The 3-Arylpyrrolidine Alkaloid Synthon.[1] A New Synthesis of *dl*-Mesembrine[2]

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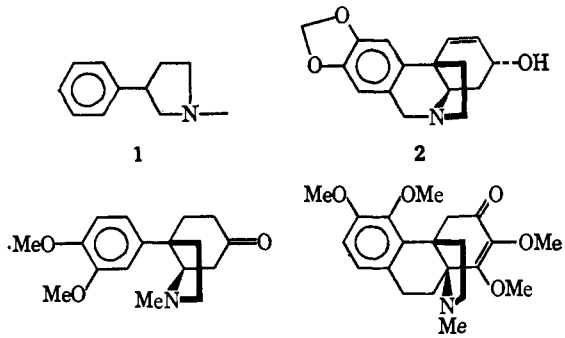
Abstract: A new synthesis of the *Aizoaceae* alkaloid mesembrine (**3**) has been accomplished by the reaction of methyl vinyl ketone with 1-methyl-3-(3,4-dimethoxyphenyl)-2-pyrroline (**8**). The pyrroline was conveniently prepared in four steps from 3,4-dimethoxyphenylacetonitrile as follows. Treatment of a DMSO solution of thenitrile with $BrCH_2CH_2Br$ and $(NaCH_2)(CH_3)SO$ converted it to 1-(3,4-dimethoxyphenyl)-1-cyanocyclopropane; $HAl(i\text{-}C_4H_9)_2$ reduction of the cyanocyclopropane yielded the corresponding aldehyde. Condensation of the aldehyde with methylamine gave imine **15** which, when heated at 160° in the presence of a trace of NH_4Cl, yielded **8**. This general synthetic approach may also be of utility in syntheses of *Amaryllidaceae* and *Menispermaceae* alkaloids.

A number of alkaloids from diverse sources have a common structural denominator in the 3-arylpyrrolidine (**1**) skeletal unit. Among others, specific examples include crinine (**2**),[4] mesembrine (**3**),[5] and hasubanonine (**4**)[6] which are produced by plants of the

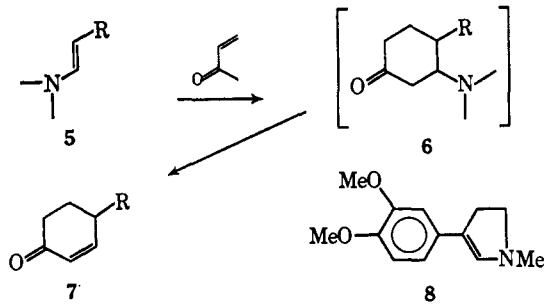


1 **2**

3 **4**

Amaryllidaceae, *Aizoaceae*, and *Menispermaceae*, respectively. It would seem this observation could be used to good advantage in the design of a synthesis of these alkaloids for, if a useful route to any one of them utilizing a 3-arylpyrrolidine unit were developed, the others might well be prepared by an appropriately modified version of the same scheme. In view of the apparent and largely uninvestigated potential of this approach, we decided to test its applicability in a new synthesis of the simplest of the alkaloids aforementioned, mesembrine.[7,8]

The use of a 3-arylpyrrolidine unit in a synthesis of mesembrine would introduce the nitrogen of the alkaloid at a point at which one carbocyclic ring remains to be fashioned before even the basic skeleton of the alkaloid will be complete. Although the presence of the nitrogen could complicate the chemistry of the later steps, it could, alternatively, play a useful role in the subsequent synthetic operations. One realization of this second possibility might be based on the Stork modification of the Robinson annelation reaction.[9,10] In the Stork procedure, the reaction between methyl vinyl ketone and an enamine yields an α,β-unsaturated ketone which is almost certainly formed by way of β-amino ketone **6** (*e.g.*, **5**–**7**). Mesembrine is a β-amino ketone and an inspection of its skeleton shows it might be obtained directly by the reaction of methyl vinyl ketone with enamine **8**, 1-methyl-3-(3,4-dimethoxyphenyl)-2-pyrroline. Although the enamine chemistry of 2-pyrrolines has not received exhaustive study,[11,12] there seems no compelling reason to expect it should be unusual.[12]



5 **6**

7 **8**

Even if the Robinson annelation reaction will occur, the question remains whether the cyclization product will possess a *cis*- (that found in mesembrine) or a *trans*-fused perhydroindole system. In the *trans*-fused

(1) "These [synthons] are defined as structural units within a molecule which are related to possible synthetic operations (and, therefore, to the reverse operations of degradation)." E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967).

(2) For a preliminary account of this work see: S. L. Keely, Jr., and F. C. Tahk, *Chem. Commun.*, 441 (1968).

(3) Recipient of a National Aeronautics and Space Administration Predoctoral Traineeship, 1967 to present.

(4) H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, **82**, 3368 (1960).

(5) A. Popelak, E. Haack, G. Lettenbauer, and H. Spingler, *Naturwissenschaften*, **47**, 156 (1960).

(6) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, and M. Matsui, *Tetrahedron Lett.*, 2937 (1964).

(7) A previous synthesis has been reported: M. Shamma and H. R. Rodriguez, *ibid.*, 4847 (1965).

(8) (a) Professor R. V. Stevens of Rice University kindly informed us prior to publication of his independent synthesis by the route described here. His findings, which are in accord with our own, are reported in an adjoining paper. (b) Another synthesis of mesembrine, also involving in the final step the annelation reaction between pyrroline **15** and methyl vinyl ketone, has recently been reported: T. J. Curphey and H. L. Kim, *Tetrahedron Lett.*, 1441 (1968). The conditions used by these workers to effect the annelation reaction differ from those described here and are reported to give excellent yields of the alkaloid.

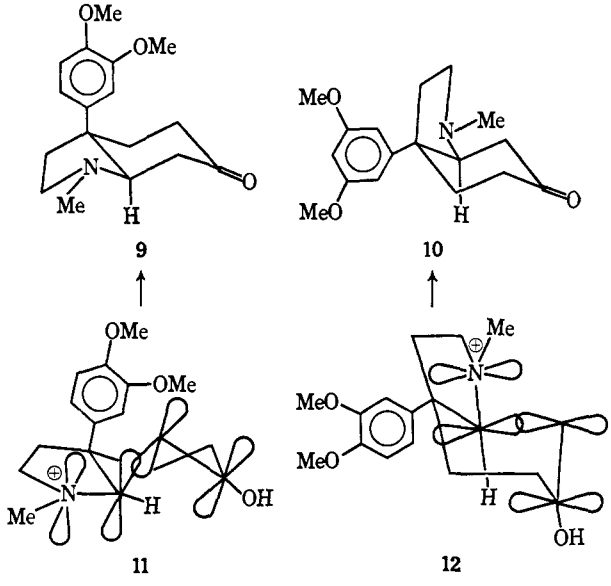
(9) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(10) J. Szmuszkovicz, *Advan. Org. Chem.*, **4**, 1 (1963).

(11) K. Bláha and O. Červinka, *Advan. Heterocyclic Chem.*, **6**, 147 (1966).

(12) The facile dimerization and trimerization reactions often characteristic of 2-pyrrolines seem to be much less common in those cases in which the ring is substituted in the 3 position and such processes were not expected to seriously complicate the chemistry of pyrroline **8**. See: N. J. Leonard and A. G. Cook, *J. Amer. Chem. Soc.*, **81**, 5627 (1959).

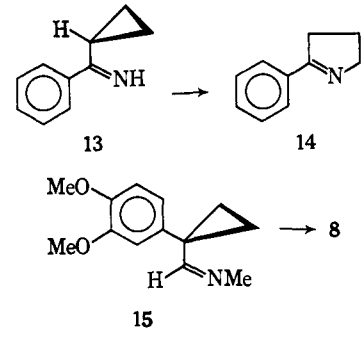
product (**9**), the molecular framework would be rigid with the aryl substituent axial to both of the other rings. In the case of *cis* fusion, however, the molecule is more flexible and two stable conformations of the perhydroindole moiety are possible. If if is assumed the results of conformational studies on analogous carbocyclic systems can be applied to the problem at hand, two observations are of note. *cis*- and *trans*-fused perhydroindans are approximately equally stable and the difference in stability between axially and equatorially disposed ring substituents seems to be substantially greater when the ring is cyclohexane than when it is cyclopentane.[13] Reasonably, then, the conformation of the *cis*-fused system in which the aryl substituent is equatorial to the cyclohexane ring (**10**) should be more stable than *trans*-fused **9** with its axial relationship between this same substituent and the other two rings; hence **10** should be the major product if the reaction is thermodynamically controlled. Further, whatever other species may intervene in this reaction,[14] the transition state for the final step of the cyclization surely involves partial overlap of the ends of the π systems of the immonium ion and the enol of the ketone as shown in **11** (leading to **9**) or **12** (leading to **10**). In both cases, there is a resemblance between the transition state complex and product so the conformational arguments just presented should also apply if the process is kinetically controlled with **10** again predicted to be the major product.



9 **10** **11** **12**

Believing that the considerations discussed here represented a reasonable approach to mesembrine, we turned to more immediate problems attending the realization of the synthesis.

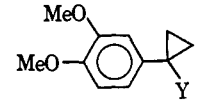
The preparation of requisite pyrroline **8** did not appear a major task even though reports of preparative methods leading to 3-aryl-2-pyrrolines were relatively scarce. After other approaches had been tried and abandoned as unsatisfactory, the method of choice, in terms of expedience if not yield, proved to be an adaptation of a 1-pyrroline synthesis. Some years ago, Cloke[15,16] reported that imine **13**, derived from phenyl cyclopropyl ketone, underwent a smooth thermal rearrangement at temperatures below 200° to 1-pyrroline **14**. Since one might expect that imine **15** would undergo an analogous rearrangement to **8**, we undertook an investigation of this route.



13 **14**

15

Cyclopropane derivative **16** was prepared from the anion of 3,4-dimethoxyphenylacetonitrile and 1,2-dibromoethane with dimethyl sulfoxide and its sodium salt as solvent and base. Although the yields of **16** (estimated by nmr spectroscopy) in the the unpurified reaction product mixture seemed to be about 40%, difficulty was experienced in separating product from starting material and the amounts of pure material obtained averaged 15% of theory. Reduction of **16** by ethereal diisobutylaluminum hydride[17] gave aldehyde **17**, yields of the purified product exceeding 50%. An excess of methylamine in benzene–ether solution with calcium oxide the dehydrating agent, effected the essentially quantitative conversion, at room temperature, of **17** to imine **15** which was purified by vacuum distillation with little material loss.



16, Y = CN
17, Y = CHO

Attempts to rearrange **15** to **8** by Cloke's usual method were unrewarding. Even heating the pure imine in a sealed tube at 198° for 66 hr left it unchanged and, consequently, other conditions under which the transformation might occur were sought.

Cloke had mentioned[15] that the rearrangement of **13** could be catalyzed by acid, traces of the hydrochloride proving a suitable proton source. Rather than test the ability of the hydrochloride of **15** to catalyze its isomerization, we tried a more readily available substance of about equal acidity, ammonium chloride. In the presence of a small amount of this salt, rearrangement of the neat imine to pyrroline **8** proceeded smoothly at 160° and was complete within 1 hr. The nmr spectrum of the crude product was, with the exception of a small amount of ill-defined background absorption, essentially identical with that of the purified material. The pure pyrroline can be handled briefly in air without special

(13) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, pp 44, 202, and 230.

(14) Dihydropyran and cyclobutane derivatives are possibilities. See ref 9, 10, and G. Opitz and H. Holtmann, *Justus Liebigs Ann. Chem.*, **684**, 79 (1965).

(15) J. B. Cloke, *J. Amer. Chem. Soc.*, **51**, 1174 (1929).

(16) J. B. Cloke, L. H. Baer, J. M. Robbins, and G. E. Smith, *ibid.*, **67**, 2155 (1945).

(17) L. I. Zakharkin and I. M. Khorlina, *Dokl. Akad. Nauk SSSR*, **116**, 422 (1957); *Chem. Abstr.*, **52**, 8040 (1958).

precautions although it appears to undergo slow decomposition under these conditions. Both crude and purified **8** have been used with success in the final step of the synthesis.

The addition of methyl vinyl ketone to the pyrroline was accomplished by dissolving equimolar amounts of the reactants in 1,2-dimethoxyethane and refluxing the reaction mixture until mesembrine production appeared to have ceased. The ir and nmr solution spectra of the naturally occurring alkaloid and that obtained from the synthesis were identical and, in each of six different solvent systems used for development, the tlc R_f values were the same. Yields of pure mesembrine obtained in this last step of the synthesis are, disappointingly, only about 5%.[8b] Nonetheless, the brevity of the synthesis seems to compensate for this drawback and suggests the value of 3-aryl-2-pyrrolines and related endocyclic enamines as intermediates in alkaloid synthesis.[18]

Experimental Section[19]

1-(3,4-Dimethoxyphenyl)-1-cyanocyclopropane (16). Half the volume of a DMSO solution of the sodium salt of DMSO (dimsylsodium, prepared by dissolving at 65° 4.8 g (0.20 mol) of NaH in 100 ml of DMSO) was added dropwise over a 30-min period to a mechanically stirred solution of 17.7 g (0.10 mol) of 3,4-dimethoxyphenylacetonitrile in 40 ml of dry DMSO contained in a flame-dried flask under a dry N_2 atmosphere. Dropwise addition of 20.7 g (0.11 mol) of 1,2-dibromoethane to this mixture was completed in 30 min and the resulting thick slurry diluted with 25 ml of the solvent while stirring continued. After 10 min, the remainder of the dimsylsodium solution was added over an interval of 50 min and the solution stirred for another hour. The reaction mixture was then poured into 500 ml of water, the emulsion thereby formed extracted with three 200-ml portions of ether, and the combined ether layers dried over $MgSO_4$. Removal of the drying agent and, by distillation *in vacuo*, the solvent gave 16.2 g of an orange semisolid. The nmr spectrum of this material (cyclopropyl to aromatic H peak area comparisons) indicated approximately 50% of this mixture was the desired product. Two recrystallizations of the crude substance from 95% ethanol gave 3.39 g (17%) of 1-(3,4-dimethoxyphenyl)-1-cyanocyclopropane, mp 68.5–69.2°; ir (CH_2Cl_2) *ca.* 2250 cm^{-1}; nmr ($CDCl_3$) τ 3.18 (sym m, 3), 6.10 and 6.14 (2s, 6), and 8.52 ppm (sym m, 4). A single recrystallization of the purified product from ethanol–water gave an analytical sample, mp 69.2–69.7°.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.77; H, 6.54; N, 6.83.

1-(3,4-Dimethoxyphenyl)cyclopropanecarboxaldehyde (17). Dropwise addition of 1.56 g (0.0110 mol) of diisobutylaluminum hydride in 33 ml of dry Et_2O to a stirred Et_2O solution of 2.03 g (0.0100 mol) of 1-(3,4-dimethoxyphenyl)cyanocyclopropane on a 25–27° water bath under a dry N_2 atmosphere was completed in 25 min. The resulting pale yellow-brown solution was stirred for 45 min at room temperature and then for an additional 30 min while heated at gentle reflux. While the reaction mixture was stirred on an ice–water bath, 15 ml of dioxane containing 1.0 ml of H_2O was cautiously added; the mixture was then diluted and shaken with 100 ml of 1 *N* HCl. The two-phase system was allowed to stand 15 min and then shaken again. After the ether layer was removed, the aqueous phase was twice extracted with 50-ml portions of ether. All ether layers were then combined, washed with 50 ml of 2% aqueous Na_2CO_3 and 50 ml of H_2O, and dried over $MgSO_4$. Removal of the drying agent and, by distillation *in vacuo*, the solvent gave, as an oil which soon crystallized, 1.98 g (96%) of 1-(3,4-dimethoxyphenyl)cyclopropanecarboxaldehyde, mp (vac) 60.6–63.6°. Recrystallization from ethanol–water gave a total of 1.03 g (50%) of purified material, mp (vac) 63.6–63.8° (only 0.14 g of additional product of lower purity was recovered from the mother liquors); ir (CH_2Cl_2) 1712 cm^{-1}; nmr ($CDCl_3$) τ 0.75 (s, 1), 3.14 (s, 3), 6.12 and 6.13 (2s, 6), and 8.53 ppm (sym m, 4). A single recrystallization of the purified aldehyde from ethanol–water gave an analytical sample, mp (vac) 63.3–63.9°.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.75; H, 6.89.

N-Methyl-1-(3,4-dimethoxyphenyl)cyclopropanecarboxaldimine (15). To a mixture of 0.31 g (1.50 mmol) of 1-(3,4-dimethoxyphenyl)cyclopropanecarboxaldehyde and 0.25 g (4.50 mmol) of CaO powder were added 40 ml of dry ether and 15 ml of benzene previously saturated at 15° with methylamine. The mixture was stirred at room temperature in a sealed flask until, after 60 hr, ir spectra on samples taken from it no longer showed the carbonyl absorption (*ca.* 1710 cm^{-1}) characteristic of the aldehyde. Filtration of the reaction mixture and removal of the solvent by distillation *in vacuo* gave, as a crystalline solid, 0.31 g (94%) of 1-(3,4-dimethoxyphenyl)cyclopropanecarboxaldimine, mp (vac) 45.5–47.0°. An analytical sample was obtained by sealing a small sample of the product under vacuum (*ca.* 0.15 mm) in one arm of an angle tube, heating that arm to 190°, and permitting the distillate to collect in the second, wherein it subsequently crystallized, mp (vac) 47.8–48.9°.[20] In larger scale preparations, the imine was more conveniently purified by vacuum distillation, bp 114–116° (0.75 mm) and, after crystallization, mp 47.0–48.0°; ir (CH_2Cl_2) 1665 cm^{-1}; nmr ($CDCl_3$) τ 2.45 (q, 1, J = 1.5 cps) 3.16 (s, 3), 6.13 and 6.15 (2s, 6), 6.78 (d, 3, J = 1.5 cps), and 8.80 ppm (sym m, 4).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.01; H, 7.94; N, 6.41.

1-Methyl-3-(3,4-dimethoxyphenyl)-2-pyrroline (8). Under oil pump vacuum (*ca.* 0.15 mm), 0.50 g (2.30 mmol) of N-methyl-1-(3,4-dimethoxyphenyl)cyclopropanecarboxaldimine and 25 mg of NH_4Cl were sealed into a glass ampoule. The ampoule was heated 1 hr in an oil bath maintained at 160° and shaken 2 min at 10-min intervals to ensure thorough mixing of reactant and catalyst. The resulting yellow oil, decanted while still hot from undissolved NH_4Cl, formed a crystalline solid, mp (vac) 64.0–66.5°, on cooling. The nmr spectrum of the crude material prepared in this manner was, with the exception of a small amount of general background absorption, essentially identical with one obtained on the purified product. Purification of a 0.673-g sample of crude pyrroline prepared as described here was effected by dissolving it in benzene–petroleum ether (bp 30–60°), decanting the resulting solution from the gummy precipitates formed, and recrystallization from the solvent. Considerable material loss attended this purification; only 0.140 g (21% recovery) of the pure crystalline pyrroline, mp (vac) 72.9–73.9°, was obtained. A subsequent recrystallization from the same solvent yielded an analytical sample: mp (vac) 74.0–74.6°; ir (CH_2Cl_2) 1619 cm^{-1}; nmr ($CDCl_3$) τ 3.25 (m, 3), 3.80 (asym t, 1), 6.13 and 6.16 (2s, 6), *ca.* 7.05 (m, 4), and 7.37 ppm (s, 3).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.40; H, 7.87; N, 6.39.

***dl*-Mesembrine (3).** A solution of 280 mg (1.28 mmol) of 1-methyl-3-(3,4-dimethoxyphenyl)-2-pyrroline (crude product obtained directly from the rearrangement) and 90 mg (1.28 mmol) of methyl vinyl ketone (containing 1% hydroquinone stabilizer) in 2.5 ml of dry 1,2-dimethoxyethane was gently refluxed under dry N_2 for 1 day, at which time tlc on samples of the reaction mixture indicated that the production of mesembrine had ceased. The reaction solution was poured into 3.0 ml of 1 *N* HCl, extracted with three 3-ml portions of ether which were discarded, and then brought to pH 9–10 by the addition of solid K_2CO_3. This basic solution was extracted with three 10-ml portions of ether, and the combined ether layers were washed with several small volumes of 1% aqueous K_2CO_3 and dried over $MgSO_4$. Filtration and removal of the solvent by distillation *in vacuo* gave 156 mg of a yellow-brown gum.

(18) For other examples of the use of endocyclic enamines in alkaloid synthesis see: E. Wenkert, *Accounts Chem. Res.*, **1**, 78 (1968).

(19) Melting points (oil bath) reported are uncorrected and those taken in an evacuated capillary are designated by "(vac)." Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Nuclear magnetic resonance spectra were taken on a Varian A-60 spectrometer with $CDCl_3$ the solvent and tetramethylsilane the standard. Infrared spectra were obtained on a Perkin-Elmer 21 spectrophotometer. In the isolation of the synthetic alkaloid, thin layer chromatography was carried out on 8 × 8 in. glass plates coated with *ca.* 0.5 mm thick layers of Mallinckrodt SilicAR TLC-4G. For nonpreparative tlc work, Eastman Chromatogram Sheet 6061 (silica gel) was used with iodine the indicating reagent. Natural (−)-mesembrine was obtained in the form of its hydrochloride from S. B. Penick and Co., New York, N. Y.

(20) Recent work has shown the imine can also exist in a second, more stable crystalline modification, mp 57–58°. Whether the two crystalline forms correspond to *syn* and *anti* isomers of the imine or to polymorphism of the crystals of one of these isomers has not been established.

Tlc (Eastman Chromatogram Sheets, $CHCl_3$–EtOAc–CH_3OH (2:2:1) developer) showed the gum was a complex mixture. One component had the same R_f value as natural (−)-mesembrine and was not separated from it on tlc. The gum was purified by tlc on Mallinckrodt SilicAR adsorbant using the solvent system last mentioned as the developer. In this system, natural mesembrine appeared in the 0.35–0.50-R_f range and, accordingly, in the purification, silica gel in this range was removed from the developed plates and extracted with 30 ml and again with 20 ml of 1 *N* HCl. The combined aqueous solutions were basified with 2 *N* NH_4OH and extracted with three 20-ml portions of $CHCl_3$. The combined organic layers were dried over Na_2SO_4. The drying agent and, by distillation *in vacuo*, the solvent were removed giving, as a pale yellow gum, 28 mg (7.5%) of *dl*-mesembrine. The ir and nmr solution ($CDCl_3$) spectra of this material were, except for the presence of minor contaminants such as stopcock grease, identical with that of the alkaloid. This synthetic material and 36.9 mg of that of equivalent purity from a previous synthesis were combined in 10 ml of HCl and the solution extracted with several small portions of CH_2Cl_2 (discarded), basified with 2 *N* NH_4OH, extracted with three 10-ml portions of CH_2Cl_2 and the combined organic layers dried over Na_2SO_4. Removal of the drying agent and, by distillation *in vacuo*, the solvent left 38.3 mg (4.6% after correction for dilution) of the synthetic alkaloid whose ir and nmr spectra were now identical with that of (−)-mesembrine. Tlc on Eastman Chromatogram Sheets of the natural alkaloid, the synthetic alkaloid, and a mixture of the two was carried out using six different developers. Each run showed only one spot and, with any one developer and within a few per cent, at the same R_f value: Et_2O–CH_3OH (4:1), R_f 0.43; $CHCl_3$–CH_3OH (3:1), R_f 0.73; $CHCl_3$, R_f 0.58; $CHCl_3$–EtOAc–CH_3OH (2:2:1), R_f 0.53; C_6H_6–CH_3OH (4:1), R_f 0.58; Et_2O, R_f 0.09.

dl-Mesembrine has also been prepared in the above manner (although reaction times appeared to be somewhat longer) and in comparable yield (*ca.* 3.0%) using the purified pyrroline as the starting material.

Acknowledgment. Support of this work by National Institutes of Health Research Grant GM-14222 is gratefully acknowledged. We also wish to thank Dr. Jack Houser of the University of Akron for his kind cooperation in the obtaining of some of the nmr data.

Synthesis of Rhodoquinone and Other Multiprenyl-1,4-benzoquinones Biosynthetically Related to Ubiquinone[1a]

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Contribution from the Stanford Research Institute, Menlo Park, California.
Received March 14, 1968

Abstract: The knowledge of the biosynthetic sequence from *p*-hydroxybenzoic acid (HBA) to ubiquinone and then rhodoquinone has been confirmed and enlarged by the organic synthesis of three multiprenyl-1,4-benzoquinones, which correspond to biosynthetic precursors. They are 2-amino-3-hydroxy-5-decaprenyl-6-methyl-1,4-benzoquinone (rhodoquinone), 2-hydroxy-3-methoxy-5-decaprenyl-6-methyl-1,4-benzoquinone, and 2-methoxy-5-methyl-6-decaprenyl-1,4-benzoquinone. Boron trifluoride catalyzed condensation of decaprenol with 2-methoxy-5-methyl-1,4-benzohydroquinone followed by oxidation of the hydroquinone gave 2-methoxy-5-methyl-6-decaprenyl-1,4-benzoquinone which, in turn, reacted with ammonia by 1,4 addition to give rhodoquinone-10. Deamination of rhodoquinone-10 with cupric chloride in acetic acid yielded 2-hydroxy-3-methoxy-5-decaprenyl-6-methyl-1,4-benzoquinone. The three analogous and isomeric decaprenyl derivatives were synthesized similarly from 2-methoxy-6-methyl-1,4-benzoquinone, and other related compounds were prepared. In the past, complete structure elucidation, on a microscale, of newly isolated compounds of the ubiquinone group was often difficult or not feasible. The spectral and chromatographic data on the new synthetic 5- and 6-decaprenyl analogs of ubiquinone and related compounds now greatly facilitate structural elucidations in this field. New data on the relative rates of conversion of these benzoquinones to their corresponding chromenols also extend the feasibility of structural elucidation on a microscale.

The isolation of a series of multiprenylphenols[2] and multiprenyl-1,4-benzoquinones[3,4] from *Rhodospirillum rubrum* resulted in the formulation of a complete biosynthetic sequence[3] from *p*-hydroxybenzoic acid (HBA) to ubiquinone (Q, **1a**). Parson and Rudney[5] had earlier demonstrated that ubiquinone (**1a**) is a precursor to rhodoquinone (**2a**) in *R. rubrum*. The biosynthetic and structural relationships of the last four compounds in this sequence are given (Scheme I).

Compounds **2**, **3**, and **4** differ from ubiquinone (**1a**) in that one methoxy group is replaced by hydrogen (**3**) or by another substituent (**2**, **4**). This paper reports the syntheses of these products, 2-amino-3-methoxy-5-decaprenyl-6-methyl-1,4-benzoquinone (rhodoquinone-10,[6–8] **2a**, $n = 9$), 2-hydroxy-3-methoxy-5-decaprenyl-6-methyl-1,4-benzoquinone[4] (**4a**, $n = 9$), and 2-methoxy-5-methyl-6-decaprenyl-1,4-benzoquinone[3] (**3a**, $n = 9$) as well as their position isomers **12a**, **13a**, and **9a** and other related compounds. The availability of these synthetic compounds has made possible a study

(1) (a) Coenzyme Q. CII. (b) The Royal Veterinary and Agricultural College, Copenhagen, Denmark.
(2) (a) The nomenclature used in this paper is based on a recommendation of an IUPAC–IUB Commission of Biochemical Nomenclature, *Biochim. Biophys. Acta*, 107, 5 (1965). (b) R. K. Olsen, G. D. Daves, Jr., H. W. Moore, K. Folkers, W. W. Parson, and H. Rudney, *J. Amer. Chem. Soc.*, **88**, 5915 (1966).
(3) P. Friis, G. D. Daves, Jr., and K. Folkers, *ibid.*, **88**, 4754 (1966).
(4) P. Friis, J. L. G. Nilsson, G. D. Daves, Jr., and K. Folkers, *Biochem. Biophys. Res. Commun.*, **28**, 324 (1967).
(5) W. W. Parson and H. Rudney, *J. Biol. Chem.*, **240**, 1853 (1965).
(6) J. Glover and D. R. Threlfall, *Biochem. J.*, **85**, 14p (1962).
(7) N. G. Carr, *ibid.*, **91**, 28p (1964).
(8) R. Powls and F. W. Hemming, *Phytochem.*, **5**, 1235 (1966).