (1.5 ml), 15% aqueous sodium hydroxide solution (1.5 ml), and finally water (4.5 ml). The coagulated alumina was separated by filtration and washed with THF. The combined washings and filtrate was evaporated to give the amino alcohol **4** as a very viscous yellow oil[8]: yield 2.2 g (89%); ir ($CHCl_3$) 3630, 3300 (free and bonded hydroxyl), 2863, 2920, 2778 (*trans*-quinolizidine), 1600, 1575, 1480, and 1440 cm^{-1} (pyridyl); nmr ($CDCl_3$) δ 8.42, 7.50, 7.08 (doublet of triplets, 1 H, apparent pentet, 1 H, triplet of doublets, 2 H, all pyridyl protons), 3.75, 2.90, 1.70 (broad doublet, 5 H, broad triplet, 3 H, broad envelope, 11 H, quinolizidine and hydroxymethyl protons).

Conversion of *r*-(1*R*,3*S*,10*S*)-1-Hydroxymethyl-3-(2-pyridyl)-quinolizidine (4) to (±)-Anagyrine (3).—The following account is a modification of the original procedure of van Tamelen and Baran.[6]

The amino alcohol **4** (2.2 g, 0.0089 mol), as obtained from the previous step, was dissolved in 48% aqueous hydrobromic acid (60 ml) and heated under reflux for 22 hr. All solvent was evaporated from the acidic reaction mixture under reduced pressure (*ca.* 35 mm). The residue was dissolved in water (20 ml) before the whole was cooled in an ice bath and transferred to a separatory funnel (benzene washes). The cold solution of hydrobromide salt was made strongly basic by the addition of cold, 3 *N* sodium hydroxide. The liberated bromo amine was quickly extracted into cold benzene (50 ml). After the combined benzene extracts were dried (anhydrous sodium sulfate), they were boiled under gentle reflux for 2 hr. Recrystallization (acetone) of the collected crystalline material deposited from the benzene solution gave the crude tetracyclic quaternary salt **6**, yield 492 mg (18%), mp 209–214° (lit.[6] mp 209–215°).

To a portion of this material (**6**) (356 mg, 1.15 mmol) dissolved in water (2 ml) was added an aqueous solution (4 ml) of sodium hydroxide (600 mg, 15 mmol) and potassium ferricyanide (800 mg, 2.43 mmol), and the whole was heated on a steam bath during 24 hr after an additional portion of water (2 ml) was used to clarify the cloudy reaction mixture. The cooled solution was exhaustively extracted with benzene (15 × 5 ml), and the combined extracts were dried (anhydrous sodium sulfate), filtered, and evaporated to a residue which was introduced into a modified Späth bulb and molecularly distilled [150° (0.05 mm), air bath] to give (±)-anagyrine (**3**): yield 129 mg (46.0%); pale yellow glass. This material was identical with authentic (−)-anagyrine generated from its hydrobromide salt,[16] as shown by chromatographic behavior [tlc, R_f 0.29 (acetone)] and by superimposability of infrared spectra.

Registry No.—**3**, 34389-11-2; **4**, 34389-12-3; **8** (R = CH_3), 34407-56-2; **9c**, 34407-57-3.

(16) L. Light and Co. Ltd., Colnbrook, England.

The Isolation, Structure, Synthesis, and Absolute Configuration of the Cactus Alkaloid Gigantine[1,2]

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The predominant feature of the desert landscape of southern Arizona and western Sonora, Mexico, is the giant sahuaro cactus, *Carnegiea gigantea.*[3] The presence of alkaloids in this cactus was discovered over 40 years ago with the isolation[4] and the determination[5] of structure of carnegine (**1**).

As part of our survey of cactus alkaloids[6,7] the basic fraction of *C. gigantea* was reexamined by gas chromatography[8] and found to contain at least two major and two minor alkaloids. The most abundant alkaloid (70% of the basic fraction) was an optically inactive oil which was characterized as carnegine (**1**) by comparison of its properties and those of its derivatives with a synthetic sample.[5] The other major alkaloid (25–30% of the basic fraction in the whole plant or about 50% in the growing tip) was obtained as an optically active crystalline solid whose properties differed from those of the

(1) Taken from the Texas Christian University Ph.D. Dissertations of (a) J. L. Massingill, 1968 [*Diss. Abstr.*, **29**, 2814B (1969)] and (b) S. D. Brown, 1969 [*ibid.*, **30**, 3547B (1970)].

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