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ON THE HOMO DIELS-ALDER REACTION OF SUBSTITUTED NORBORNADIENES AS A POSSIBLE ROUTE TO LONGICYCLENE.

AN INTRAMOLECULAR ENE REACTION.

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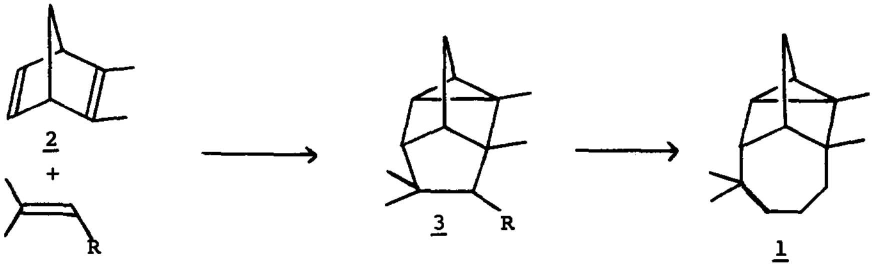
Nearly ten years ago Nayak and Dev reported[1] the structure of the first identified tetracyclic sesquiterpene, longicyclene (1). More recently[2] other tetracyclic sesquiterpenes have been both characterized[2] and synthesized but no[3,20] total synthesis of longicyclene has yet been achieved despite a number of attempts[5].

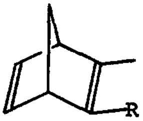
In our projected synthesis of longicyclene (1) one of the routes we have considered utilizes as the major constructive step the homo Diels-Alder reaction[6] between a substituted norbornadiene and a suitable dienophile (e.g. Equation 1). We wish to report our findings regarding the feasibility of this approach to the synthesis of longicyclene.



(Eq.1)

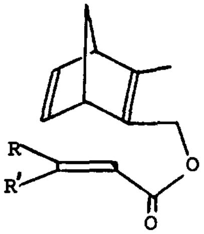
2,3-Dimethylnorbornadiene (2)[7] which can be prepared (in abysmal yield) from cyclopentadiene and 2-butyne[8] at 300° was heated with a variety[9] of dienophiles at temperatures up to 200° both with[10] and without[6] added $(\emptyset_3\mathrm{P})_2\mathrm{Ni(CO)}_2$. In no case was any of the desired cycloadduct (e.g. 3) formed, the usual product being an intractable tar.

In view of the well-known[6] tendency of norbornadiene itself to undergo homo Diels-Alder reactions, the lack of reactivity observed in the case of 2 is almost certainly a result of kinetic and not thermodynamic factors. Consequently we felt that the chances of successfully effecting the desired cycloaddition could be significantly enhanced by modifying the basic synthetic scheme to permit an intramolecular homo Diels-Alder reaction. α,β-Unsaturated esters of dienol 4 seemed attractive candidates for this intramolecular cycloaddition for a number of reasons including (a) relative ease of synthesis, (b) potential for easy variation of the dienophilic component, and (c) abundance of methods available for



4, R=CH_2OH

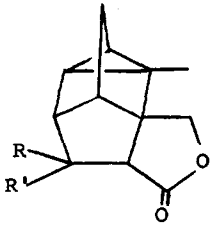
5, R=CHO



6, R=R'=H

8, R=H,R'=$COOCH_3$

9, R=R'=$COOCH_3$



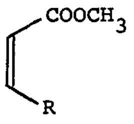
7, R=R'=H

10, R=R'=$COOCH_3$

the ultimate conversion of the $-CH_2O-$ moiety to a methyl group.

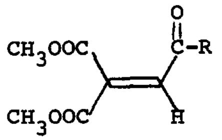
Dienol 4[7,11] was prepared by $LiAlH_4$ reduction of aldehyde 5 which in turn is formed from cyclopentadiene and but-2-ynal[12] at 100°. Reaction of 4 with acrylyl chloride triethylamine gives 6. Thermolysis of 6 with or without $(\phi_3P)_2Ni(CO)_2$ at temperatures up to 200° resulted primarily in the formation of polymer as judged by tlc. Infrared spectra of the crude reaction products were devoid of absorptions attributable to a γ-lactone (e.g. 7).

The corresponding maleate 8[7,11] was prepared by reaction of 4 with 11, the latter being formed by the action of oxalyl chloride on 12.[13] Thermolysis of 8 again gave no isolable products but the observation that in some runs the ir spectrum of the crude product had a small but nevertheless definite band at 1780 cm^{-1} provided sufficient incentive to prepare the synthetically less accessible triester 9.



11, R=COCl

12, R=COO^-K^+

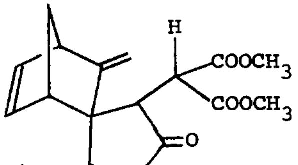


13, R=$OC(CH_3)_3$

14, R=OH

15, $R{=}O\overset{O}{\overset{\|}{C}}CF_3$

Condensation[14] (piperidine, refluxing benzene, removal of H_2O) of dimethyl malonate and *t*-butyl glyoxylate[15] gives 13[7,11] (bp 87-95°/0.05 mm, 70%) which is converted cleanly to the diester acid 14[7,11] (mp 65-68°) upon treatment with trifluoroacetic acid. To our knowledge no other report of a partial ester of ethenetricarboxylic acid has appeared in the literature. The diester acid 14 was converted to the mixed anhydride 15[7] upon refluxing in trifluoroacetic anhydride. When 15 was added at room temperature to a pyridine solution of dienol 4 tlc indicated the immediate formation of a new compound whose tlc characteristics (r_f, color with detecting agents) were entirely consistent with structure 9. Subsequent tlc's of the reaction mixture revealed that 9 quickly underwent reaction to give a new compound, "X", which could be isolated by preparative layer or vapor phase chromatography. The new compound, which is almost the sole product of the reaction, possesses a molecular weight (M+ = 280) and absorption in the ir (1790, 1740 cm^{-1}) consistent with the structure of the desired product (10). But the nmr spectrum of "X", which is devoid of peaks attributable to a $C-CH_3$ group and contains several olefinic resonances in addition to an expected peak due to the methoxyls, is totally incompatible with structure 10. These spectral data are, however, completely consistent with structure 16[11] (stereochemistry of lactone unassigned) and the nmr spectra of "X" and 17[5a,16] display a striking resemblance in the olefinic region. Structure 16 may be rationalized mechanistically as the product of an intramolecular ene[17] reaction. The formation of 16 is the only[17] example of an ene reaction involving a 1,8-transfer of hydrogen between carbon atoms and is particularly noteworthy for the exceptionally mild conditions under which it occurs. The conversion of 9 into 16 is unaffected by the presence of $(\phi_3P)_3Ni(CO)_2$ in the reaction of 15 and 4.



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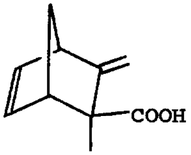

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It is perhaps noteworthy that virtually all homo Diels-Alder reactions are observed in systems (e.g. norbornadiene, barrelene[18]) where ene reactions could occur only with concurrent violation of Bredt's rule.[19] The formation of 16 suggests that where both reaction pathways are available the ene reaction may well be the one which is usually favored.[19] In any event the foregoing results suggest that the homo Diels-Alder reaction will not be the cornerstone of our yet-to-be realized synthesis of 1. We are presently exploring other routes to longicyclene

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Footnotes and References

1. U.R. Nayak and Sukh Dev, Tetrahedron Letters, 243 (1963); Tetrahedron, 24, 4099 (1968).
2. See T.K. Devon and A.I. Scott, "Handbook of Naturally Occurring Compounds", Volume II, "Terpenes", Academic Press, London, 1972, p. 181.
3. In view of the fact that Nayak and Dev demonstrated[1] that (+)-longicyclene and (+)-longifolene are interconverted by cupric acetate in acetic acid, the two recorded syntheses[4] of (±) longifolene also constitute, in a formal sense, syntheses of longicyclene.
4. E.J. Corey, M. Ohno, R.B. Mitra, and P.A. Vatakencherry, J. Amer. Chem. Soc., 86, 478 (1964); J.E. McMurry and S.J. Isser, ibid., 94, 7132 (1972).
5. E.g. see (a) W.E. Barnett and J.C. McKenna, Tetrahedron Letters, 227 (1971); (b) Steven C. Welch, Ph.D. Thesis, University of Southern California, 1969; Diss. Abstr. B, 29, 3685 (1969).
6. For leading references see (a) R.C. Cookson, J. Dance and J. Hudec, J. Chem. Soc., 5416 (1964); (b) P.K. Freeman, D.M. Balls and J.N. Blazevich, J. Amer. Chem. Soc., 92, 2051 (1970); (c) reference 12 in H.G. Kuivila and C.R. Warner, J. Org. Chem., 29, 2845 (1964).
7. Ir and nmr spectra of this compound are completely consistent with the assigned structure.
8. Farchan Research Laboratories, Willoughby, Ohio. We are also grateful to Professor Ernst Koerner von Gustorf for a generous gift of 2-butyne.
9. Dienophiles examined include acrylonitrile, maleic anhydride, dimethyl acetylenedicarboxylate, fumaronitrile, and tetracyanoethylene.
10. G.N. Schrauzer and P. Glockner, Ber., 97, 2451 (1964).
11. The elemental analysis of this compound supports the assigned structure.
12. J. C. Lunt and F. Sondheimer, J. Chem. Soc., 3361 (1950).
13. J. Shields, J. Chem. Soc., 59, 736 (1891).
14. G. Jones, Org. Reactions, 15, 204 (1967).
15. L.A. Carpino, J. Org. Chem., 29, 2820 (1964).
16. We are grateful to Dr. James McKenna for making available an nmr spectrum of this compound.
17. For a recent review see H.M.R. Hoffman, Angew. Chem. Internat. Edit., 8, 556 (1969).
18. H.E. Zimmerman and G.L. Grunewald, J. Amer. Chem. Soc., 86, 1434 (1964).
19. For an exception to this generalization see J.K. Williams and R.E. Benson, ibid., 84, 1257 (1962).
20. After this manuscript had been completed Professor Steven Welch informed us of the synthesis of (±)-longicyclene in his laboratory. We thank him for communicating his results prior to publication.