The Formation of Cycl[3,2,2]azines from Pyridines and Methyl Propiolate

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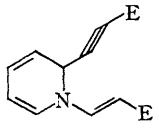
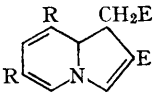
THE cyclazine (IV) was the sole product isolable from pyridine and methyl propiolate in acetonitrile. Anhydrous conditions were aimed at although the complete absence of water could not be guaranteed. Alkaline hydrolysis of the cyclazine gave a dicarboxylic acid identified from its mass spectrum, which decarboxylated with copper chromite in boiling quinoline to 1-methyl[3,2,2]cyclazine (VI), the ultraviolet absorption spectrum of which, in both neutral and strongly acid solutions, was very similar to the corresponding spectra of [3,2,2]-cyclazine[1] and its 2-methyl derivative.[2] The nuclear magnetic resonance spectrum of 1-methylcyclazine (1-Me, τ 7·27; 2-H, τ 2·68; 3-H, τ 2·53; 4-H, τ 2·85; 5-H, τ 2·12; 6-H, τ 2·43; and 7-H, τ 2·17; $J_{3,4} = 4{\cdot}3$; $J_{5,6} = J_{6,7} = 8{\cdot}0$; $J_{5,7} < 0{\cdot}5$ c./sec.) showed the expected resemblances to those for [3,2,2]cyclazine[2,3] and 2-methylcyclazine;[2] agreement between the line position and intensity for the calculated[4] and observed ABC spectrum from the 5-, 6-, and 7-protons was excellent. As the corresponding protons from both cyclazine and the 2-methyl derivative appear as A_2B systems the 1-position of the methyl group is confirmed. Only six peaks having an intensity greater than 5% of the base peak, *viz.*, the molecular ion *m/e* 155 (61·5%), 154 (100), 153 (13·8), 152 (8·4), 77·5 (5·1) and 77 (10·6), appear in the mass spectrum of 1-methylcyclazine thereby demonstrating the stability of this ring system. The last two peaks are probably doubly charged fragments of mass 155 and 154 respectively, and the base peak could well be due to the aromatic cycl[3,3,2]azinium cation (VII) formed by ring expansion of the cyclazine after loss of an electron and a hydrogen atom.

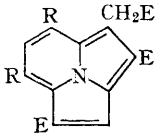
Similar results were obtained with 3- and 4-methylpyridine while 3,5-dimethylpyridine gave the cyclazine (V) along with the indolizine (III)



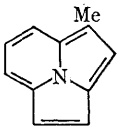
(I)



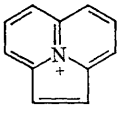
(II; R = H)
(III; R = Me)



(IV; R = H)
(V; R = Me)



(VI)



(VII)

E = CO_2Me

which was converted to the cyclazine (V) on refluxing in toluene with methyl propiolate and palladium on charcoal.[5] The orientation of this addition is established by the deshielding effect of the 4-ester group on the 5-proton, and is in agreement with the mode of addition of methyl propiolate to indolizine.[5]

The formation of the indolizines and cyclazines probably involves intermediates such as (I), which has in fact been isolated[6] from pyridine and methyl propiolate in ether although we only obtained the indolizine (II) containing a small quantity of the cyclazine (IV) under these conditions, and cyclises[6] with piperidine to the indolizine (II). Electrophilic attack of methyl propiolate at position 1, followed by cyclisation and aromatisation as suggested earlier,[5] accounts for the cyclazine formation.

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[1] F. Gerson, E. Heilbronner, N. Joop, and H. Zimmermann, *Helv. Chim. Acta*, 1963, **46**, 1940.
[2] L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Austral. J. Chem.*, 1965, **18**, 1221.
[3] V. Boekelheide, F. Gerson, E. Heilbronner, and D. Meuche, *Helv. Chim. Acta*, 1963, **46**, 1951.
[4] Calculations were done using the Oxford University KDF9 computer using a programme kindly provided by Dr. C. E. Klopfenstein (*vide* C. L. Wilkins and C. E. Klopfenstein, *J. Chem. Educ.*, 1966, **43**, 10). Translation from Fortran II into Algol was by Dr. D F. Mayers.
[5] V. Boekelheide and T. Small, *J. Amer. Chem. Soc.*, 1961, **83**, 462, and earlier papers in this series and references cited therein.