Total Synthesis of Naturally Occurring Substances. II. The Synthesis of the Hasubanan Carbocyclic System

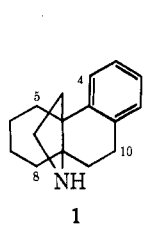
DAVID A. EVANS,* CARL A. BRYAN, AND GEOFFREY M. WAHL

Contribution No. 2554 from the Department of Chemistry, University of California, Los Angeles, California 90024

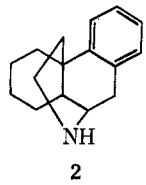
Received April 3, 1970

Two approaches to the total synthesis of 7-oxo-*N*-methylhasubanan (**6**) have been described utilizing 2-tetralone as a convenient starting point. As a prerequisite for one approach, an efficient two-step synthesis of 3-methyl-1,2,4,5-tetrahydro-3*H*-benz[*e*]indole (**5**) was developed. Methyl vinyl ketone annelation of **5** produced **6**. The structure of **6** was confirmed by an alternate synthesis.

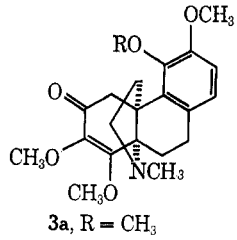
The hasubanan alkaloids[1] represent a class of naturally occurring compounds which bear a close structural relationship to the morphine bases. The name for this group of bases was derived from that of the first member of this group, hasubanonine (**3a**), whose structure has been established by Tomita and coworkers.[2] More recently, Kupchan has unambiguously determined the structure of 4-demethylhasubanonine (aknadinine, **3b**)[3] and has interrelated this substance with **3a**, thereby firmly establishing the stereostructures of this interesting class of compounds.



1



2



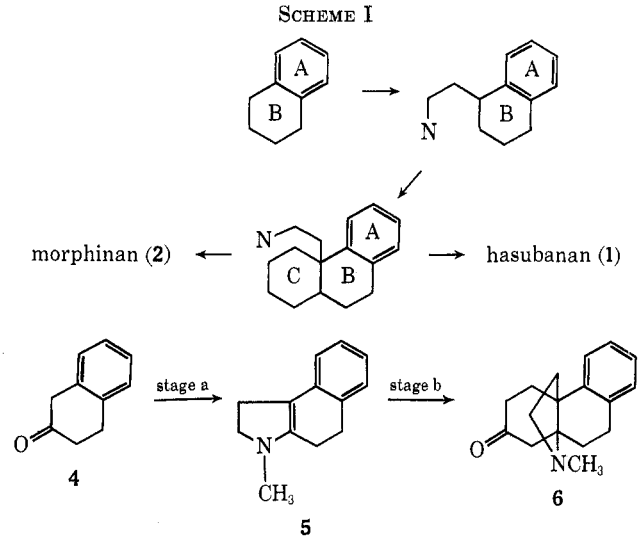
3a, R = CH_3
b, R = H

The similarity of hasubanan (**1**) to morphinan (**2**) has prompted us[1] and others[4] to attempt the synthesis of this interesting carbocyclic system. At least in small part our interest in the hasubanan skeleton has been derived from the possibility that structures such as **1** may also have interesting physiological properties.

A close examination of potential syntheses of systems such as **1** and **2** reveals a number of similar architectural problems common to both structures. Our long-range approach to synthesis in this area has been to develop a general route which embodied enough flexibility to achieve the synthesis of either carbocycle from some common intermediate. The general plan in its most elementary form is illustrated in Scheme I.

Starting from an appropriately functionalized bicyclic molecule which will constitute the A–B portion of the molecule, the ethanamine bridge will be introduced followed by the elaboration of ring C. The

SCHEME I



closure of the nitrogen bridge to either C-8a or C-9, respectively, could then represent the approach to either the hasubanan or morphine skeleton. The subject of this communication will deal with the former problem; specifically, the synthesis of the hasubanan skeleton.[5] The solution to the problems associated with the synthesis of the morphinan system will be discussed at a future time. Our synthetic objectives may be conveniently broken down into the two stages shown,[5,6] and for the sake of clarity will be discussed in that order.

A. Synthesis of 3-Methyl-1,2,4,5-tetrahydro-3*H*-benz[*e*]indole (5).—At the conception of our work, there existed no efficient methods which we felt could be readily adapted for the efficient synthesis of Δ^2-pyrrolines such as **5**.[7] Toward this end we have developed a new two-step annelation sequence which will be generally applicable to the synthesis of a variety of cyclic enamines useful in alkaloid synthesis.[8] This synthesis is outlined in Scheme II.

Treatment of 2-tetralone with excess monomethylamine in ether followed by the addition of a pentane solution of titanium tetrachloride[9] afforded a 92%

* To whom correspondence should be addressed.

(1) A preliminary account of this work has appeared: D. A. Evans, *Tetrahedron Lett.*, 1573 (1969).

(2) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, and M. Matsui, *ibid.*, 2937 (1964).

(3) (a) J. Kunimoto, Y. Okamoto, E. Yuge, and Y. Nagai, *ibid.*, 3287 (1969); (b) S. M. Kupchan, M. I. Suffness, D. J. N. White, A. T. McPhail, and G. A. Sim, *J. Org. Chem.*, **33** 4529 (1968), and references cited therein.

(4) (a) Partial syntheses from the morphines keleton: S. Okuda, K. Tsuda, and S. Yamaguchi, *J. Org. Chem.*, **27**, 4121 (1962); T. Ibuka and M. Kitano, *Chem. Pharm. Bull.*, **15**, 1944 (1967). (b) Total synthesis of cepharamine: Y. Inubushi, T. Ibuka, and M. Kitano, *Tetrahedron Lett.*, 1611 (1969). (c) Professor F. C. Tahk of Kent State University has kindly informed us, prior to publication, that he has also completed a synthesis of 7-oxo-*N*-methylhasubanan by a route similar to that described here.

(5) In the text, the (±) prefix will be omitted and all intermediates are presumed to be racemic.

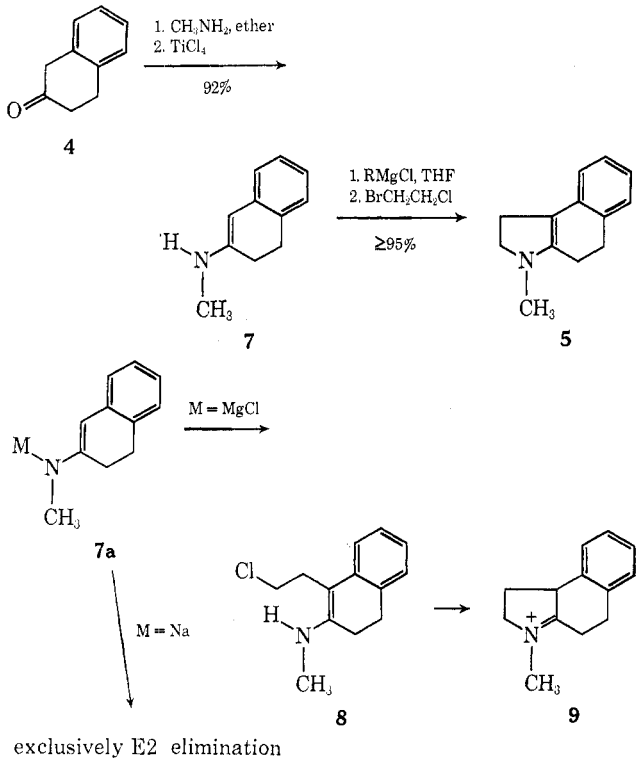
(6) While this work was in progress, Keely and Tahk published a synthesis of mesembrine which utilized this basic approach and pointed to the feasibility of synthesizing the hasubanan skeleton by a similar route: S. L. Keely, Jr., and F. C. Tahk, *J. Amer. Chem. Soc.*, **90**, 5584 (1968).

(7) K. Bláha and O. Cervinka, *Advan. Heterocycl. Chem.*, **6**, 147 (1966).

(8) The scope of this annelation sequence will be published in the near future.

(9) H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, **32**, 3246 (1967).

SCHEME II



exclusively E2 elimination

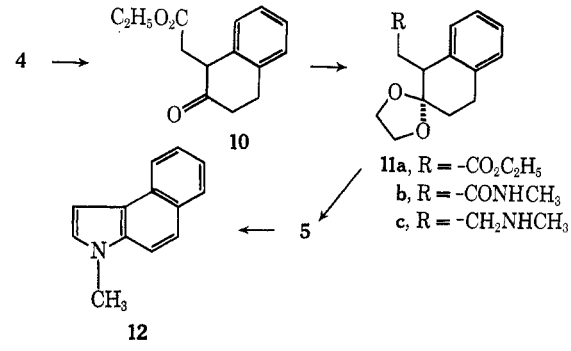
yield of the enamine **7**. There was no evidence that any of the imine form was present as indicated by nmr spectroscopy. If carefully stored under an inert atmosphere, this oxygen-sensitive compound could be stored at 0° for several months. Compound **7** was then transformed into a "bidentate" nucleophile by treatment with isopropylmagnesium chloride. Addition of bromochloroethane to the enamine anion then resulted in bis alkylation. Unfortunately, the rate of the second alkylation step (*i.e.*, **8** → **9**) was competitive with the primary alkylation reaction and the imminium salt **9** served as a proton source to partially quench the anion **7a**. Consequently, if 1 equiv of Grignard reagent was used, only a 60–70% conversion to **5** was effected. However, the addition of more base resulted in completing the reaction in an excellent yield. The alternative enamine structure with the double bond out of conjugation with the benzene ring was ruled out because of the lack of any olefinic proton resonance in the region δ 3.3–6.3.[10] Interestingly, if the sodium salt of **7a** was used in the alkylation sequence under otherwise identical conditions, the results of the reaction were dehydrohalogenation of the alkyl halide accompanied by less than 1% alkylation. Additional proof for the structure of the desired enamine was obtained by the independent synthesis outlined in Scheme III.

The alkylation of 2-tetralone with ethyl bromoacetate by Stork's enamine procedure[11] afforded the keto ester **10** in an excellent yield. The transformation of **10** into the ketal amine **11c** was carried out without incident. Acidic hydrolysis of **11c** afforded a pale yellow oil in 95% yield which was identical in every respect to the enamine **5** produced by the two-step

(10) M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, **31**, 4125 (1966).

(11) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrel, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

SCHEME III



synthesis illustrated in Scheme II.[12] Confirmation of the tricyclic nature of **5** was obtained by dehydrogenation of the base with 10% palladium on charcoal in refluxing mesitylene. The resulting 3-methylbenz[*e*]-indole (**12**) was obtained in 75% yield. The mass spectrum showed a parent ion at *m/e* 181 ($C_{13}H_{11}N$) and additional ions at 166 and 139. This mode of fragmentation has been substantiated for benz[*e*]-indoles and is not unlike that of 1-methylindole.[13,14]

B. Synthesis of *d*-1-7-Oxo-*N*-methylhasubanan (6).—An analysis of the ring-C oxygenation pattern of all of the known hasubanan alkaloids reveals that C-7 always bears an oxygen atom in one form or another. Other points of oxygenation appear at C-6 and C-8. From a standpoint of versatility, therefore, 7-oxo-*N*-methylhasubanan (**6**) should prove to be an important intermediate in any synthetic studies related to this group of alkaloids. The methyl vinyl ketone annelation approach which had been chosen for this problem has recently been successfully used in the total synthesis of mesembrine,[6,15] the construction of the *Erythrina* alkaloid skeleton,[16] and the synthesis of a useful *Aspidosperma* alkaloid precursor.[17]

On treatment of enamine **5** with methyl vinyl ketone (MVK) in a variety of solvents followed by heating in the presence of acetic acid, moderate yields of the desired keto amine **6** were obtained. If the course of this reaction was followed by nmr and ir spectroscopy, evidence for the intervention of both the dihydropyran **13** and the isomeric mixture of acetylcyclobutane isomers **15** was obtained. Admixture of MVK with **5** in benzene in an nmr tube resulted in the rapid disappearance of the *N*-methyl resonance associated with **5** with the simultaneous production of a new sharp singlet at δ 2.39 as well as a singlet at δ 1.75 and a broad triplet at δ 4.25 (J = 4.0 Hz); these signals were assigned to an *N*-methyl, vinyl methyl, and vinyl hydrogen, respectively. Irradiation of the vinyl methyl resonance resulted in a sharpening of the low-field triplet. An infrared spectrum of this solution exhibited a band at 1670 cm^{-1}. These results conform quite closely to the suggested dihydropyran structure **13**. Recently Fleming and Karger have provided

(12) Tahk and coworkers have recently reported an independent synthesis of **5**, and the nmr spectra supplied by them was identical to our material: S. L. Keely, Jr., A. J. Martinez, and F. C. Tahk, *Tetrahedron Lett.*, 2763 (1969).

(13) U. K. Pandit, H. J. Hofman, and H. O. Huisman, *Tetrahedron*, **20**, 1679 (1964).

(14) J. C. Powers, *J. Org. Chem.*, **33**, 2045 (1968).

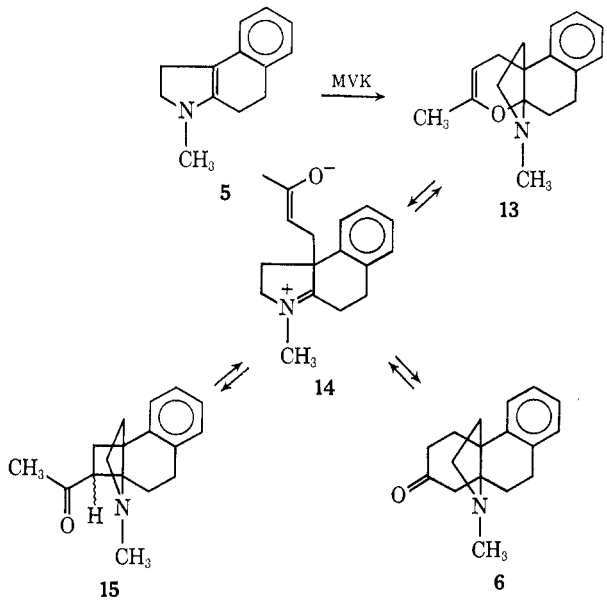
(15) R. V. Stevens and M. P. Wentland, *J. Amer. Chem. Soc.*, **90**, 5580 (1968); T. J. Curphey and H. L. Kim, *Tetrahedron Lett.*, 1441 (1968).

(16) R. V. Stevens and M. P. Wentland, *Chem. Commun.*, 1104 (1968).

(17) R. V. Stevens, R. K. Mehra, and R. L. Zimmerman, *ibid.*, 877 (1969).

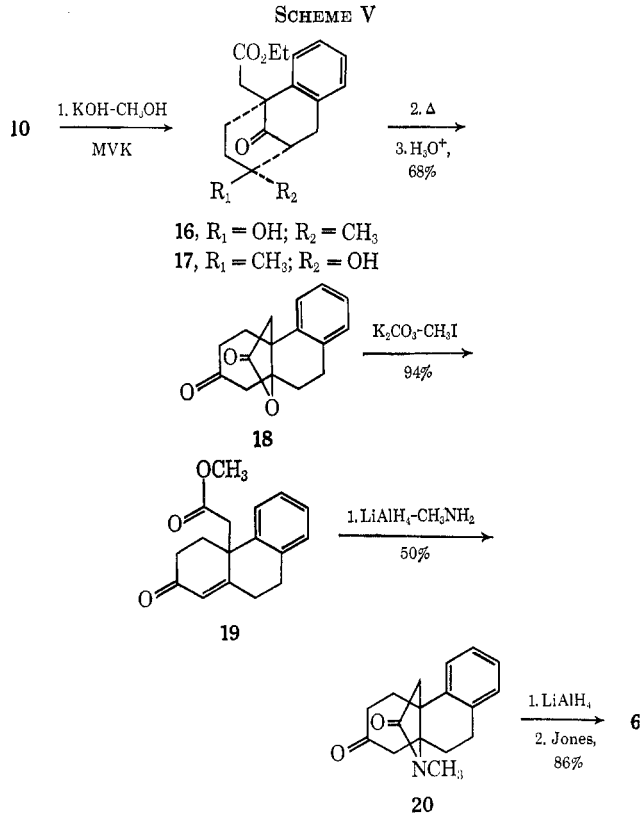
spectroscopic evidence substantiating the intervention of dihydropyran intermediates in the reaction of MVK with aldehyde enamines.[18] The spectral data obtained on **13** closely agree with the results of these workers (Scheme IV).

SCHEME IV



The stability of dihydropyran **13** in solution was observed to be quite solvent dependent. In contrast to its slow rearrangement in benzene, **13** rapidly isomerized into two new compounds in chloroform at room temperature. The nmr spectrum ($CDCl_3$) of the suspected mixture shows two sharp singlets of nearly equal intensity at δ 1.95 and 2.12 which show an upfield benzene-induced solvent shift of 20 and 23 Hz, respectively. These results are in harmony with the expected chemical shifts of methyl ketones in these solvents.[19] The infrared spectrum of this mixture exhibited a strong band at 1707 cm^{-1} which is suggestive of the presence of a saturated ketone function. The above information is consistent with a possible cyclobutane formulation such as **15**.[20] The implication of cyclobutane isomers in the reactions of enamines with electrophilic olefins is not without precedent.[21] At this point in the reaction, there was no evidence of any hasubanan ketone **6** in the mixture. In fact, **15** exhibited some reluctance in undergoing isomerization to the desired product both in refluxing chloroform and in ethanol. However, heating a chloroform or acetonitrile solution of **15** in the presence of acetic acid caused the desired transformation to take place. The hasubanan ketone **6** was obtained as a crystalline solid in 32% yield from the enamine **5**. The structure of this compound was unambiguously determined by the independent synthesis shown in Scheme V.

SCHEME V



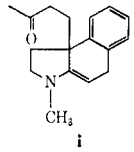
The design of this alternate route to the hasubanan skeleton coincided in its basic form with the recently published work of Tomita and coworkers.[22] Treatment of the keto ester **10** with MVK under the usual conditions afforded mainly a mixture of the ketols **16** and **17** in a 2:1 ratio which was separable by column chromotography.[23] The nmr spectra of both isomers were compatible with the bridged ketol structures shown rather than the alternative octahydrophenanthrene ketol isomer. This conclusion rests heavily on the observation of a sharp three-proton singlet at δ 1.3 in each spectrum which is compatible with the presence of a tertiary methyl group. The stereochemistry of the hydroxyl group was deduced by the observation that a 0.015 *M* solution of **16** in carbon tetrachloride exhibits a large amount of intramolecular hydrogen bonding in the infrared spectrum while **17** shows virtually no hydrogen bonding. Treatment of the mixture of ketols with aqueous base at reflux for several hours followed by acidification afforded the keto lactone **18** in an overall yield from **10** of 68%. Normally, the ketol esters **16** and **17** were not isolated but were transformed directly into **18**.

The next stage of the synthesis which required the introduction of nitrogen into the molecule proved to be

(18) I. Fleming and M. H. Karger, *J. Chem. Soc. C*, 226 (1967).

(19) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 170.

(20) One of the referees has pointed out the fact that the enamino ketone i shown below could be a possible methyl ketone structure which should also



i

be considered. We ruled out such a structure in favor of the cyclobutane **15** based upon the fact that the nmr spectrum of the product mixture exhibited no vinyl proton resonances over the region 4–6.5 ppm, the region where such enamine vinyl proton resonances normally appear.[19]

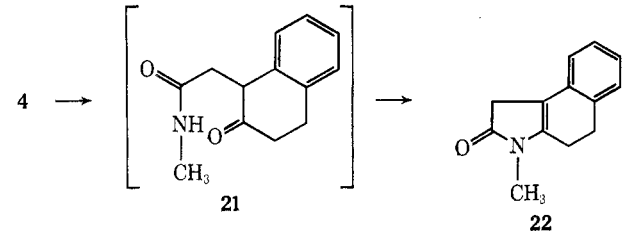
(21) G. H. Alt in "Enamines: Synthesis, Structure, and Reactions," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 4.

(22) M. Tomita, M. Kitano, and T. Ibuka, *Tetrahedron Lett.*, 3391 (1968).

(23) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).

quite troublesome. A number of unsuccessful attempts were made to find a method which would effect the direct transformation of lactone **18** into lactam **20** in a single operation. In view of our rather unpromising results toward this end, we concurrently considered the option of incorporating the nitrogen at the 2-tetralone stage. This plan was abandoned, however, when it was found that, on attempted enamine alkylation of 2-tetralone (**4**) with 2-bromo-*N*-methylacetamide, the keto amide **21** readily dehydrated to the lactam **22** which proved to be of marginal utility.

A solution to the problem of introducing the nitrogen at the tricyclic stage is illustrated in Scheme V. Treatment of the keto lactone **18** with potassium carbonate and methyl iodide resulted in producing the unsaturated keto ester **19** in an excellent yield. The desired lactam **20** was then obtained *via* **19** on treatment of the ester with lithium aluminum hydride–monomethylamine reagent.[24] Reduction of the lactam **20** with lithium aluminum hydride followed by Jones oxidation[25] of the epimeric alcohol mixture afforded 7-oxo-*N*-methylhasubanan (**6**) which proved to be identical in every respect with the material synthesized by the three-step enamine synthesis described earlier.[26]



With the completion of this stage of the work, two independent methods have been developed which provide an efficient solution to some of the problems associated with the synthesis of both the hasubanan and morphinan carbocyclic skeletons. The structural features associated with this problem have forced us to develop a new and potentially versatile endocyclic enamine synthesis which should prove to be generally useful in the synthesis of nitrogen heterocycles.[8] In addition we have shown that the methyl vinyl ketone annelation of these easily prepared cyclic enamines is a synthetically feasible operation. The impact of this approach to alkaloid synthesis has already been substantial.[6,15-17,27]

Experimental Section[28]

2-*N*-Methylamino-3,4-dihydronaphthalene (7).—The desired enamine was prepared according to the general procedure described by Weingarten and coworkers.[9] To a dry, nitrogen-purged, four-necked, 100-ml reaction vessel equipped with addition funnel, Dry Ice condenser, mechanical stirrer, and gas inlet tube was added a solution of 10.0 g (68.0 mmol) of 2-tetralone in 100 ml of anhydrous ether. The vessel was cooled to −18° (ice–methanol) and an excess of anhydrous monomethylamine (*ca.* 12 ml) was distilled into the reaction flask. During the cooling process, some of the tetralone crystallized out of the reaction mixture. However, this did not impair the results in any way. A solution of titanium tetrachloride, 39.5 ml of a 0.91 *M* solution (35.9 mmol), in pentane was added dropwise with stirring over a 0.5-hr period. On completion of the addition, the reaction was stirred at room temperature for 0.5 hr, diluted with 100 ml of ether, and filtered. The solid residue was carefully washed with ether, and the filtrate was concentrated *in vacuo*. The resulting oxygen-sensitive oil was shown by glc[28] to be composed of a single isomer greater than 99% yield. A short-path distillation afforded 10.0 g (91.7%) of the desired enamine: bp 91–93° (0.005 mm); ir (neat) 3430 (NH), 1630 cm^{-1} (C=C); nmr (CCl_4) δ 2.22 (m, benzylic H's), 2.59 (d, J = 3.0 cps, NCH_3), 2.92 (broad, NH), 2.50 (m, allylic H's), 4.20 (s, C-1 H); uv (CH_3OH) λ_{max} 300 mμ (ε 16,500).

Anal. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23. Found: C, 82.85; H, 8.27.

3-Methyl-1,2,4,5-tetrahydro-3*H*-benz[*e*]indole (5). A. From Hydrolysis of Ketal Amine 11c.—A solution of 189 mg (0.765 mmol) of ketal amine **11c** and 2 ml of 6 *N* sulfuric acid in 3 ml of ethanol was stirred under a nitrogen atmosphere for 1.5 hr at room temperature, transferred to a separatory funnel, and made basic with 5 *N* sodium hydroxide solution. The aqueous solution was extracted with two 50-ml portions of a 1:1 ether–benzene solution. The organic phase was then washed with water until neutral and the product isolated according to the standard procedure.[28] The desired enamine was obtained as a pale yellow oil, 135 mg (95%), which exhibited a sensitivity to oxygen. Evaporative distillation at 60° (0.01 mm) afforded the desired enamine, 100 mg, as a pale yellow oil, which crystallized on standing at 0° to give a low-melting solid. Glc analysis[28] of the distilled sample indicated the presence of several components. However, this was later shown to be due to the thermal instability of the material: ir (neat) 1630 cm^{-1} (C=C); nmr ($CHCl_3$) δ 2.59 (s, NCH_3), 2.1–3.5 (8 aliphatic H's plus NCH_3), 7.04 (m, aromatic H's); mass spectrum (15 eV) *m/e* 185; precise mass 185.1201 ± 0.0005, consistent only with $C_{13}H_{15}N$ (185.12044).

B. From 2-*N*-Methylamino-3,4-dihydronaphthalene (7).—To a dry, nitrogen-filled flask equipped with reflux condenser and serum cap was added 50 g (31.4 mmol) of enamine **7** and 6 ml of dry tetrahydrofuran (THF). Fifteen ml (40 mmol) of 2.65 *M* isopropylmagnesium chloride in THF was then added slowly *via* a syringe at a rate which maintained a gentle reflux (addition time 10 min). Bromochloroethane, 3.39 ml (40 mmol), was then added to the warm reaction mixture, again at such a rate that the reflux temperature was maintained. On completion of the addition of the alkyl halide, an additional 8 ml (21.2 mmol) of Grignard reagent was added to the reaction. Glc analysis of the reaction mixture at this point indicated the complete transformation to enamine **5**. The reaction mixture was then diluted with 50 ml of a 1.0 *M* aqueous solution of ethylenediaminetetraacetic acid tetrasodium salt and 150 ml of a 1:1 ether–benzene solution.[29] The organic layer was extracted with water until neutral and the crude product was isolated by a standard technique.[28] After removing residual solvents from the desired enamine under high vacuum there was obtained 5.8 g (100%) of material which was at least 99% pure as evidenced by glc analysis. The desired enamine **5** prepared by this method was identical with the material prepared in part A above. Because of the thermal lability of this material, subsequent reactions were carried out with the crude enamine.

7-Oxo-*N*-methylhasubanan (6). A. From Enamine 5.—A solution of 445 mg (2.40 mmol) of enamine **5** and 186 mg (2.65 mmol) of methyl vinyl ketone in acetonitrile was stirred under a nitrogen atmosphere for 1 hr. Acetic acid, 144 mg (2.4 mmol),

(24) J. Petit and R. Poisson, *C. R. Acad. Sci., Ser. C*, **247**, 1628 (1958).

(25) K. Bowden, I. M. Heilbron, E. H. R. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(26) Professor F. C. Tahk and coworkers have independently synthesized **6** and a comparison of the two samples confirms their identity.

(27) S. L. Keely, Jr., A. J. Martinez, and F. C. Tahk, *Tetrahedron*, in press.

(28) All melting points were taken on a Kofler hot stage and are uncorrected. Infrared spectra were taken on a Perkin–Elmer spectrometer Model 700. Nuclear magnetic resonance spectra were taken on a Varian Associates Model A-60D spectrometer. All gas chromatographic analyses were carried out on a Varian Aerograph Model 1200 gas chromatograph using a 7-ft column of 5% silicone gum rubber (SE-30) on a 60–80 mesh silanized (DMCS) Chromosorb W support. The "standard work-up procedure" referred to in this section consists of extracting the organic layer once with saturated salt solution, drying the solution over anhydrous sodium sulfate, and removing the solvent on a rotary evaporator. The term "dry" refers to commercial grade solvents which have been distilled from lithium aluminum hydride. All microanalyses have been performed by Miss Heather King, Department of Chemistry, University of California, Los Angeles, Calif.

(29) The use of an aqueous solution of EDTA tetrasodium salt in the work-up of a Grignard reaction under basic conditions does not appear to have been reported in the literature. We have found this technique to work extremely well.

was added and the solution heated at 80° for 3 hr. The reaction was diluted with chloroform and extracted once with 10% sodium bicarbonate solution and then with water until neutral. The crude reaction mixture, isolated by the standard procedure,[28] was chromatographed on 30 g of alumina (neutral activity III). The desired keto amine **6**, 194 mg (32%), was obtained as a colorless crystalline solid on elution with benzene. An analytical sample was prepared by recrystallization from ether–hexane: mp 70–71°; ir ($CHCl_3$) 1712 cm^{-1}; nmr ($CDCl_3$) δ 2.24 (s, NCH_3); mass spectrum (70 eV) *m/e* 255, 186, 185.

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29. Found: C, 80.11; H, 8.34.

As a further point of comparison, the crystalline hydrochloride was prepared, mp (sealed capillary) 160–160.4° dec.

Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.96; H, 7.53. Found: C, 69.80; H, 7.58.

B. From Keto Lactam 20.—A solution of 265 mg (0.98 mmol) of keto lactam **20** in 7.0 ml of dry tetrahydrofuran (THF) was cooled to 0° and 3.5 ml of a 1.25 *M* solution of lithium aluminum hydride in THF was introduced dropwise. The reaction was stirred at room temperature for 72 hr, 1.0 ml of water was added, followed by 0.5 ml of a 3.0 *N* aqueous sodium hydroxide solution, and stirring was continued for an additional 10 min. The granular inorganic precipitate was filtered and rinsed with 100 ml of ether and the resulting ether solution was washed with water and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded 234 mg of a pale yellow crystalline solid which consisted of an epimeric mixture of hydroxy amines. An ir spectrum of the reduction mixture affirmed the absence of any unreduced lactam. Trituration of this material with cold ether afforded a colorless crystalline epimeric mixture of alcohols which was then treated with Jones reagent at 0° for 0.5 hr to give the desired keto amine **6** in a quantitative yield. The material prepared by this procedure was identical in every respect with the material prepared in part A above.

Ethyl 3,4-Dihydro-2(1*H*)-naphthalenone-1-acetate (10).—A solution of 59.6 g (0.47 mol) of 2-tetralone and 100 ml of freshly distilled pyrrolidine in 1 l. of benzene was refluxed under a water separator in a nitrogen atmosphere for 3.5 hr. After the theoretical quantity of water had been collected, the benzene and excess pyrrolidine were distilled from the reaction vessel which was then charged with 400 ml of dry benzene, and a solution of 95 g (0.56 mol) of ethyl bromoacetate in 50 ml of benzene was added over 5 min. The reaction was heated at reflux for 4 hr during which time the immonium bromide separated from the benzene solution. The benzene was distilled from the reaction vessel and replaced with 400 ml of methanol and 300 ml of water. Hydrolysis of the immonium salt was effected by refluxing the solution for 1 hr. The reaction was diluted with 500 ml of 10% aqueous hydrochloric acid solution and extracted with seven 150-ml portions of benzene. The organic layer was washed with water until neutral and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded a pale yellow oil. On distillation at reduced pressure there was obtained 84.4 g (88.5%) of the desired keto ester **10**, bp 125–127° (0.08 mm), as a colorless oil: ir (neat) 1721 (ketone C=O), 1735 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 1.18, 4.10 (t, q, CH_3CH_2O), 3.92 (t, methyne H).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.33; H, 6.90.

Ethyl 2,2-Ethylenedioxy-1,2,3,4-tetrahydronaphthalene-1-acetate (11a).—A solution of 25.0 g (0.110 mol) of keto ester **10**, 0.20 g of toluenesulfonic acid monohydrate, 20 ml of ethylene glycol, and 300 ml of benzene was heated in a nitrogen atmosphere at reflux under a water separator until the theoretical amount of water had been collected (4 hr). The reaction was cooled and extracted with 100 ml of a 10% sodium bicarbonate solution. The organic layer was washed with water until neutral and the product isolated by the standard procedure.[28] The crude ketal ester **11a**, 28.4 g (95%) was obtained as a colorless oil. Glc analysis[28] indicated the presence of a single component. A small portion of the material was evaporatively distilled to obtain material of analytical purity: bp 140° (0.03 mm); ir (neat) 1725 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.25, 4.17 (t and q, OCH_2CH_3), 3.55 (t, methyne H), 3.95 (s, ketal H's), 7.11 (s, aromatic H's).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.66; H, 7.41.

***N*-Methyl 2,2-Ethylenedioxy-1,2,3,4-tetrahydronaphthalene-1-acetamide (11b).**—The amide **11b** was prepared according to the general procedure of Petit and Poisson.[24] To a dry, 250-ml three-necked flask equipped with a mechanical stirrer, dropping funnel, and Dry Ice condenser was added 275 mg of finely pulverized lithium aluminum hydride followed by 50 ml of anhydrous ether. Anhydrous monomethylamine was slowly distilled into the reaction vessel until all of the hydride had been consumed. The amine reagent was allowed to stir for 0.5 hr after which the excess amine was allowed to distilled from the system. The apparatus was purged with nitrogen, and a solution of 2.0 g (7.25 mmol) of ketal ester **11a** in 15 ml of ether was added dropwise over a 5-min period. The contents were allowed to stir at room temperature for 5 hr; 5 ml of 5 *N* sodium hydroxide solution was then added with stirring, the granular precipitate filtered through a Celite pad, and the precipitate washed with ether. The organic layer was washed with water until neutral and the crude product was isolated by the standard procedure.[28] The resulting pale yellow oil, 1.65 g, crystallized on cooling. Recrystallization of the desired material from 1:1 ether–hexane afforded 1.10 g (61.4%) of colorless prisms: mp 127.5–128.5°; ir ($CHCl_3$) 3475 (NH), 1660 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.76 (d, *N*-methyl), 3.59 (t, methyne H), 4.0 (s, ketal H's), 7.14 (s, aromatic H's).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33. Found: C, 68.92; H, 7.39.

1-(2-*N*-Methylaminoethyl)-2,2-ethylenedioxy-1,2,3,4-tetrahydronaphthalene (11c).—To a dry, nitrogen-filled 250-ml three-necked flask equipped with a septum and a dropping funnel was added 52 ml (55 mmol) of a 1.06 *M* solution of lithium aluminum hydride in tetrahydrofuran (THF). The contents were cooled to −5° and 1.47 ml (55 mequiv) of 100% sulfuric acid (37.2 *N*) was slowly added dropwise to the stirred solution *via* a syringe equipped with a polyethylene needle. On completion of the addition, the reaction was allowed to stir at room temperature for 0.5 hr. A solution of 9.0 g (34.5 mmol) of amide **11b** in 70 ml of dry THF was added dropwise, and the resulting solution stirred at room temperature for 46 hr. Glc analysis[28] of a small portion of isolated material indicated approximately 90% reaction had resulted. The reaction was diluted with successive portions of 100 ml of ether, 1.5 ml of water, 1.5 ml of 5 *N* sodium hydroxide solution, and then 4.5 ml of water.[30] After stirring for 0.5 hr the granular inorganic precipitate was filtered off and the filtrate concentrated *in vacuo*. The resulting pale yellow oil, 8.7 g, was distilled through a short-path distillation apparatus at reduced pressure. The desired amine was obtained as a colorless oil: 5.0 g (58.7%); bp 117–120° (0.13 mm); nmr ($CDCl_3$) δ 1.08 (s, NH), 2.44 (s, NCH_3), 3.98 (s ketal H's); mass spectrum (70 eV) *m/e* 247.

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.84; H, 8.43.

3-Methylbenz[*e*]indole (12).—A solution of 219 mg (1.21 mmol) of enamine **5** and 200 mg of 10% palladium on carbon in 3 ml of mesitylene was heated at reflux under a nitrogen atmosphere for 2.5 hr. The reaction was cooled, diluted with 50 ml of ether, and filtered through a Celite pad; the ether was removed on the rotary evaporator and the mesitylene removed under high vacuum. The pale yellow crystalline residue was purified by thick layer chromatography on alumina in 2:1 hexane–benzene. The desired benzindole, 164 mg (75%), was obtained as colorless needles which, on recrystallization from 5:1 hexane–ether, exhibited mp 54–55.5°: ir ($CHCl_3$) 1495, 1387, 1275, 1245, 1080, 945 cm^{-1}; nmr ($CDCl_3$) δ 3.67 (s, NCH_3), 6.98 (s, C-1, C-2 H's); mass spectrum (70 eV) *m/e* 181, 166, 152, 140, 139.

Anal. Calcd for $C_{13}H_{11}N$: C, 86.15; H, 6.12. Found: C, 86.20; H, 6.11.

10a-Hydroxy-3,4,4a,1,10,10a-hexahydro-2(1*H*)-4a-phenanthroneacetic Acid Lactone (18).—A solution of 27.3 g (0.12 mol) of keto ester **10** in 200 ml of methanol was cooled with stirring to −10°. The reaction vessel was purged with nitrogen and a prechilled solution of 13.2 g (0.234 mol) of potassium hydroxide dissolved in 18 ml of water and 36 ml of methanol added in one lot. A solution of 9.70 g (0.136 mol) of methyl vinyl ketone in 20 ml of methanol was then added dropwise over a 1.5-hr period at −10°.[31] The temperature was maintained at −10° for 2 hr; the mixture was allowed to stand at room temperature for 13 hr more. Dehydration and hydrolysis of the resulting mixture of ketol esters was accomplished by heating the reaction mixture at reflux for 2 hr. The solution was cooled to 0° and

(30) V. M. Micovic and M. L. J. Mihailović, *J. Org. Chem.*, **18**, 1190 (1953).

(31) A. Herschberg addition funnel is conveniently used in this step.

acidified to pH 3–5 with concentrated hydrochloric acid. The reaction mixture was diluted with 700 ml of water and extracted with three 200-ml portions of chloroform. The organic layer was washed with water until neutral and the product isolated by the standard procedure.[28] After trituration of the crude crystalline product with ether, there was obtained 20.3 g (68%) of the desired keto lactone as colorless prisms, mp 167–168°. An analytically pure sample was obtained by two additional recrystallizations from ethanol–acetone (4:1): mp 169–171°; ir ($CHCl_3$) 1720, 1770 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.98; H, 6.35.

If the annelation reaction was worked up before the basic hydrolysis step, the products consisted largely of the two ketol esters **16** and **17**. These isomers could easily be separated by column chromatography (Al_2O_3, neutral activity III). The isomer **17** was eluted with 1:1 ether–benzene as a colorless oil which crystallized on standing. Recrystallization from ether–hexane (4:1) afforded colorless prisms: mp 90–92°; ir ($CHCl_3$) 3300–3600 (OH) and 1720 cm^{-1}; ir (CCl_4) 0.016 *M*, 3600 cm^{-1}; nmr ($CDCl_3$) δ 1.29 and 4.87 (triplet and quartet for OCH_2CH_3), 1.27 (s, 3, methyl), 2.17 (broad, OH); mass spectrum (10 eV) *m/e* 302, 284, 257.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.47; H, 7.38.

The isomer **16** was eluted with 1:9 ethanol–ether as an oil which crystallized on standing. Recrystallization from ether–hexane afforded colorless prisms: mp 85.5–87.5°; ir ($CHCl_3$) 3300–3600 (OH) and 1720 cm^{-1}; ir (CCl_4) 0.015 *M* 3600, 3430 cm^{-1}; nmr ($CDCl_3$) δ 1.04 and 3.94 (triplet and quartet for OCH_2CH_3), 1.18 (s, 3, methyl), 2.58 (OH); mass spectrum (10 eV) 302, 284, 257.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.47; H, 7.24.

A discussion of the stereochemical assignments was included in the discussion.

Methyl 4,4a,9,10-Tetrahydro-2(3*H*)-phenanthrone-4a-acetate (19).—A slurry of 3.00 g (0.017 mol) of keto lactone **18** and 1.62 g of anhydrous potassium carbonate in 100 ml of acetone was heated at reflux under nitrogen for 0.5 hr. Methyl iodide, 2 ml, was added, and heating continued for 2 hr. An additional 2 ml of methyl iodide was then added followed by 2 hr of heating. The acetone was removed *in vacuo*, and 300 ml of benzene and 100 ml of water were added to the concentrate. The organic layer was separated and extracted once with 10% sodium thiosulfate solution and then with water until neutral. The standard work-up procedure[28] afforded a pale yellow crystalline substance. Trituration of this material with 1:1 pentane–ether afforded 2.89 g (94%) of crystalline keto ester **19**, mp 101–102°. Material of analytical purity was obtained by two additional crystallizations from acetone–hexane: mp 102–102.5°; ir ($CHCl_3$) 1723, 1660 (C=O's), 1625 cm^{-1} (C=C); nmr ($CHCl_3$) δ 3.52 (s, methoxyl), 6.04 (s, vinyl H).

Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.48; H, 6.63.

7,12-Dioxo-*N*-methylhasubanan (20).—The procedure followed in this experiment was essentially the same as that followed in the preparation of amide **11b**. To a dry, nitrogen-purged, 250-ml reaction vessel equipped with a Dry Ice condenser and addition funnel was added 150 ml of dry ether and 0.511 g (13.5 mmol) of pulverized lithium aluminum hydride. Anhydrous monomethylamine was distilled into the reaction vessel until all visible hydrogen evolution had ceased. The contents were allowed to stir for 1 hr, the Dry Ice condenser was replaced with a water-cooled condenser, and the solution heated at reflux for 0.5 hr and cooled to room temperature. The keto ester **19**, 1.0 g (3.4 mmol), in 100 ml of ether was added dropwise over a 3-min period and the reaction was allowed to stir at room temperature for 22 hr. Water, 150 ml, was added to the reaction and the contents were extracted with chloroform. The organic layer was washed with water until neutral and dried ($MgSO_4$). Removal of the solvent afforded 0.77 g of oil which was chromatographed on alumina (neutral activity III). Elution with 3:1 chloroform–ether afforded 0.654 g of crystalline lactam. On recrystallization from ethanol there was obtained 0.459 g (50%) of desired **20**: mp 146–147°; ir ($CHCl_3$) 1680, 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.8 (s, NCH_3); mass spectrum (70 eV) *m/e* 269, 240, 226, 212.

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11. Found: C, 75.84; H, 6.90.

Registry No.—**5**, 23657-79-6; **6**, 23953-64-2; **6** (HCl), 23953-65-3; **7**, 26156-79-6; **10**, 26210-99-1; **11a**, 26146-02-1; **11b**, 26146-03-2; **11c**, 26146-04-3; **12**, 23840-48-4; **16**, 26146-05-4; **17**, 26146-06-5; **18**, 26146-07-6; **19**, 26146-08-7; **20**, 26146-09-8.

Acknowledgments.—The authors are grateful to the Public Health Service (NB–08245) and the Petroleum Research Fund (PRF–1278–G1) for support of this work. The Varian A-60D spectrophotometer was made available through funds supplied by Du Pont.

Synthesis of *trans*- and *cis*-Sphingosine[1]

ELMER J. REIST* AND PAMELA H. CHRISTIE

Stanford Research Institute, Menlo Park, California 94025

Received May 26, 1970

The Wittig reaction between the ylide **3** from tetradecyltriphenylphosphonium bromide (**2**) and 3-deoxy-3-ethoxycarbonylamino-1,2-*O*-isopropylidene-α-D-ribopentodialdo-1,4-furanose (**11**) yielded either 2,2-dimethyl-6-ethoxycarbonylamino-5-(1-*trans*-pentadecenyl)-3a,5,6,6a-tetrahydro-D-ribofuro[2,3-*d*]dioxolane (**13a**) or the cis isomer **13b** as the predominant product depending upon the reaction conditions. Subsequent deacetonation and degradative chain shortening gave *trans*-sphingosine (**17a**) and its triacetate **18a** or *cis*-sphingosine (**17b**) and its triacetate **18b**.

In a previous publication from these laboratories,[2a] a stereospecific synthesis of dihydrosphingosine was described. The condensation of 3-benzyloxycarbonylamino-3-deoxy-1,2-*O*-isopropylidene-α-D-ribopentodialdo-1,4-furanose (**9**) with the Wittig reagent (**3**) prepared from tetradecyltriphenylphosphonium bromide (**2**) was carried out to give an olefin **12** as a mixture of cis and trans isomers in which the cis isomer predominated. This olefin (**12a** and **b**) was transformed in four steps to dihydrosphingosine (2-amino-D-erythro-octadecane-1,3-diol). In order for the synthesis to be useful for the preparation of naturally occurring *trans*-sphingosine[2b] it was necessary to devise Wittig conditions which would result in the formation of trans olefin **12a** as the predominant product.

Among the variables that have been reported to affect the course of a Wittig reaction is the nature of the cation

* To whom correspondence should be addressed.

(1) This investigation was supported by the U. S. Public Health Service Research Grant NS 07776 from the National Institute of Neurological Diseases and Stroke.

(2) (a) E. J. Reist and P. H. Christie, *J. Org. Chem.*, **35**, 3521 (1970). (b) In this article, 2-amino-D-erythro-4-octadecene-1,3-diol is referred to as sphingosine.