distilled triethylamine and stirred at room temperature for 48 hr. The reaction mixture was diluted with 30 ml of CHCl$_3$ and extracted with 3% NaOH (3 × 20 ml) to remove 0.475 g of unreacted gigantine. The CHCl$_3$ layer was washed with saturated NaCl solution and dried over CaSO$_4$, the solvent was evaporated, and residual water was removed by azeotropic distillation with 50 ml of dry benzene.

The crude phosphate ester (1.353 g, 84%) was dissolved in 5 ml of dry, peroxide-free THF in a flask equipped with a Dry Ice condenser and a CaCl$_2$ drying tube. About 10 ml of dry NH$_3$ was passed through a NaOH drying tower and condensed into the reaction flask. The reaction mixture was cooled in an acetone–Dry Ice bath while 0.172 g (0.008 g-atom) of sodium metal was added in small pieces. The solution was allowed to warm up until the ammonia began to reflux in order to prevent the phosphate ester from crystallizing. When the blue color of the dissolved sodium vanished (30 min), 5 ml of absolute ethanol was added and the ammonia was allowed to evaporate. The residue was dissolved in CHCl$_3$ (100 ml), and the solution was extracted with water (3 × 50 ml), dried by shaking with a saturated salt solution (2 × 50 ml), and filtered through CaSO$_4$. Distillation of the solvent at reduced pressure left (*S*)-carnegine [(−)-*N*-methylsalsolidine] (**11**) as an oil which was converted to 0.475 g (43% from **10**) of an hydrochloride, whose infrared spectrum (KBr) and that of the hydrochloride of natural, racemic carnegine (**1**) were identical, as were the nmr spectra (DCCl$_3$) of the free bases (**11** and **1**); a picrate, mp 229–232° (lit.[27] mp 233–234°), was also prepared. A distilled (0.03 mm) sample of the free base **11** regenerated from this picrate by passage through an Al$_2$O$_3$ column with CHCl$_3$–CH$_3$OH had the following rotations: $[M]^{25}\text{D}$ −110° (*c* 1.78, benzene), −51.5° (*c* 1.70 absolute EtOH), and +16.5° (*c* 1.22, 1 *N* HCl) [lit.[27] $[M]^{22}\text{D}$ −115 °(*c* ~4.5, benzene), −55° (*c* 4.45, absolute EtOH), and +17° (*c* ~4.5, 1 *N* HCl)].

**Registry No.**—**1**, 490-53-9; **6**, 34407-54-0; **9** acetamide, 30666-18-3; **10**, 34408-15-6; **10** HCl, 34408-16-7; 5-benzyloxy-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 30666-19-4, 34402-63-6 (methiodide); 5-benzyloxy-6,7-dimethoxy-1,2-dimethyltetrahydroisoquinoline, 34389-05-4, 34402-64-7 (picrate).

**Acknowledgment.**—This research was generously supported by grants from the Texas Christian University Research Foundation and the Robert A. Welch Foundation. We would also like to thank Mr. Chongsuh Pyun and Mr. Robert Daubert for experimental assistance, Mr. Ernst Ellis for the preparation of (±)-carnegine, Dr. J. R. Zimmerman and the Mobil Oil Co. of Dallas for the mass spectra, and Mr. W. H. Earle, Director of Desert Botanical Gardens, Tempe, Ariz., for classifying *C. gigantea.*

---

# Convenient Synthesis of Frontalin—1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane

T. D. J. D'Silva* and D. W. Peck

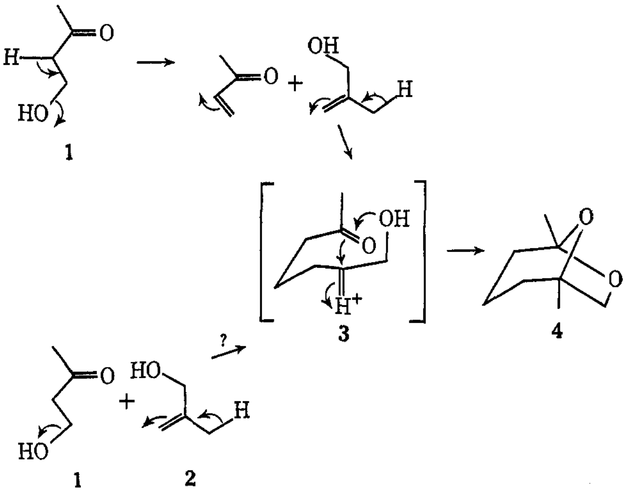
*Research and Development Department,*
*Union Carbide Corporation, Chemicals and Plastics,*
*South Charleston, West Virgina 25303*

*Received December 27, 1971*

Frontalin is an aggregating pheromone of the southern pine beetle and other related bark beetles.[1] Kinzer, *et al.*,[2] reported the synthesis of the attractant without experimental details, and in unspecified yield,[3] by heating methyl vinyl ketone (MVK) and methallyl alcohol. We wish to report a simple, one-step synthesis of frontalin by heating a mixture of formaldehyde (as formalin, paraformaldehyde, or trioxane), excess of acetone, and methallyl alcohol, *without any catalyst*, in a stainless steel autoclave or sealed glass tube at 250–275° for 1 hr. Up to 35–40% of frontalin (based on methallyl alcohol consumed) has been isolated. The yield of frontalin was markedly increased (see Experimental Section) with toluene as solvent, albeit with a loss in efficiency due to loss of methallyl alcohol.

Although the yields have not been optimized, this process offers great advantage over the use of MVK or other synthetic routes for the large-scale production of frontalin.

Heating methallyl alcohol with 4-hydroxy-2-butanone, the first reaction product between formaldehyde and acetone, also yields frontalin. From glc analysis of the samples taken at shorter reaction times, MVK and its dimer have been detected (in one instance MVK was also isolated), but they disappear with time. It is, therefore, apparent that the reaction leading to the formation of frontalin proceeds *via* the intermediary of MVK formed *in situ*. This could then react with methallyl alcohol in Diels–Alder fashion[2] or by an "ene-type reaction" as shown below. A direct reaction between methallyl alcohol and 4-hydroxy-2-butanone, although less likely, cannot be ruled out.



Some of the physical properties of frontalin are recorded in the Experimental Section.

## Experimental Section

**Synthesis of Frontalin Using Acetone and Paraformaldehyde without Solvent.**—A suspension of 480.0 g (16.0 mol) of paraformaldehyde, 1152.0 g (16.0 mol) of methallyl alcohol, and 6720.0 g (96.0 mol) of acetone was heated in a 5-gallon autoclave for 1 hr at 250°. Distillation yielded 6070.0 g of acetone, 31.0 g of methyl vinyl ketone, 770.0 g of methallyl alcohol, 267.0 g of frontalin (~98% pure), bp 60–62° (30 mm), 450.0 g of high-boiling fraction, bp 142–162° (0.8–0.9 mm), and 322.0 g of residue. Pure frontalin had bp 155° (760 mm), 91° (100 mm), $n^{20}\text{D}$ 1.4386, sp gr (20°) 0.9889. Its nmr spectrum was identical with that of the material obtained by Kinzer's method. The yield of frontalin based on reacted methallyl alcohol was 35.4%.

---

[1] J. P. Vité and G. P. Pitman, *J. Econ. Entomol.*, **63**, 1132 (1970), and references cited therein.

[2] G. W. Kinzer, A. F. Feintiman, Jr., T. F. Page, Jr., R. L. Foltz, J. P. Vité, and G. P. Pitman, *Nature (London)*, **221**, 477 (1969).

[3] B. P. Mundy, R. D. Otzenberger, and A. R. DeBernardis, *J. Org. Chem.*, **36**, 2390 (1971), recently reported the synthesis *via* a Diels–Alder reaction of MVK and methyl methacrylate, followed by reduction to the alcohol and cyclization, in overall yields of less than 10%.

**Synthesis of Frontalin with Toluene as Solvent.**—The same mixture as above was diluted with 2845.0 g (32.0 mol) of toluene and heated for 1.25 hr at 250°. Distillation yielded 6018.0 g of acetone, 356.0 g of methallyl alcohol, 2785.0 g of toluene, 376.0 g of frontalin, 270.0 g of high-boiling fraction, and 376.0 g of residue. The yield of frontalin based on reacted methallyl alcohol was 24.0%.

**Synthesis of Frontalin Using 4-Hydroxy-2-butanone.**—A mixture of 7.2 g (0.1 mol) of methallyl alcohol, 8.8 g (0.1 mol) of 4-hydroxy-2-butanone, and 46.0 g (0.5 mol) of toluene was heated in a sealed glass tube for 1 hr at 250°. The glc analysis (excluding the toluene peak) indicated the presence of 30.5% frontalin, 52.0% unreacted methallyl alcohol, and 12.4% higher boiling by-products.

**Registry No.**—Frontalin, 28401-39-0.

# A Highly Stereoselective Synthesis of *meso-N,N'*-Dicarbethoxy-2,4-diaminopentane and *meso*-2,4-Diaminopentane

ROBERT O. HUTCHINS* AND BRUCE E. MARYANOFF

*Department of Chemistry, Drexel University,*
*Philadelphia, Pennsylvania 19104*

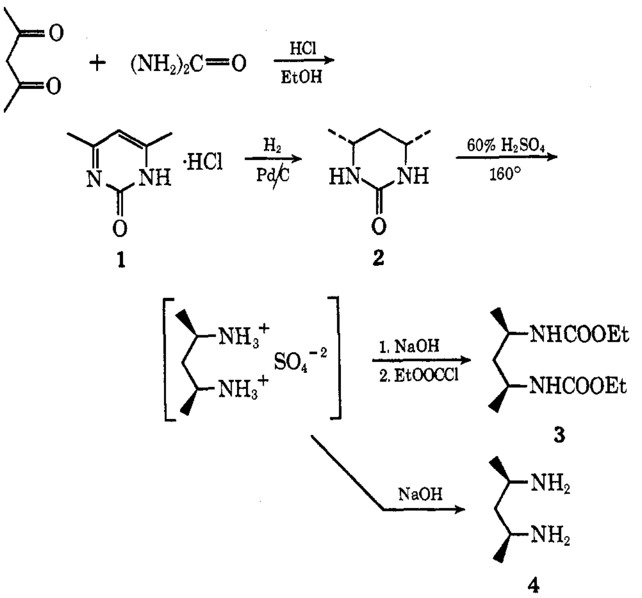
*Received November 3, 1971*

In the course of another study we required *meso*-2,4-diaminopentane. This note reports a unique, highly stereoselective synthesis of this material and its more conveniently isolated *N,N'*-dicarbethoxy derivative, which was also needed for further synthetic operations.

2,4-Diaminopentane has been prepared by reduction of 2,4-pentanedione dioxime by various methods,[1] the best of which was sodium in ethanol.[1] This procedure, which is inefficient and unwieldy, results in an 80% yield of product (as the dihydrochloride), only 30% of which is the meso diastereomer.[1] In addition, the meso and *dl* compounds must be separated, which is a tedious and yield-reducing process.[1] Our attempts to obtain a more favorable meso/*dl* ratio using other reducing agents did not meet with success. For example, aluminum hydride (an excellent reducing agent for oximes[2]) afforded a good yield of the diamine but the mixture contained only *ca.* 50% (by nmr) of the meso stereoisomer.

In order to obtain more conveniently the desired meso isomer, we devised a method in which the stereochemistry could be more easily controlled. The approach (outlined in Scheme I) involved establishing the proper atom arrangement within a readily formed pyrimidine ring (1) followed by catalytic hydrogenation[3] to the saturated cyclic urea 2 containing the correctly oriented *cis*-methyl groups. Hydrolysis then provided the desired meso diamine. The procedure takes advantage of the situation that any equilibration of 2 during hydrogenation should greatly favor the cis diequatorial disposition of the methyl groups and thus reinforce the predominance of the wanted stereoisomer.

SCHEME I



The reaction of acetylacetone with urea in refluxing acidic 95% ethanol[4] furnished a good yield (70–75%) of 2-hydroxy-4,6-dimethylpyrimidine hydrochloride (**1**). The 2-one tautomeric structure is suggested for **1** on the basis of ir and uv spectra. An aqueous solution of **1** was hydrogenated[5] using palladium on carbon[6] and the crude cyclic urea was obtained. Recrystallization gave diastereomerically pure **2**, which *required* sublimation in order to remove the solvent (mostly water). The cis cyclic urea **2** was hydrolyzed[7] in 60% sulfuric acid and the resulting diammonium salt was converted to the dicarbamate **3** in moderate yield (50–57%), or to the free diamine **4** in fair yield (25–30%).

The assignment of the cis configuration for the cyclic urea was made on the basis of nmr comparison with *cis*- and *trans*-2-phenyl-4,6-dimethyl-2-bora-1,3-dioxacyclohexane[8] and was consistent with a noninterconverting ring with diequatorial methyl groups. The nmr spectrum of the dicarbethoxy compound **3** is consistent with the presence of the vertical mirror plane contained in the meso isomer.

## Experimental Section

Melting points and boiling points are uncorrected. Microanalyses were performed by Alfred Bernhardt Microanalytisches Laboratorium, West Germany. Infrared spectra were taken on a Perkin-Elmer Model 457 spectrophotometer. Nmr spectra were obtained on a Varian A-60 or HA-100 spectrometer using tetramethylsilane as an internal reference. Ultraviolet spectra were recorded on a Perkin-Elmer Model 402 spectrophotometer.

**2-Hydroxy-4,6-dimethylpyrimidine Hydrochloride (1).**—To acetylacetone (24.0 g, 0.24 mol) and urea (12.0 g, 0.20 mol) in 250 ml of 95% ethanol was added 50 ml of concentrated hydrochloric acid. The mixture was stirred under reflux for 2 hr, cooled in ice, and filtered. The colorless crystals were rinsed with ice-cold absolute ethanol and then with dry ether, and dried *in vacuo* to afford 20–22 g (70–75%) of colorless **1**, mp 260° dec

---

(1) C. J. Dippel, *Recl. Trav. Chim. Pays-Bas*, **50**, 525 (1931), and references cited therein.

(2) N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 2927 (1968).

(3) Catalytic hydrogenation was anticipated to provide a predominance of the cis isomer. See (a) O. V. Bragin and A. L. Liberman, *Russ. Chem. Rev.*, **39** (12), 1017 (1970); (b) E. A. Mistryukov, E. L. Ilkova, and M. A. Ryashentseva, *Tetrahedron Lett.*, 1691 (1971).

(4) R. R. Hunt, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 525 (1959); also see W. J. Hale, *J. Amer. Chem. Soc.*, **36**, 104 (1914).

(5) V. H. Smith and B. E. Christensen, *J. Org. Chem.*, **20**, 829 (1955).

(6) Use of activated Raney nickel as a catalyst under similar conditions resulted in complete recovery of the starting material (**1**) which was contaminated with Ni(II): J. J. Fox and D. Van Pragg, *J. Amer. Chem. Soc.*, **82**, 486 (1960).

(7) G. S. Skinner, R. H. Hall, and P. V. Susi, *ibid.*, **79**, 3786 (1957).

(8) We thank Dr. F. A. Davis and I. Turchi for nmr spectra of the boron heterocycles (to be published in *J. Org. Chem.*), which were chosen as models for comparison because of the expected geometric similarity of these rings to the corresponding cyclic ureas.