

HETERODIENOPHILES VII.¹ A NOVEL SYNTHESIS OF AZABICYCLICS FROM METHYLENEBISURETHANE AND p-MENTHADIENES BY FORMAL 1,3-CYCLOADDITION REACTIONS.

Grant R. Krow, R. Rodebaugh, U. K. Nadir, and A. Gaspari
Temple University, Philadelphia, Pa. 19122

(Received in USA 3 June 1976; received in UK for publication 9 July 1976)

The acid-catalyzed reactions of alkylidene bisurethanes and conjugated dienes offers a convenient synthetic route to diverse azacyclic and azabicyclic² molecules formed by 1,4- (or 1,6)³-addition to the conjugated system by an acyl imine **3**. We here wish to report the first example of formal 1,3-cycloadditions during the reaction of acyl imines **3** with dienes. Methylene bisurethane **1** has been found to react with p-menthadienes under conditions of acid catalysis to form N-carbethoxy-1-methyl-4-isopropenyl-6-azabicyclo[3.2.1]octane **4** and N-carbethoxy-3,7,7-trimethyl-9-azabicyclo[3.3.0]nonane **5**.

Utilizing a general procedure described previously³ a solution of methylene bisurethane^{2e} **1** (11.5g), α -phellandrene **2** (8.2g), BF₃-etherate (1 ml) in chloroform (150 ml) with CuBr₂ (1g) added was refluxed for 5 hr. Workup and distillation (0.15mm) afforded **4**, 3.4g, bp 103-108°, 22%. A higher boiling cut, 1.5g, bp 110-120°, consisted mainly of a 60/40 mixture of **4** and **5** separable by vpc (6' x 1/4" SF-96 on Chrom W, 140°). Azabicyclo[3.2.1]octane **4** was readily converted to 1-methyl-6-azabicyclo[3.2.1]oct-4-one **6**, bp 100-110° (0.05mm, molecular distillation), 91% yield, using a Welsbach ozonator with dimethylsulfide workup.⁴ Structural assignments of **4-6** were made utilizing spin decoupled nmr spectra (Table 1).

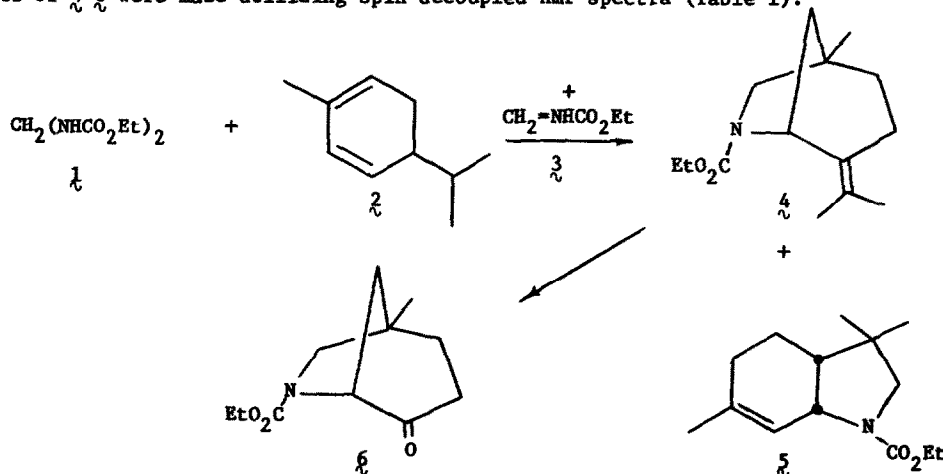
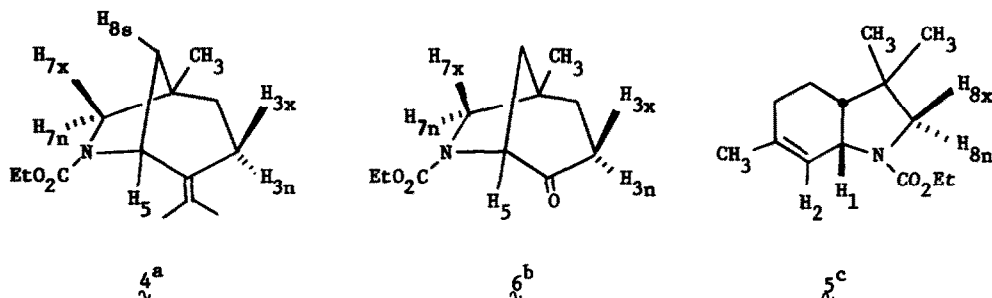
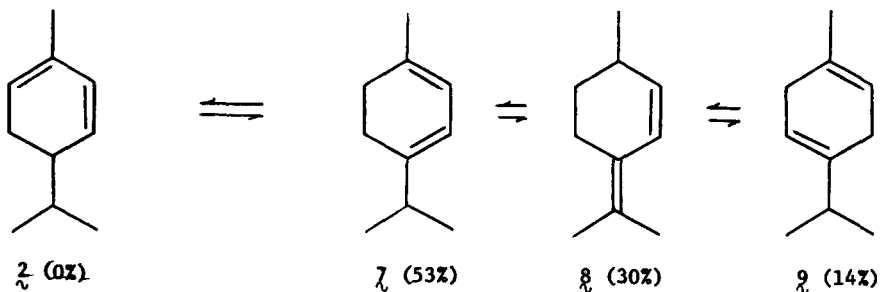


Table 1. Major NMR Peaks. 100MHz Spectra of Azabicyclics 4-6.



Proton	Shift (δ) ^d	Proton	Shift (δ) ^j	Proton	Shift (δ) ^d
H ₅	4.84 ^e	H ₅	4.14 ^k	H ₁	4.20 ^P
H _{7x}	3.26 ^f	H _{7x}	3.36 ^l	H ₂	5.94 ^q
H _{7n}	3.02 ^g	H _{7n}	3.08 ^m		
H _{3x(3n)}	2.48 ^h	H _{3x(3n)}	1.8-2.50 ⁿ		
H _{8s}	1.76			H _{8x,8n}	3.32, 3.10 ^r
CH ₃	1.05	CH ₃	0.78 ^o	CH ₃	1.02, 0.98 ^o
CH ₃ -C=	1.60 ⁱ			CH ₃ -C=	1.72 ^o

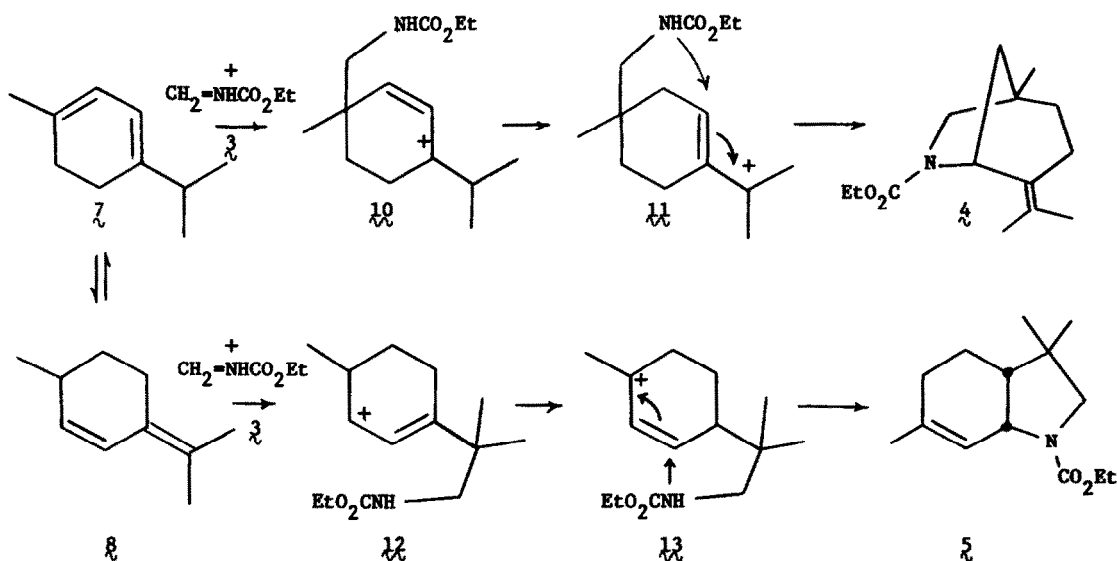
(a) broad complex envelope, δ 0.80-2.0; (b) broad, δ 1.0-1.8; (c) broad, δ 1.1-2.0; (d) CDCl₃, 80°; (e) d, $J_{5,8s}$ = 6Hz; (f) d, J = 10Hz; (g) d; (h) dd, J = 15Hz, 6Hz; (i) δ 1.61, 1.71 in acetone-d₆; (j) benzene-d₆; (k) d, $J_{5,8s}$ = 5.8Hz; (l) d, J = 10.3Hz; (m) dd, J = 10.3Hz, 1.5Hz; (n) broad multiplet; (o) s; (p) buried under CH₂ of ethyl ester; (q) broad, narrows to a broadened doublet, J = 3Hz upon irradiation of H₁; (r) d, J = 11 Hz.

SCHEME 1. Equilibrium Concentrations of p-Menthadienes in Acid.⁵

Equilibration studies⁵ of p-menthadienes in sulfuric acid (Scheme 1) show that α -phellandrene λ , the starting material in our synthesis of ζ and ξ , is nearly totally converted to a mixture of α -terpinene η , isoterpinolene θ , γ -terpinene ρ , and other minor components. Upon consideration of the data of Scheme 1 a postulated mechanism for formation of ζ and ξ from p-menthadienes in acidic medium is shown in Scheme 2. Addition of an acid complexed iminourethane ζ to the less hindered end of the major conjugated diene η will afford cation λ_0 . Proton loss and reprotonation will give a new allylic cation λ_1 , which upon internal trapping by the proximate nucleophilic urethane nitrogen gives ζ . Similarly, addition of protonated iminourethane ζ to the exocyclic terminus of θ will afford allylic cation λ_2 . Deprotonation of λ_2 and reprotonation to give λ_3 will lead to ξ upon intramolecular cyclization by urethane nitrogen.

Consistent with the proposed mechanism α -terpinene⁷ η reacted according to the general procedure to give ζ and ξ in a 60/40 ratio. The greater percentage of ξ in this reaction possibly indicates a greater percentage of θ in a preequilibrium mixture of p-menthadienes than found in the reaction with α -phellandrene λ . It is worth noting that longer reaction times result in product decomposition and formation of higher molecular weight materials. Although the p-menthadiene equilibrium has been reached from α -pinene⁸, attempted reactions with α - and β -pinene, Δ -carene, or limonene did not lead to a clean formation of ζ and ξ , but to mixtures of numerous components. This is reasonable since the numerous dienic species can be trapped by protonated iminourethanes or by protons and urethane before the equilibrium mixture of p-menthadienes rich in η and θ can be reached.

SCHEME 2. Proposed Mechanisms for Formation of 4 and 5.



Previous syntheses of 4(2)-substituted-6(7)-azabicyclo[3.2.1]octanes have primarily involved ring closure on N-halo- or N-nitrosamines¹⁰ by an intramolecular π -route, reduction and ring closure of substituted pyrroles,¹¹ ring opening of tricyclic aziridinium ions,¹² and molecular rearrangement of other bicyclic systems.¹³ By comparison the present two-step conversion of α -phellandrene to ξ represents one of the simplest synthetic routes to this ring system.

Acknowledgment: We acknowledge support of this research by the National Institutes of Health CA-12020. We thank C. Pyun, K. Cleaver, and D. Weir for technical assistance.

References

1. For the previous paper in this series see, G. R. Krow, C. Pyun, C. Leitz, J. Marakowski, and K. Ramey, J. Org. Chem., **39**, 2449 (1974).
2. (a) H. E. Zaug, Synthesis, **2**, 49 (1970), has reviewed reactions of N-ethoxycarbonylimines. (b) J. D. Hobson and W. D. Riddell, Chem. Commun., 1180 (1968); (c) H. Harter and S. Liisberg, Acta Chem. Scand., **22**, 2685 (1968); (d) T. Sasaki, S. Eguchi, M. Sugimoto, and F. Hibi, J. Org. Chem., **37**, 2317 (1972); (e) M. Cava, C. Wilkens, D. Dalton, and K. Bessho, ibid., **30**, 3772 (1965).
3. G. R. Krow, R. Rodebaugh, M. Grippi, G. DeVicaris, C. Hyndman, and J. Marakowski, ibid., **38**, 3094 (1973).
4. J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, Tetrahedron Lett., 4273 (1966).
5. R. B. Bates, E. S. Caldwell, and H. P. Klein, J. Org. Chem., **34**, 2615 (1969).
6. The parent tri-desmethyl hexahydroindole ring system of ζ has been prepared by an intramolecular Diels-Alder route; W. Oppolzer and W. Fröstl, Helv. Chim. Acta, **58**, 590 (1975).
7. O. Wallach, Ann., **275**, 105 (1893).
8. W. A. Mosher, J. Amer. Chem. Soc., **69**, 2139 (1947).
9. (a) P. Gassman, J. Dygos, Tetrahedron Lett., 4745 (1970); (b) J. M. Surzur, L. Stella, R. Nougier, ibid., 903 (1971); (c) G. Esposito, R. Furstoss, B. Waegell, ibid., 899 (1971).
10. Y. L. Chow, R. A. Perry, and B. C. Menon, ibid., 1549 (1971).
11. W. Davies, A. Pinder, I. Morris, Tetrahedron, **18**, 405 (1962).
12. W. Nagata, S. Hirai, K. Kawata, T. Aoki, J. Amer. Chem. Soc., **89**, 5045 (1967).
13. (a) J. Huffman, T. Kamiya, C. Rao, J. Org. Chem., **32**, 700 (1967); (b) L. A. Paquette, J. F. Kelly, ibid., **36**, 442 (1971); (c) R. O. Hutchins, L. Rua, ibid., **40**, 2567 (1975); (d) G. R. Krow, R. Rodebaugh, C. Hyndman, R. Carmosin, G. DeVicaris, Tetrahedron Lett., 2175 (1973).