

## Synthesis of Ageratochromene Dimer

Meyer Schwarz

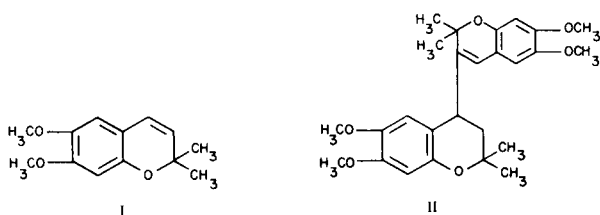
Biologically Active Natural Products Laboratory,  
Agricultural Environmental Quality Institute,  
Agricultural Research Service, USDA, Beltsville, Maryland 20705

Received November 1, 1976

Reflux of a benzene solution of 2,2-dimethyl-6,7-dimethoxy-4-chromanol in the presence of a catalytic amount of *p*-toluenesulfonic acid leads to ageratochromene dimer (II) rather than to ageratochromene (I). Treatment of I under the same conditions also produces II which is identical with the dimer of ageratochromene isolated by Kasturi and Manithomas from *Ageratum conyzoides* L.

*J. Heterocyclic Chem.*, 14, 333 (1977).

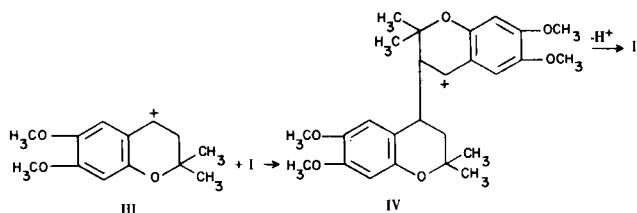
In 1967, Kasturi and Manithomas (1) reported the isolation of a dimer of ageratochromene (I) from *Ageratum conyzoides* L. They tentatively assigned structure II to the compound, since it was the only ageratochromene dimer out of a possible four, whose nmr spectrum was compatible with that of structure II.



The recent disclosure by Bowers (2) of the anti-allatropic activity of I and of 6-demethoxyageratochromene prompted us to synthesize these two compounds. The synthetic route to I chosen was that reported by Bowers *et al.* (2). 2,2-Dimethyl-6,7-dimethoxy-4-chromanone prepared from 3-methyl-2-butenic acid and 3,4-dimethoxyphenol in polyphosphoric acid was reduced to the corresponding chromanol (3) with lithium aluminum hydride. In the Bowers synthesis the reduction mixture was treated directly with 4*N* hydrochloric acid to yield I, while Huls (3) reported that dehydration of the chromanol with aluminum oxide also leads to ageratochromene. When a solution of 2,2-dimethyl-6,7-dimethoxy-4-chromanol was refluxed for 15 minutes in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, the expected ageratochromene was not obtained but a substance of identical m.p. and spectral properties with the dimer of ageratochromene described by Kasturi and Manithomas (1) was isolated in quantitative yield.

This dimerization reaction may be rationalized by the addition of the carbonium ion III to I to form the

carbonium ion IV which then loses a proton to yield II. Indeed when authentic ageratochromene was treated under the same conditions again a quantitative yield of II was obtained.



This synthesis of II thus confirms the original assignment made by Kasturi and Manithomas (1). It is interesting to note that refluxing of 2,2-dimethyl-7-methoxychromanol with *p*-toluenesulfonic acid in benzene leads neither to a dimer nor to 6-demethoxyageratochromene but to noncrystalline, presumably polymeric, materials, whereas treatment with aqueous hydrochloric acid (2) or with phosphoryl chloride pyridine in benzene (4) yields the expected chromene.

## EXPERIMENTAL

Melting points were determined on a Büchi apparatus and were uncorrected. The following instruments were used for the spectra described. Beckman DK2A (UV), Perkin Elmer 521 (ir), Varian T-60 with tetramethylsilane as internal standard (nmr) and Hewlett-Packard 5930A (mass spectrum).

## 2,2-Dimethyl-6,7-dimethoxy-4-chromanone.

A mixture of 3,4-dimethoxyphenol (10.8 g., 0.07 mole) and 3-methyl-2-butenic acid (8.0 g., 0.08 mole) was added to polyphosphoric acid (80 g.) preheated to 60°. The mixture was stirred vigorously to promote rapid dissolution, the temperature rose rapidly to 100°; after 5 minutes the reaction mixture was cooled and decomposed with ice-water (longer contact times

lead to drastically reduced yields). The product which crystallized was filtered, dissolved in methylene chloride and washed with 5% aqueous sodium hydroxide and water. Evaporation of the methylene chloride and recrystallization from ether-petroleum ether provided 12.3 g. (76%) of the title compound m.p. 106-108° [lit. m.p. 106° (3)]; ir (Nujol): 1670  $\text{cm}^{-1}$  (C=O); nmr (deuteriochloroform):  $\delta$  1.45 (s, 6H,  $\text{CH}_3$ ), 2.5 (s, 2H,  $\text{CH}_2$ ), 3.85, 3.9 (2s, 6H,  $\text{OCH}_3$ ), 6.4 (s, 1H, arom.), 7.2 (s, 1H, arom.). Ageratochromene dimer (II).

2,2-Dimethyl-6,7-dimethoxy-4-chromanone (2.3 g., 0.01 mole) was reduced with lithium aluminum hydride (0.40 g., 0.01 mole) in the usual manner in diethyl ether and the reaction worked up with saturated ammonium chloride. The ether was evaporated to afford 2.3 g. of crude 2,2-dimethyl-6,7-dimethoxy-4-chromanol (3) as a syrupy liquid, which was dissolved in 50 ml. of benzene containing 50 mg. of *p*-toluenesulfonic acid and refluxed in a Dean-Stark apparatus for 15 minutes. The cooled reaction mixture was extracted with 10% sodium carbonate, washed with water, dried and evaporated to dryness to afford 2.1 g. (99%) of the title compound m.p. 154-155° [lit. m.p. 154-154.5° (1)]. Recrystallization from methanol-water or ether-pentane did not raise the melting point; uv  $\lambda$  max (ethanol): 324 nm ( $\epsilon = 10,100$ ), 293 nm ( $\epsilon = 9,000$ ); ir (Nujol): 1655, 1618, 1595, 1370, 1240, 1030  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  1.25, 1.45, 1.5, 1.6 (4s, 12H,  $\text{CH}_3$ ), 2 (m, 2H,  $\text{CH}_2$ ), 3.5 (t, 1H, benzylic), 3.7, 3.75, 3.8 (3s, 12H,  $\text{OCH}_3$ ), 6.0, 6.4, 6.45, 6.6 (4s, 5H, vinylic and aromatic); mass spectrum (5): m/e 441 (M+1) 440 ( $\text{M}^+$ ), 425 (M- $\text{CH}_3$ ), 409 (M- $\text{OCH}_3$ ) 221, 219 (monomeric ions) [lit. UV  $\lambda$

max (ethanol): 323 nm ( $\epsilon = 9,086$ ), 293 nm ( $\epsilon = 8,232$ ); ir (Nujol): 1658, 1618, 1595, 1370, 1240, 1038  $\text{cm}^{-1}$ ; nmr (deuteriochloroform):  $\delta$  1.25, 1.45, 1.5, 1.6 (4s, 12H), 1.85 (m, 2H), 3.45 (m, 1H), 3.7, 3.8, 3.85 (3s, 12H), 6.0, 6.4, 6.45 6.6 (4s, 5H); mass spectrum: m/e 440, 221, 219 (1)].

Anal. Calcd. for  $\text{C}_{26}\text{H}_{32}\text{O}_6$ : C, 70.91; H, 7.29. Found: C, 70.83; H, 7.26.

When a solution of authentic ageratochromene (2) in benzene was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid for 15 minutes, ageratochromene dimer was isolated in quantitative yield, after the work-up procedure outlined above.

#### REFERENCES AND NOTES

- (1) T. R. Kasturi and T. Manithomas, *Tetrahedron Letters*, 2573 (1967).
- (2a) W. S. Bowers in "The Juvenile Hormones," L. I. Gilbert, Ed., Plenum Press, New York, N. Y. 1976, pp. 394-408; (b) W. S. Bowers, T. Ohta, J. S. Cleve, and P. A. Marsella, *Science*, 193, 542 (1976).
- (3a) R. Huls, *Bull. Soc. Chim. Belges*, 66, 409 (1957); (b) R. Huls, *ibid.*, 67, 22 (1958).
- (4) J. R. Beck, R. Kwok, R. N. Booher, A. C. Brown, L. E. Patterson, D. Pranc, B. Rokey, and A. Pohland, *J. Am. Chem. Soc.*, 90, 4706 (1968).
- (5) Measurements by R. F. Thomas are gratefully acknowledged.