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THE SYNTHESIS OF THE DRUGSTORE BEETLE PHEROMONE (STEGOBINONE)

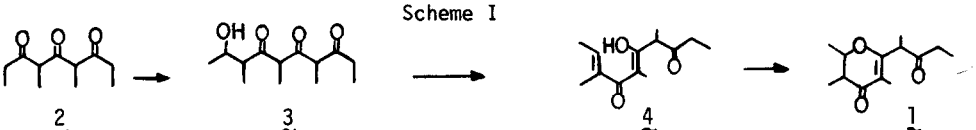
Jay M. Ansell and Alfred Hassner*
Department of Chemistry, State University of New York at Binghamton, New York 13901

W. E. Burkholder
The Stored Product and Household Insects Laboratory, USDA-SEA and the
Department of Entomology, University of Wisconsin, Madison, Wisconsin 53706

Summary: 2,3-Dihydro-2,3,5-trimethyl-6-(1-methyl-2-oxobutyl)-4H-pyran-4-one (1) (Stegobinone), the sex pheromone of the drugstore beetle, was successfully prepared from 4,6-dimethyl-3,5,7-nonatrione (2) by a biogenetically plausible scheme.

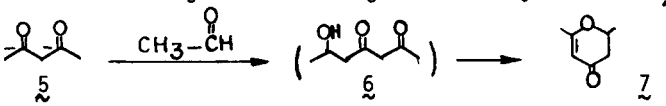
We wish to report the first synthesis of 1, the sex pheromone of the drugstore beetle, Stegobium paniceum (L.), for which we propose the trivial name stegobinone. The drugstore beetle and related anobiid beetles are ubiquitous pests found to thrive on almost any dry organic foodstuff.[1] This fact coupled with the small size of the beetles, which renders visual determination difficult, make pheromone techniques ideally suited for pest management of these beetles. The presence of a sex pheromone in the drugstore beetle was demonstrated by Kuwahara et al. when 7.8 mg of the pheromone was isolated from 30,000 female insects.[1] This compound was later identified as 2,3-dihydro-2,3,5-trimethyl-6-(1-methyl-2-oxobutyl)-4H-pyran-4-one (1).[2] The pivot of our approach to the synthesis of 1 involves the preferential intramolecular Michael cyclization via oxygen[3] of a properly functionalized polyketo chain (i.e., 4). If trione 2 can be converted via its trianion to alcohol 3, then one might expect elimination of water followed by O-cyclization of the enol 4 to lead directly to the desired pyranone 1 (Scheme I). An analogy is provided by the acylation of triketone trianions with β-keto esters

Scheme I



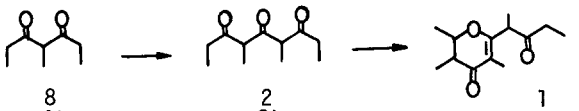
2 3 4 1

to produce polyketones.[4] To test the feasibility of Scheme I, we allowed the dianion of diketone 5 to react with acetaldehyde and isolated upon acid work-up, the pyranone 7, the spectral properties of which were identical to those reported.[5] Based on this model study the synthesis of pheromone 1 was carried out via diketone 8 and triketone 2. One can easily visualize that such a cyclization route might be occurring in the biosynthesis of 1.



5 6 7

4-Methyl-3,5-heptadione (8) readily available by the method of Dziomko[6] was converted into its dianion by the action of 2 equiv of LDA (lithium diisopropylamide) in THF at 0° and acylated with methyl propionate. The resulting 4,5-dimethyl-3,5,7-nonatrione (2) [74% conversion from 8] bp (@ 0.1 mm) 125-130° [bath]; nmr ($CDCl_3$) δ 3.80 (2H, q, C-H), 2.53 (4H, q, $\underline{CH_2}$-CH_3), 1.93 (s, CH_3), 1.35 (6H, d, J=6.5 Hz, $\underline{CH_3}$-C-H), 1.06 (6H, t, $\underline{CH_3}$-CH_2); ir ($CHCl_3$) 2990, 2950, 2890, 1795, 1715, 1660, 1615, [$Cu(OAc)_2$ chelate dark green mp 120-121°] was treated with 3 equiv of LDA at 0° followed by acetaldehyde. After work-up the crude oil was



8 2 1

subjected to methanolic HCl and chromatographed on a silica gel column [PhH:EtOAc 9:1 elution]. The fraction at Rf .24 of the four fractions (Rf .68, .44, .24, .06) was rechromatographed on prep TLC plates (Woelm Silica Gel GF 2000 μ PhH:EtOAc 3:1) yielding two bands of which the lower one was identified as (±)-stegobinone 1 by comparison of ir and nmr with authentic pheromone. The more mobile fraction was tentatively identified as a diastereomer of 1. Ir (neat film) 2990, 2950, 2890, 1730, 1670, 1620, 1460, 1420 (w), 1387, 1365, 1350 (shoulder), 1290 (w), 1260 (w), 1200, 1180 (w), 1150, 1080, 1055, 1022, 968, 925, 860 (w), 815 (w), 790 (w), 660 (m); nmr ($CDCl_3$) δ 1.07-1.47 (12H, m), 1.83 (3H, s), 1.47 (3H, m), 3.65 (1H, q, J=7 Hz), 4.10 (1H, m, J_{H}-CH_3=6 Hz, J_{H-H}=1.5 Hz). Interestingly, this isomer shows some pheromone activity as well.

Synthetic (±)-Stegobinone 1 was active as a sex attractant in a bioassay with a threshold amount of approximately 10^{-4} μg.[7] The described rational synthesis of 1 provides confirmation of the assignment to the pheromone and at the same time represents a possible biosynthetic pathway to 1 involving polyketones. Further studies directed toward the optically active pheromone are underway.

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References

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