TABLE I

OXIDATION OF VICINAL DIOLS TO α DIKETONES[a]

Diol	Diketone	Catalyst	Hydrogen acceptor	Time, hr	Yield, %
cis-1	2	$(Ph_3P)_3RuCl_2$	Benzalacetone	6	53
		$(Ph_3P)_3RhCl$			20
		$(PhCN)_2PdCl_2$			14
		$(Ph_3P)_2IrCOCl$			7
		Pd/C			4
		$(Ph_3P)_3RuCl_2$	Chalcone		48
			Mesityl Oxide		34
			1-Docosene		20
cis-1			Benzalacetone	10	78 (50)[b]
trans-1				10	100
2,3-Norbornanediol	2,3-Norbornanedione			1	74
trans-1,2-Cyclohexanediol	1,2-Cyclohexanedione			1	85
2,3-Butanediol	2,3-Butanedione			4	70 (40)[b]
1,2-Diphenyl-1,2-dihydroxyethane	Benzil			2	63
9,10-Dihydroxystearic acid	9,10-Diketostearic acid			4	22
α-Hydroxycyclododecanone	2			10	84

[a] Unless noted otherwise, reactions were carried out using the following starting concentrations: [diol], 0.2 *M*; [hydrogen acceptor], 1.0 *M*; [catalyst], 0.0025 *M*. Tetrahydrofuran was used as solvent; the reaction temperature was 195°. Yields were obtained by glpc. [b] Isolated yield; 1,2-bis(2-methoxyethoxy)ethane was used as solvent.

version of **1** to **2** proceeds in an unexceptional two-stage oxidation through intermediate **3**.

The advantage of this procedure for the preparation of α diketones lies in its simplicity and in its avoidance of the reactive oxidants and strong Lewis acids employed in certain of the other syntheses of these compounds; its principal disadvantage is the high temperature at which the reaction is carried out. However, perhaps because the reactions are carried out under neutral conditions, it has proved possible to obtain good yields of certain α diketones (in particular 2,3-butanedione and 1,2-cyclohexanedione) that cannot be obtained in satisfactory yields by the most convenient of these alternative procedures.[7]

Experimental Section[9]

General Methods.—Unless otherwise specified, all reagents were obtained commercially and were used without further purification. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl under a nitrogen atmosphere. The 1,2-bis(2-methoxyethoxy)ethane used was purified by distillation from calcium hydride under a nitrogen atmosphere. The following commercial catalysts (sources) were used: $(Ph_3P)_3RuCl_2$ and $(Ph_3P)_2IrCOCl$ (Strem Chemical Co); $(Ph_3P)_3RhCl$ (Alpha Inorganics); Pd/C (Engelhard).

General Procedure for Small-Scale Reactions.—Procedures similar to that described for the conversion of *cis*-1,2-cyclododecanediol to 1,2-cyclododecanedione were followed for all of the small scale oxidations described in Table I. A mixture of 16 mg (0.08 mmol) of *cis*-1,2-cyclododecanediol, 35 mg (0.24 mmol) of benzalacetone, 1 mg (0.001 mmol) of tris(triphenylphosphine)-ruthenium dichloride, and 0.4 ml of tetrahydrofuran was sealed under a nitrogen atmosphere in a 4-in., 5-mm Pyrex tube. The tube was placed in an oil bath, maintained at 195° for 10 hr, withdrawn, and cooled. An internal standard was then added to the reaction mixture, and the mixture was analyzed by glpc using a UC-W98 on Chromosorb W column.

Oxidation of *cis*-1,2-Cyclododecanediol.—To a mixture of 10 g (0.05 mol) of *cis*-1,2-cyclododecanediol, 14.6 g (0.1 mol) of benzalacetone, and 0.2 g (0.0002 mol) of tris(triphenylphosphine)-ruthenium dichloride was added 55 ml of freshly distilled 1,2-bis(2-methoxyethoxy)ethane, and the resulting solution was heated under nitrogen at 195°. The course of the reaction was monitored by glpc (the end of the reaction was indicated by the disappearance of benzalacetone from the reaction mixture). After 10 hr, the reaction mixture was cooled, poured into 300 ml of water, and extracted with 100 ml of ether. The ether solution was dried and concentrated, and the residue was distilled through a 10-cm vacuum-jacketed stainless steel spinning-band column to yield 5 g (50%) of 1,2-cyclododecanedione having bp 98–100° (1.5 mm) [lit.[10] bp 100° (1.5 mm)] and an ir and a mass spectrum indistinguishable from those of an authentic sample.[11,12]

(9) Boiling points are uncorrected. Ir spectra were taken in sodium chloride cells using a Perkin-Elmer Model 237-B spectrophotometer. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6D mass spectrometer. Product mixtures were analyzed by glpc on an F & M Model 810 flame ionization instrument.

Registry No.—*cis*-**1**, 4422-05-3; **2**, 3008-41-1.

Acknowledgment.—We are grateful to our colleagues Rudy Lauer and Tom Flood for gifts of α-hydroxycyclododecanone and *trans*-1,2-cyclododecanediol and to Larry Trzupek and Brian Andresen for recording mass spectra.

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(12) S. Cenini, A. Fusi, and G. Capparella [*Inorg. Nucl. Chem. Lett.*, 127 (1972)] have reported the rapid reaction of $(Ph_3P)_3RuCl_2$ with molecular oxygen. Thus, these oxidations should be carried out with careful exclusion of oxygen.

A Convenient Synthesis of 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine

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The indole alkaloid 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**) was first synthesized 20 years ago[2] and in 1966 it was found to occur in nature,

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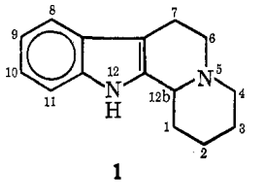
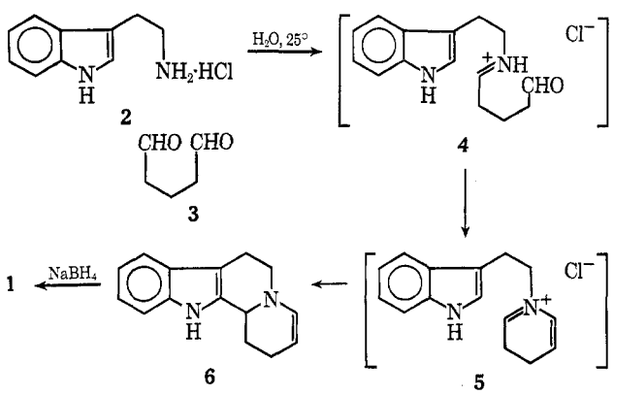


1

being isolated[3] from *Dracontomelum mangiferum*. This alkaloid is of biogenetic interest since it lacks the typical C_9–C_{10} unit found in more than 800 indole alkaloids.[4] Other syntheses of **1** have subsequently appeared[5–12] as well as a determination[13,14] of its absolute configuration.

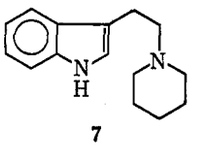
We now wish to describe a simple one-pot synthesis of **1**. Thus, an aqueous solution of tryptamine hydrochloride (**2**) and glutaraldehyde (**3**) was allowed to stand at room temperature for 7–10 days. The solution was diluted with ethanol and treated with excess sodium borohydride. Work-up of the mixture and column chromatography of the reaction product gave pure **1** in 52–55% yield, identical with authentic material.[5,9,12] A yield of 69% of **1** was obtained when a mixture of **2** and **3** was allowed to stand at 4° for 3 months in water. Lower yields of **1** were obtained when the reaction was run at 80–90° and/or when reaction periods were shorter than several days. The synthesis of **1** and a proposed reaction sequence are summarized in Scheme I.

SCHEME I

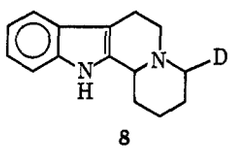


Presumably, **2** and **3** initially react to form iminium aldehyde **4** which, after deprotonation, cyclizes to dihydropyridinium ion **5**. Finally, **5** undergoes ring closure to **6** (or the corresponding iminium ion) which is reduced to **1** upon sodium borohydride treatment. This route is favored over one involving cyclization of **4** to the indole ring, giving a tetrahydro-β-carboline, because of the isolation of **7** under certain conditions (*vide infra*). There may, however, be a dependence of mechanism on pH not uncovered by the present work.

If the reaction is run in the presence of sodium cyanoborohydride[15] (at pH 6.5 or 8) of if sodium borohydride is added after a much shorter reaction period between **2** and **3**, *N*-[2-(3-indolyl)ethyl]piperidine (**7**)



7

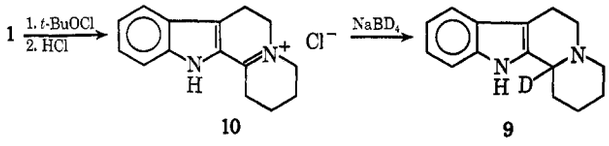


8

is the major or exclusive product, isolated pure, after column chromatography, in yields up to 86%. This material was identical with authentic material[9] and represents a very convenient and efficient synthesis of this compound. Presumably, in this case either **4** or **5** is reduced before cyclization to **6** can occur.

Evidence for the structure of intermediate **6** was obtained by subjecting the reaction mixture to sodium borodeuteride. Work-up gave **8** and not **9**, which was independently synthesized from **1** as shown in Scheme II. The structures of **8** and **9** are supported by infrared[16] and mass spectroscopy[17] (see Experimental Section). The mass spectrum of **8** shows an M − 1 peak, while **9** shows an M − 2 peak, corresponding to **10**.[17]

SCHEME II



10

9

Enamine **6** could also be isolated from the reaction mixture and subjected to $NaBH_4$ or $NaBD_4$ in separate reactions to give **1** and **8**, respectively.

Experimental Section

Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Infrared spectra were measured with Perkin-Elmer 137 or 337 instruments. Woelm alumina was used for column chromatography and silica gel G (Merck) was used for thin layer chromatography (tlc). The tlc solvent system generally used was EtOAc–Et_3N (~95:5) and plates were developed with a spray of 3% $Ce(SO_4)_2$–10% H_2SO_4 followed by a brief heat treatment at 110°. Organic solutions were dried with anhydrous granular K_2CO_3 and concentrated *in vacuo* with a Buchler rotary evaporator. Mass spectra were determined by Mr. Herbert A. Kirst at Harvard University.

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (1).—To a stirred ice-cold solution of 0.50 g (0.0025 mol) of tryptamine hydrochloride (**2**) (Eastern Chemical Co.) in 500 ml of distilled H_2O was added over 10 min 1.5 g (0.0038 mol) of a 25% aqueous solution of glutaraldehyde (**3**) (Aldrich Chemical Co.). The solution was stirred at 0–5° for 1 hr and then allowed

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to stand under nitrogen at room temperature for 10 days. The yellow solution was cooled in an ice bath, diluted with 200 ml of 95% aqueous EtOH, and treated with 8 g of $NaBH_4$ (pellets) in portions over 3 min. The mixture was stirred at 0–5° for 1 hr and then at room temperature for 8 hr. The mixture was made strongly basic with 6 *N* NaOH and extracted with CH_2Cl_2. The organic extract was washed with aqueous NaCl, dried, and concentrated to give a yellow foam. Chromatography over 15 g of activity III basic alumina gave, with benzene elution in four 30-ml fractions, a total of 0.32 g (55%) of **1** as a white solid, mp 151–152°. Recrystallization from ether gave tiny colorless crystals, mp 153–154° (lit.[9] mp 152–153°). This material was identical (infrared, tlc) with authentic **1**.[5,9,12]

N-[2-(3-Indolyl)ethyl]piperidine (7).—To a stirred ice-cold solution of 0.50 g (0.0025 mol) of **2**, 15 ml of a KH_2PO_4–$NaHPO_4$ concentrated 6.50 pH buffer solution (Radiometer, Copenhagen), 0.20 g (0.0032 mol) of $NaCNBH_3$ (Alfa Chemical Co.) in 500 ml of distilled H_2O was added dropwise over a few min 1.5 g (0.0038 mol) of a 25% aqueous solution of **3**. The solution (pH 6–7) was stirred at 0–5° for 1 hr and then allowed to stand at room temperature for 12 days. The mixture was made strongly basic with 6 *N* NaOH and extracted with CH_2Cl_2. The organic extract was washed with water, dried, and concentrated to give 0.55 g of a white crystalline mass. Chromatography over activity III basic alumina gave, with benzene elution in 12 30-ml fractions, 0.50 g (86%) of **7** as a white solid, mp 149–151°. Recrystallization from ether gave colorless prisms, mp 151–152° (lit.[9,18] mp 151–152°). This material was identical (infrared, tlc) with authentic **7**.[9,18]

Isolation of 1,2,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine (6) and Conversion to 4-*d*-1,2,3,4,6,7,12,12b-Octahydroindolo-[2,3-*a*]quinolizine (8).—The reaction mixture from 0.50 g of **2** and 1.2 g of a 25% aqueous solution of **3** after 4 days at 25° was cooled to 5°, made strongly basic with 6 *N* NaOH, and extracted with CH_2Cl_2. Concentration of the organic extract *in vacuo* gave **6** as an amber syrup. Tlc showed a single yellow-green spot of about the same R_f as **1** but with a distinctly different color pattern. No **1**, **2**, or **7** could be detected.

A mixture of 0.11 g of crude **6**, 0.30 g of $NaBH_4$, and 20 ml of 79% aqueous EtOH was stirred at 5° for 1 hr and then at 25° for 10 hr. Extraction with CH_2Cl_2 followed by the usual work-up and column chromatography (see entry for **1**) gave 0.027 g (24%) of pure **1**, identical (tlc, infrared, melting point) with authentic material.

A mixture of 0.125 g of crude **6**, 0.125 g of $NaBD_4$, and 20 ml of 70% aqueous EtOH was stirred at 5° for 1 hr and then at 25° for 10 hr. The usual work-up and chromatography gave 0.034 g (27%) of pure **8** (tlc; same as **1**), mp 150° dec.

Pertinent spectral data for **8** are as follows: ir ($CHCl_3$) 3460 (NH), 2930, 2850, 2800 (CH), and 2040 cm^{-1} (CD); mass spectrum (70 eV) *m/e* 227, 226, 198, 170, and 169.

12b-*d*-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (9).—This was prepared from **10** which in turn was synthesized from **1** according to the standard method.[12,19] To a stirred solution of 0.88 g (0.0039 mol) of **1**, 0.5 ml of Et_3N, and 100 ml of dry CH_2Cl_2 at −5 to −20° was added 0.49 g (0.0045 mol) of *tert*-butyl hypochlorite in 13 ml of dry CCl_4 dropwise over 1 hr. The mixture was then stirred at 25° for 90 min, washed with water, dried, and concentrated *in vacuo* at 25° to give an amber syrup. This was dissolved in 30 ml of dry EtOH which had been saturated with HCl gas. The mixture was refluxed for 1 hr and then concentrated *in vacuo*. The residue (crude **10**) was treated with 0.60 g of $NaBD_4$ in the usual fashion. Work-up and column chromatography gave 0.25 g (29%) of pure **9** (tlc; same as **1**), mp 150–151° dec.

Pertinent spectral data for **9** are as follows: ir ($CHCl_3$) 3465 (NH), 2940, 2850, 2800, 2750, (CH), and 2000 cm^{-1} (CD); mass spectrum (70 eV) *m/e* 227, 226, 225, 198, 171, and 170.

Registry No.—**1**, 4802-79-3; **8**, 34388-08-4; **9**, 34388-09-5.

Acknowledgment.—The author is indebted to Professor Richard F. Borch (University of Minnesota) for a discussion involving the use of sodium cyanoborohydride and for kindly informing the author of related unpublished work, and to the referees for incisive comments.

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A Convenient Synthetic Approach to 3- and 4-Alkyl-2,3-dihydrofurans

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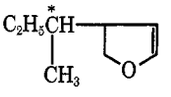
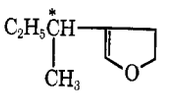
A summary survey of the possible synthetic routes leading to 2,3-dihydrofurans reported in the literature[2–7] convinced us that none could be simply applied to the preparation of optically active monoalkyl-substituted 2,3-dihydrofurans (**1a**, **2a**) containing an



1a



2a

asymmetric carbon atom directly bonded to the heterocyclic ring. Our interest in these optically active compounds and the attention received by 2,3-dihydrofurans in recent years[8–10] prompted us to develop a general procedure for the preparation of isomerically pure 2,3-dihydrofurans.

The key precursor of both series **1** and **2** is the appropriate γ-hydroxyaldehyde, readily accessible through rhodium-catalyzed hydroformylation, respectively of a 2-alkyl-allyl alcohol (Scheme I) and of a 2-alkyl-acrolein diethyl acetal[11] (followed in the second case by reduction of the free carbonyl group) (Scheme II).

The hydroformylation of allylic alcohols was long ago suggested as a promising synthetic route to γ-hydroxyaldehydes,[12] but, because of the substantial isomerization of the substrate promoted by the cobalt catalyst and simultaneous formation of several by-products,[13] no generally useful syntheses could be developed.

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