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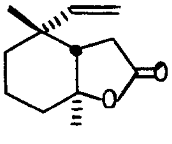
ANASTREPHIN AND EPIANASTREPHIN, NOVEL LACTONE COMPONENTS ISOLATED FROM THE SEX PHEROMONE BLEND OF MALE CARIBBEAN AND MEXICAN FRUIT FLIES[1]

Merle A. Battiste,* Lucjan Strekowski, David P. Vanderbilt,
Melean Visnick, and Roy W. King
Department of Chemistry, University of Florida, Gainesville, FL 32611
James L. Nation
Department of Entomology and Nematology, University of Florida, Gainesville, FL 32611

SUMMARY: Anastrephin and epianastrephin, novel lactone components isolated from the male produced pheromone of two *Anastrepha* fruit fly species (Caribbean and Mexican) are assigned the structure and relative stereochemistry 1 and 2, respectively, on the basis of spectroscopic and chemical evidence including synthesis.

Courting male Caribbean fruit flies, *Anastrepha suspensa* (Loew), produce and release a four-component sex pheromone[2] which in addition to attracting females for mating also acts as an aggregation pheromone for both sexes in the field.[3] Chromatography of male *A. suspensa* extracts on silver nitrate-impregnated silicic acid afforded four individually bioactive components (I-IV) each isolated in >95% purity. Components I and II are C_9 unsaturated alcohols[2b] and were readily identified as Z-3-nonen-1-ol and Z,Z-3,6-nonadien-1-ol, respectively.[4] Synthetic samples of I and II were also shown to have behavioral activity in laboratory bioassays with 10-day-old female flies.[4] Components III and IV, henceforth referred to as anastrephin and epianastrephin, constitute the major fraction, by weight, of the extracted pheromone blend and have now been identified as the diastereoisomeric *trans*-fused bicyclic γ-lactones 1 and 2, respectively.[5]

In this paper we report the structure elucidation of lactones 1 and 2 by spectroscopic means as well as chemical synthesis. In addition we describe the results of a companion study which convincingly demonstrates the presence of lactones 1 and 2, along with Z-3-nonen-1-ol and Z,Z-3,6-nonadien-1-ol, in the extracts of males of the closely related Mexican fruit fly, *Anastrepha ludens* (Loew). As such these results constitute the first structural identification of the multi-component pheromone blends of fruit flies of the species *Anastrepha*.



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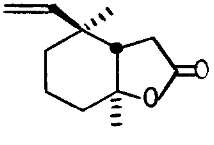
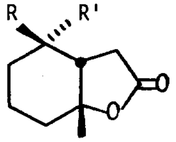


2

Anastrephin (1), m.p. 78-80°C, $[\alpha]_D^{23}$-7.5°(pentane, c=1.8)[5], and epianastrephin (2), oil, $[\alpha]_D^{23}$-4.2°(pentane, c=1.74)[5], are clearly isomeric $C_{12}H_{18}O_2$ lactones as revealed by their infrared (1, $\nu_{C=O}^{CS_2}$ 1778 cm^{-1}; 2, $\nu_{C=O}^{film}$ 1770, 1782 cm^{-1}) and mass spectra [1, M^+ m/z 194.1306 (3.9% of the base peak $C_6H_9^+$); 2, M^+ m/z 194.1307 (2.7% of the base peak $C_2H_3O^+$)]. The most revealing features in the ^1H-NMR spectra ($CDCl_3$, 100 HMz) of 1 [δ 1.03(s, 3H), 1.25(s, 3H), 1.40-2.60(m, 9H), 4.90-6.20(10 line ABX multiplet, 3H)] and 2 [δ 1.05(s, 3H), 1.37(s, 3H), 1.20-2.50(m, 9H), 4.75-5.90(10 line ABX multiplet, 3H)] are the presence of an uncomplicated vinyl pattern and two sharp methyl singlets. ^{13}C-NMR data ($CDCl_3$, 100 MHz) for 1 [δ 176.11(s), 139.97(d), 112.94(t), 86.33(s), 55.56(d), 38.62(s), 37.21(t), 36.13(t), 30.34(q), 29.02(t), 20.38(q), 20.20(t)] and 2 [δ 175.89(s), 147.57(d), 111.31(t), 85.78(s), 53.19(d), 38.23(s), 37.69(t), 36.82(t), 29.25(t), 20.66(q), 20.20(t), 16.18(q)] further confirmed the closely related, isomeric nature of the lactones and provided ample support for the hexahydrobenzofuranone skeleton of 1/2.

On the basis of the above spectral data and standard biosynthetic considerations the most reasonable structure for anastrephin and its epimer appeared to be 4-ethenyl-4,7a-dimethyl-2(3H)-hexahydrobenzofuranone[6] although the stereochemical questions remained unresolved. To this end we chose to prepare each of the four possible racemic diastereomers, i.e. 1 and 2, plus the respective *cis*-fused lactones 3 and 4.

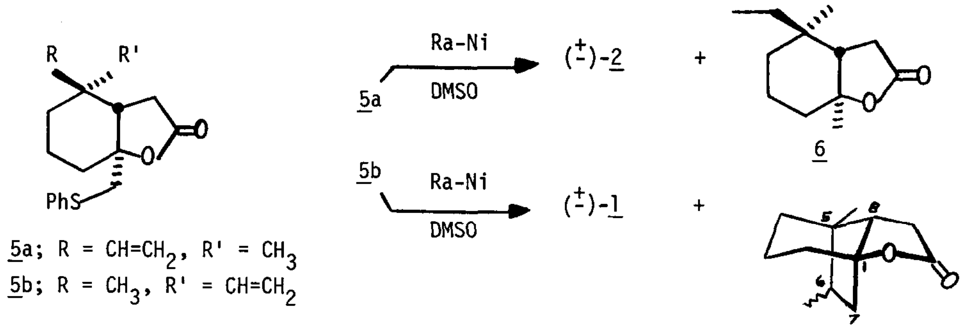


3; R = CH_3, R' = $CH{=}CH_2$

4; R = $CH{=}CH_2$, R' = CH_3

We have previously reported[7] a convenient if stereoselectively limited approach to *trans*-fused γ-lactones *via* sodium benzenethiolate promoted ring opening of appropriate γ,δ-spiroepoxyesters, the so-called spirooxirane route. As reported therein[7] pure samples of racemic lactones 1-4 were prepared by this spirooxirane approach. Although similar in their spectroscopic properties the *cis*-lactones 3 and 4 were not identical to the natural lactones III and IV. On the other hand the ^1H- and ^{13}C-NMR spectra and other spectral properties of the synthetic *trans*-lactones (±)-1 and (±)-2 were identical in all respects to the natural lactones, anastrephin and epianastrephin.

The relative stereochemistry of the methyl, vinyl quarternary center was also established adventitiously in the final step of the above synthesis. Thus, whereas Raney-Nickel desulfurization of the phenythiomethyl *trans*-lactone precursor of (±)-epianastrephin (i.e., 5a) proceeded smoothly to afford (±)-2 (72%) along with minor (9%) amounts of the reduced lactone, (±)-dihydroepianastrephin (6), similar desulfurization of the thiolactone precursor of (±)-anastrephin (i.e., 5b) afforded (±)-1 as a minor product (13%) together with an isomeric ($C_{12}H_{18}O_2$) saturated lactone whose spectral data are entirely consistent with the tricyclic structure 7. The ^1H-NMR spectrum of 7 at 300 MHz showed two methyl proton doublets (J=6 and 7 Hz) and two methyl singlets, each pair in a 9:1 ratio, indicating a mixture of epimeric methyl isomers. The formation of 7 as a mixture of *exo*- and *endo*-6-methyl isomers is mechanistically compatible with radical cyclization onto the proximate axial vinyl groups in



5a; R = $CH=CH_2$, R' = CH_3
5b; R = CH_3, R' = $CH=CH_2$

6

7

5b. Thus, the contrasting product distributions from desulfurization of 5a and 5b provides strong chemical support for the assigned relative stereochemistry in both synthetic and natural lactones 1 and 2.[8] Further support for these stereochemical assignments has been obtained *via* a recently completed stereoselective synthesis of (±)-anastrephin(±)-1.[9]

The Mexican fruit fly, *A. ludens* , and the Caribbean fruit fly, *A. suspensa*, are not known at present to be sympatric, and no behavioral interactions between the two species have been reported, yet females of each species are attracted in laboratory bioassays to the heterospecific male extract. Examination of the hexane extracts from about 45,000 frozen male Mexican fruit flies (*ca.* 10 days old when frozen)[10] by gas chromatography (3% OV-1 and 10% DEGS) revealed the presence of the same four pheromonal components isolated from *A. suspensa* males. Using the identical chromatographic isolation scheme developed for the Caribbean fruit fly pheromone[2b] two isomeric $C_{12}H_{18}O_2$ lactones were isolated which proved to be identical to anastrephin (1) and epianastrephin (2) by standard glpc and mass spectral comparisons. Finally, lactones 1 and 2 isolated from male Mexican fruit flies were found to attract female Caribbean fruit flies in the standard laboratory olfactometer test.[2b,11]

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References and Footnotes

1. The structures of anastrephin and epianastrephin were preliminarily disclosed in a lecture (M.A.B.) before the Organic Section of the Southeast/Southwest Combined Regional Meeting of the A.C.S., December 10-13, 1980, New Orleans, LA, paper 388.

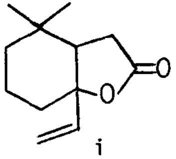
2. (a) J. L. Nation, *Ann. Entomol. Soc. Amer.*, 65, 1364 (1972);
   (b) J. L. Nation, *Environ, Entomol.*, 4, 27 (1975).

3. A. J. Perdomo, J. L. Nation, and R. M. Barranowski, *Environ. Entomol.*, 5, 1208 (1976).

4. J. L. Nation, Proc. 5th Intl. Cong. Pesticide Chem., Kyoto, Japan, Aug. 29-Sept. 5, 1982, in press.

5. (a) The natural lactones 1 and 2 isolated from cultured *A. suspensa* males are not single enantiomers, although each is enantiomerically enriched. Application of the chiral solvent method according to Pirkle[5b] indicate enantiomeric excesses in the range 55±3(-)/45±3(+). Chirality sensing by the same method also implies the absolute stereochemistry for the major enantiomer as shown in structures 1 and 2 (other sterochemical depictions in this paper are in the relative sense only). Confirmation of the absolute stereochemistry of the major/minor enantiomers of 1 and 2 awaits the results of work in progress;
   (b) W. H. Pirke, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, 42, 384 (1977), and references cited therein.

6. An alternative skeletal isomer with two chiral centers, i, was eliminated from consideration by synthesis of the *cis*-fused diastereomer of i; Z. Paryzek, unpublished results from this laboratory. Comparison of spectral data for *cis*-i with that for the natural lactones 1 and 2, particularly the mass spectral fragmentation patterns, also ruled out the corresponding *trans*-diasteromer as a structural candidate.



i

7. L. Strekowski and M. A. Battiste, *Tetrahedron Lett.*, 22, 279 (1981).

8. As expected, incorporation of selenium for sulfur *via* phenylselenide opening of the oxirane ring greatly enhances the synthetic value of the spirooxirane approach to lactones 1 and 2. Thus, Raney-Nickel deselenization of the hydroxy acid precursors to 5a(S=Se) and 5b(S=Se) affords excellent yields of (±)-1 and (±)-2 after lactonization with only traces of the dihydro or isomeric saturated lactones being detected.

9. M. Visnick, L. Strekowski, and M. A. Battiste, manuscript in preparation.

10. R. E. Esponda, Unpublished Thesis, Instituto Technologico y de Estudios Superiores de Monterey, N. L. Mexico, 1977.

11. A preliminary report of the comparative aspects of the pheromone components from *A. suspensa* and *A. ludens* has appeared in print: J. L. Nation, *Proc. Int. Soc. Citriculture* 2, 481 (1977). Because of the limited circulation of this publication and in view of the importance of the now completed structural identification of the pheromone components, the compelling features of this comparative study are summarized in this report.

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