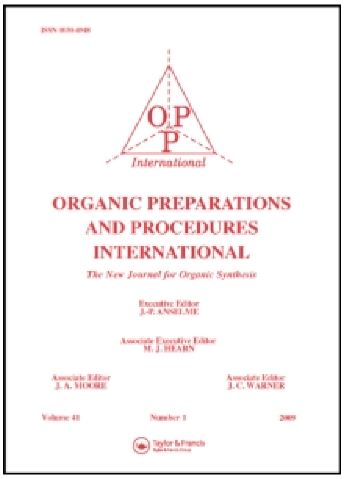


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

6,7-DIMETHOXYCARBOSTYRIL

George R. Pettit[a][b]; Benjamin Stevenson[a][b]; Gabriel Gever[a][b]
[a] Department of Chemistry, Arizona State University, Tempe, Arizona [b] Eaton Laboratories, Morton-Norwich Products, Inc., Norwich, New York

To cite this Article Pettit, George R. , Stevenson, Benjamin and Gever, Gabriel(1971) '6,7-DIMETHOXYCARBOSTYRIL', Organic Preparations and Procedures International, 3: 2, 93 — 95

To link to this Article: DOI: 10.1080/00304947109356042

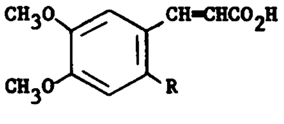
URL: http://dx.doi.org/10.1080/00304947109356042

ORGANIC PREPARATIONS AND PROCEDURES INT. 3(2), 93-95 (1971)

6,7-DIMETHOXYCARBOSTYRIL

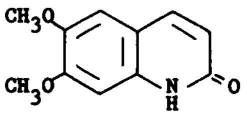
George R. Pettit, Benjamin Stevenson and Gabriel Gever
Department of Chemistry
Arizona State University, Tempe, Arizona 85281
and
Eaton Laboratories, Morton-Norwich Products, Inc., Norwich, New York

While the Béchamp reduction has been applied frequently in the preparation of aminocinnamic acids, experimental details are frequently incomplete or otherwise inadequate. Similar observations apply to the acid catalyzed cyclization of *o*-aminocinnamic acids to carbostyrils. The following conversion of *o*-nitrocinnamic acid **Ia** via amino acid **Ib** to 6,7-dimethoxycarbostyril (**II**) was found routinely useful and provides a detailed illustration of the ferrous sulfate-ammonium hydroxide reduction and intramolecular cyclization steps in this type carbostyril synthesis. The experimental procedure summarized has been repeated in essentially the same manner with reaction volumes varying from 50 mls to over 100 gallons. Comparable observations and yields were noted in each case. The product (**II**) was of interest initially as a potential hypotensive agent.



Ia, R = NO_2

Ib, R = NH_2



II

EXPERIMENTAL

3,4-dimethoxy-6-aminocinnamic acid (**Ib**)--The following synthesis is based on a method described by Kefford.[1] A well-ventilated hood should be employed with this experiment. In a 22-l. three-necked flask, equipped with a stirrer, a reflux condenser and a thermometer, was placed 8.5.1 of water, 50 ml. of concentrated hydrochloric acid, 5.54 kg. (19.9 moles) of ferrous sulfate heptahydrate (Mallinckrodt U.S.P.) and 548 g (2.16 moles) of 3,4-dimethoxy-6-nitrocinnamic acid.[2] The mixture was stirred and heated to 90° and the source of heat removed before adding[3] 4.4 l. (65 moles) of 28% aqueous ammonia over a 25 minute period. Vigorous stirring was maintained during the addition of ammonia. Stirring was continued at a moderate rate for an additional 45 minutes before filtering the hot[4] reaction mixture through a layer of ''Celite'' filter aid on a large Buchner table-type funnel. The precipitate was washed[5] with 1.5 l. of water and the combined filtrate was acidified to pH 5.2 with 910 ml of concentrated hydrochloric acid. Before collecting the light brown crystalline solid, the mixture was allowed to stand one hour. The product was washed successively with three small portions of ice water and allowed to dry at 60°. The yield of 3,4-dimethoxy-6-aminocinnamic acid was 190-212 g (39-44%), mp 142-144°. Reprecipitation from aqueous ammonia yielded golden yellow platelets melting at 147-148° (Lit.[1] mp 175-177°).

6,7-dimethoxycarbostyril (**II**).--A mixture of 185 g (0.83 mole) of crude 3,4-dimethoxy-6-aminocinnamic acid, 20 g of ''Darco'' and 3.2 l. of 4% hydrochloric acid were placed in a 5-l. three-necked flask fitted with a mechanical stirrer and reflux condenser. The mixture was stirred and heated at reflux for 1.5 hour. The hot reaction mixture was then filtered through a preheated Buchner funnel. Unless this is done, the product will crystallize before filtration can be completed. The filtrate was cooled in an ice bath and the pink colored crystalline product was collected and washed with enough 1% aqueous ammonia to remove the pink coloration. The crude cream colored 6,7-dimethoxycarbostyril weighed 120-123 g. (70-72%), mp 230-231°, and was pure enough for preparative purposes. Recrystallization from acetic acid led to colorless crystals, mp 231° (Lit.[1] mp 229°): ν_{max}^{KBr} 3160, 3030, 3000-2800, 1660, 1630, 1560, 1540, 1465, 1440, 1260, 1160, 1115, 1005, 840 and 760; pmr ($CDCl_3$ solution with tetramethylsilane as internal standard) δ, 3.68 (doublet, 6 protons), 6.20 (doublet, $J = 9H_z$), 6.75 (1 proton), 7.0 (1 proton) and 7.62 (doublet, $J = 9H_z$); and mass spec (varian CH-4B), M^+ 205.

REFERENCES

1. J. E. Kefford, *J. Chem. Soc.*, 1209 (1940).
2. The 3,4-dimethoxy-6-nitrocinnamic acid (Ia) prepared from 6-nitroveratraldehyde and malonic acid as described by Kefford[1] was used without further purification.
3. The aqueous ammonia was added through the reflux condenser at a rate which prevented blockage of the condenser by liquid. Alternatively, the thermometer was replaced with a dropping funnel.
4. The reaction mixture temperature rises to approximately 99° during the addition of ammonia and gradually falls to about 80° during the remaining 45 minutes.
5. Occasionally, a large amount of product was adsorbed by the iron oxides and additional washing proved necessary.

(Received January 11, 1971)