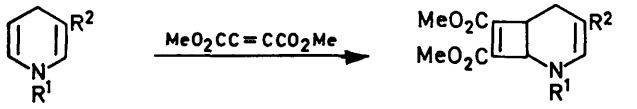
Cyclobutenes from 1-Alkyl-1,4-dihydropyridines with Dimethyl Acetylenedicarboxylate and a Novel Cyclo-elimination of a Carboxamide Group

By R. M. ACHESON* and N. D. WRIGHT

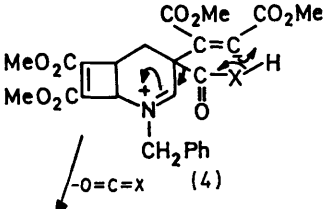
(*Department of Biochemistry, South Parks Road, Oxford* OX1 3QU)

Summary Several 1,3-disubstituted-1,4-dihydropyridines with dimethyl acetylenedicarboxylate gave 1-azabicyclo-[4,2,0]octa-2,5-dienes, and where a 3-CO_2H or a 3-CONHR group was present elimination of this group occurred through a 6-membered cyclic transition state in each case to give the corresponding 3-(*cis*-1,2-dimethoxycarbonylvinyl) derivative.

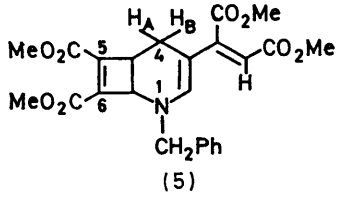
THE 1:1 molar adducts dimethyl 1-benzyl-3-(*N*-ethyl-*N*-phenylcarboxamido)-1-azabicyclo[4,2,0]octa-2,5-diene-5,6-dicarboxylate (1), and the corresponding 1-benzyl-3-cyano- and 3-cyano-1-methyl compounds (2) and (3) respectively, were obtained in 30—50% yield from the appropriate 1,3-disubstituted 1,4-dihydropyridines (prepared by dithionite reduction of the quaternary pyridinium salts in aqueous solution[1]) by treatment at room temperature with dimethyl acetylenedicarboxylate in calcium hydride-dried acetonitrile.



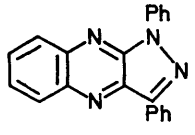
(1) $R^1 = CH_2Ph$, $R^2 = CONPhEt$
(2) $R^1 = CH_2Ph$, $R^2 = CN$
(3) $R^1 = Me$, $R^2 = CN$



(4)



(5)



(6)

In contrast, 1-benzyl-1,4-dihydropyridine-3-carboxylic acid and the corresponding -3-carboxamide and -3-carboxy-*N*-(β-phenylethyl)amide gave, on reaction with the ester, dimethyl 1-benzyl-3-(*cis*-1,2-dimethoxycarbonylvinyl)-1-azabicyclo[4,2,0]octa-2,5-diene-5,6-dicarboxylate (5), the original 3-substituent having been replaced. The structures of the bicyclo-octadienes were deduced mainly from their very similar n.m.r. spectra, and the parameters for (1) were confirmed by an excellent computer simulation of the observed 60 MHz spectrum using our usual program.[2] The relationships of the hydrogen atoms of the original dihydropyridine ring to each other in the bicyclo-octadiene (5) were established from the results of a series of decoupling and spin tickling experiments carried out at 100 MHz, and the following parameters, confirmed by a 220 MHz spectrum, were obtained: 2-H, 3·57; 4-H_A, 7·80; 4-H_B, 7·39; 4a-H, 6·35; 6a-H, 5·84, $J(2,4_A)$ 1·9; $J(2,6a)$ 0·6; $J(4_A,4_B)$ 16·0; $J(4_A,4a)$ 8·0; $J(4_B,4a)$ 1·9; $J(4a,6a)$ 5·0 Hz. The high-field resonances for four of these protons show that an additional ring must have been formed, and the data exclude alternative structures. In the mass spectrometer compounds (2) and (5) gave the molecular ions as their base peaks, although, in contrast, cleavage of the amide C–N bond gave the base peak for compound (1). Hydrogenation of the bicyclo-octadienes (1) and (2) gave the corresponding cyclobutanes, the expected changes in u.v. and n.m.r. spectra being observed together with loss in each case of dimethyl fumarate fragments in the mass spectrometer. The side-chain vinyl proton of compound (5) appeared at τ 4·70, and comparison with values reported for other compounds[3] showed that the ester groups must be *cis*.

The adducts (1), (2), and (5) appear to be the first examples of thermally stable crystalline cyclobutene adducts formed from enamines and dimethyl acetylenedicarboxylate.[4,5] The remarkable displacement of an unsubstituted carboxamide group in the formation of the azabicyclo-octadiene (5) is noteworthy since the only other displacements of this type known to the authors have been described by Dahn and his associates. They showed[6] that the oximes and phenylhydrazones of 3-aroylquinoxaline-2-carboxamides cyclised easily to isoxazolo[4,5-*b*]quinoxalines and pyrazolo[3,4-*b*]quinoxalines (*e.g.* 6) respectively with the elimination of the amide group. These reactions are thought[6] to involve nucleophilic attack by the appropriate oxygen or nitrogen atom at position 2 of the quinoxaline followed by elimination of the carboxamide group. In our case the most attractive scheme for the formation of the maleate (5) and elimination of the 3-substituent involves the prior formation of the intermediate (4) and the closely related six-membered cyclic transition state. This mechanism accounts for the stereochemistry of the product and for the requirement that the group eliminated must possess a suitably placed mobile hydrogen atom. The four-membered ring shown in structure (4) could be formed

before or after the cyclo-elimination It is interesting that in the absence of an appropriate hydrogen atom intermediates of type (4), if formed under our conditions, do not cyclise to give a tricyclic [4,2,2] system

(*Received, September 16th*, 1971, *Com* 1616)

[1] D Mauzerall and J H Westheimer, *J Amer Chem Soc*, 1955, **77**, 2261
[2] C L Wilkins and C E Klopfenstein, *J Chem Educ*, 1966, **43**, 10.
[3] J E Dolfini, *J Org Chem*, 1965, **30**, 1298
[4] G A Berchtold and G F Uhlig, *J Org Chem*, 1963, **28**, 1459
[5] C F Huebner, L Dorfman, M M Robinson, E Donoghue, W G Pierson, and P Strachan, *J Org Chem*, 1963, **28**, 3134
[6] H Dahn and J P Fumeau, *Bull Soc vaudoise sci nat*, 1970, **70**, 313, H Dahn and J Nussbaum, *Helv Chim Acta*, 1969, **52**, 1661, H. Dahn and H Moll, *Helv Chim Acta*, 1966, **49**, 2426