Tetrahedron Letters No. 19, pp 1625 - 1628, 1976. Pergamon Press. Printed in Great Britain.

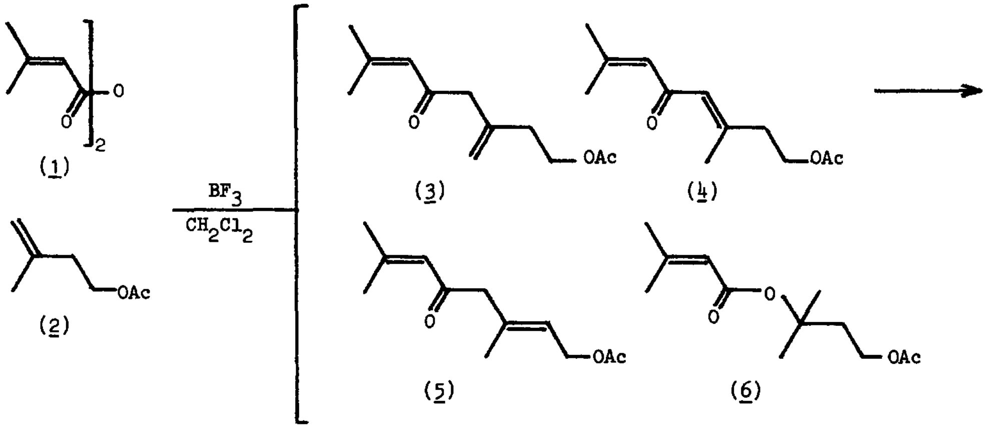
TERPENOID SYNTHESIS. V.[1] ELECTROPHILIC ADDITION REACTIONS IN THE SYNTHESIS OF THE OCIMENONES, THE ROSE OXIDES, AND A PHEROMONE OF IPS PARACONFUSUS

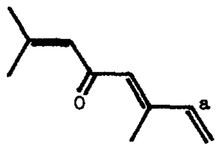
C.F. Garbers* and F. Scott[2]
Department of Chemistry, University of Stellenbosch, South Africa

(Received in UK 4 March 1976; accepted for publication 29 March 1976)

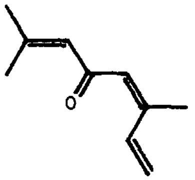
The (E)- and (Z)-ocimenones (7) and (8), major constituents of Tagetes minuta oil,[3] have been synthesized by condensation of senecioyl chloride with isoprene.[3,4] Due to their tendency to polymerize, we have investigated the synthesis of a more stable intermediate from which these ketones (7) and (8) may be readily obtained in high yield. We herewith report the synthesis of ketones (3) - (5), which proved to be versatile starting materials of increased stability. Ketones (3) - (5) were successfully employed in the synthesis of the ocimenones, the rose oxides[5] and the principal component of the aggregation pheromone of the bark beetle Ips paraconfusus.[6]

3-Methylbut-3-en-1-yl acetate (2), a by-product from the manufacture of isoprene,[7] was employed as a potential isoprene unit. This ester (2) condensed with senecioic anhydride (1) in the presence of a Lewis acid (e.g. BF_3-etherate in methylene chloride) to give a mixture (76%)[8] of ketones (3) - (5). In addition ester (6) (0.5 - 1%), resulting from the Lewis acid catalyzed addition of senecioic acid to ester (2), was also formed. The constitution of the condensation product varied with the Lewis acid employed and in a typical experiment (with BF_3-etherate as catalyst) the condensation product contained ketones (3) (70%), (4) (21%), and (5) (8%) as well as

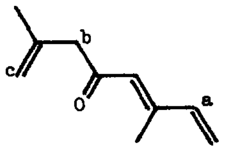




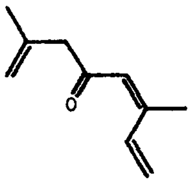
(7) 21%



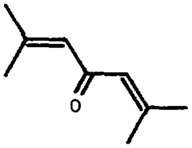
(8) 5%



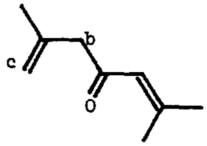
(9) 60%



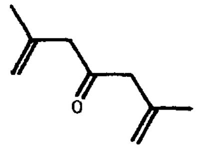
(10) 14%



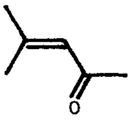
(11)



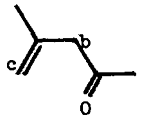
(12)



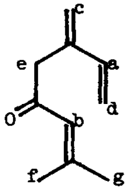
(13)



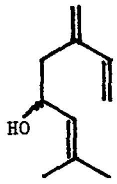
(14)



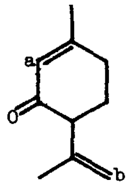
(15)



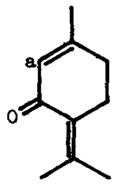
(16)



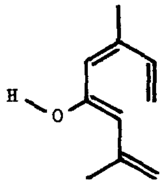
(17)



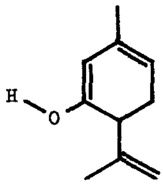
(18)



(19)



(20)



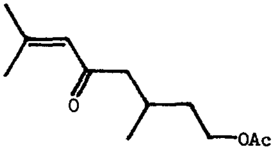
(21)

ester (6) (1%). Treatment of a mixture containing ketone (3) as major product, with tri—ethylamine in THF effected isomerisation to a mixture containing ketone (4) (72%) as major component. The latter readily underwent base catalysed elimination of acetic acid to give ketones (7) - (10), with the (E)-ketones (7) $\left[\tau_a(\mathrm{CDCl_3})\ 3.59,\ J\ 10.3 \text{ and } 17.5\ \mathrm{Hz}\right]$ and (9) $\left[\tau_a(\mathrm{CDCl_3})\ 3.60,\ J\ 10.3 \text{ and } 17\ \mathrm{Hz};\ \tau_b\ 6.84\ (\mathrm{br.});\ \tau_c\ 5.07 \text{ and } 5.16\ (\mathrm{m,\ 1H\ each})\right]$ predominating. For example, treatment of an ethereal solution of esters (3) - (5), containing small amounts of the corresponding (Z)-isomers of esters (4) and (5), with $\mathrm{KNH_2}$ in liquid ammonia gave a mixture (60%) of ketones from which the ocimenones (7) and (8) (26%) and α-ocimenones (9) and (10) (74%)$^{9)}$ were isolated severally by preparative g.l.c. The elimination is accompanied by partial deconjugation of the cross-conjugated system and similar observations were made when phorone (11) and mesityl oxide (14) were treated with base.$^{10)}$ Although not directly comparable, treatment of mesityloxide (14) (2g) with $\mathrm{KNH_2}$ (from 0.8g K) in liquid $\mathrm{NH_3}$ (50 ml) at -40° and workup after addition of water gave a product (1.9g) consisting of mesityl oxide (24%) and ketone (15) (76%) $\left[\tau_b\ (\mathrm{CDCl_3})\ 6.88\ (\mathrm{br.});\ \tau_c\ 5.07 \text{ and } 5.19\ (\mathrm{m,\ 1H\ each})\right]$. Under similar conditions phorone gave a product (85%) consisting of ketones (11) (44%), (12) (54%) $\left[\tau_b(\mathrm{CDCl_3})\ 6.91\ (\mathrm{br.});\ \tau_c\ 5.08 \text{ and } 5.19\ (\mathrm{m,\ 1H\ each})\right]$ and (13) (2%)$^{11)}$. Elimination could also be effected with other bases (e.g. MeOK or t.BuOK in THF).

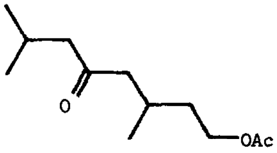
Pyrolytic elimination of acetic acid from esters (3) - (5) (535°; 0.4 mm Hg; glass tube packed with glass helices) gave three major products viz. myrcenone (16), isopiperitenone (18) $\left[\tau_a\ (\mathrm{CDCl_3})\ 4.11\ (\mathrm{m});\ \tau_b\ 5.07\ (\mathrm{m}) \text{ and } 5.25\ (\mathrm{m})\right]$, and piperitenone (19) $\left[\tau_a(\mathrm{CDCl_3})\ 4.11\ (\mathrm{m})\right]^{12)}$ Although various mechanisms may be advanced for the formation of piperitenone and isopiperitenone from esters (4) and (5), they probably originate from an electrocyclic reaction,13) which proceed *via* the enol of ketone (8) i.e. conversion of enol (20) to enol (21) and hence also to isopiperitenone.

Pyrolysis of ester (3) yielded predominantly myrcenone (16) $\left[\tau_a(\mathrm{CDCl_3})\right.$ 3.56 (J 10.3 and 17.5 Hz); τ_b 3.84 m; $\tau_{c\ \mathrm{and}\ d}$ 4.68 - 5.05; τ_e 6.72 (J *ca.* 1 Hz); τ_f 7.88 (J *ca.* 1.3 Hz); τ_g 8.13 (J *ca.* 1.3 Hz)$\left.\right]$, which on reduction with lithium aluminium hydride is converted into d,ℓ-myrcenol (17).14a) This represents a simple synthesis of the racemic mixture of the main aggregation pheromone of *Ips paraconfusus*.14)

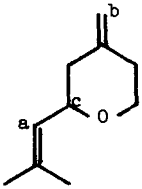
Ketones (3) - (5) also serve as excellent starting materials for the synthesis of the rose oxides and related materials. Reduction of ester (3) ($\mathrm{LiAlH_4}$; DME; -40°) yields dehydrorose oxide (24)15) $\left[\tau_a(\mathrm{CDCl_3})\right.$ 4.79 (m of d; J 8 Hz); τ_b 5.28 (br. s.)$\left.\right]$ Partial hydrogenation of ketone (3) was effected in the presence of a homogeneous rhodium catalyst16) to give the dihydroderivative (22) which on $\mathrm{LiAlH_4}$ reduction gave the *trans*- and *cis*- rose oxides (25) and (26). Similarly catalytic hydrogenation of ketones (3) - (5) gave ketone (23). The latter on reduction ($\mathrm{LiAlH_4}$) and dehydration (p-TsOH/PhMe)17) gave the *trans*- and *cis*- dihydrorose oxides (27) and (28).



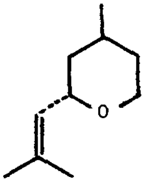
(22)



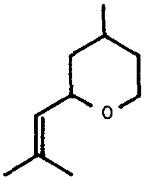
(23)



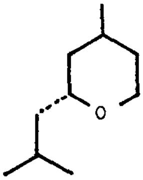
(24)



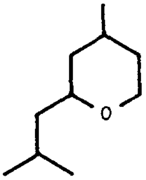
(25)



(26)



(27)



(28)

Acknowledgement: Financial assistance and a fellowship (to F.S.) by the South African Council for Scientific and Industrial Research are gratefully acknowledged. F. Scott also thanks Taueber and Corssen (Pty) Ltd for the Konrad Taueber Memorial Fellowship. We thank Prof DF Schneider and Dr BV Burger for advice.

REFERENCES AND FOOTNOTES

1. Part IV. C.F. Garbers and F. Scott, Tetrahedron Lett., in the press.
2. Abstracted from part of thesis by F. Scott (to be submitted at the University of Stellenbosch).
3. D.J.J. de Villiers, C.F. Garbers, and R.N. Laurie, Phytochemistry, 10, 1359 (1971).

4. D.R. Adams, S. Bhatnagar, R.C. Cookson and R.M. Tuddenham, J. Chem. Soc. Perk. 1, 1741 (197
5. For a recent review on the rose oxides see A.F. Thomas in "The Total Synthesis of Natural Products", Vol. 2, 167 - 169, ed. J. ApSimon, John Wiley & Sons, New York (1973).
6. R.M. Silverstein, J.O. Rodin, and D.L. Wood, Science 154, 509 (1966).
7. Nakao Kozo, Tanomura Masahisa, Nishida Takashi, Takagi Toshiaki and Itoi Kazuo, G.P. 2153894 (1972).
8. Yields were not optimised. All new compounds or known compounds prepared by new methods gave satisfactory combustion analyses. The spectral properties of all compounds are in accord with the assigned structures.
9. Ketone (10) was claimed to be a constituent of the essential oil of Ledum palustre L [M.v. Schantz and R. Hiltunen, Scientia Pharmaceutica, 39, 137 (1971)]. This claim was withdrawn subsequently [M.v. Schantz, K-G. Widen, and R. Hiltunen, Acta Chem. Scand., 27, 551 (1973)].
10. Deconjugation by acid, base or irradiationhas been established, e.g. E.C. Craven and W.R. Ward, J. Appl. Chem., 10, 18 (1960); K.J. Crowley, R.A. Schneider, and J. Meinwald, J. Chem. Soc. (C), 571 (1966); P.J. Crop and T.W. Gibson, J. Chem. Soc. (C), 143 (1967); W.C. Agosta and S. Wolff, J. Org. Chem., 40, 1699 (1975).
11. Ketone (13) was not isolated severally but its identity was determined by g.l.c.-m.s. analysis.

$^m/e$ Values	138	123	108	95	94	83	82	55	44
Compound	Relative abundance (%). Base peak: 100								
(11)	20.7	100	11.0	10.4	-	55.2	10.4	37.1	-
(12)	3.3	2.2	-	-	-	100	-	30.0	-
(13)	2.2	3.0	-	14.0	13.3	42	-	100	24.3

12. W.F. Erman, J. Amer. Chem. Soc., 89, 3828 (1967).
13. e.g. R.B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie GmbH, Weinheim, p. 53 (1970); G. Frâter, Helv. Chim. Acta, 57, 2446 (1974); J.M. Conia and P. le Perchec, Synthesis, 1 (1975).
14. For references on the synthesis of this Ips paraconfusus pheromone see: (a) C.A. Reece, J.O. Rodin, R.G. Brownlee, W.G. Duncan and R.M. Silverstein, Tetrahedron, 24, 4249 (1968); (b) R.G. Riley and R.M. Silverstein, J. Org. Chem., 39, 1957 (1974); (c) K. Mori, Agric. Biol. Chem., 38, 2045 (1974); (d) S.R. Wilson and L.R. Phillips, Tetrahedron Lett. 3047 (1975); (e) K. Mori, Tetrahedron Lett., 2187 (1975).
15. J.H.P. Tyman and B.J. Willis, Tetrahedron Lett., 4507 (1970).
16. N. Haga and W. Nagata, Org. Synth., 53, 63 (1973).
17. K.C. Brannock and H.E. Davis, J. Org. Chem., 31, 980 (1966).