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Azetidines. I. Addition to Multiple Bonds and Condensation with Carbonyl Groups[1]

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The addition of azetidine to α, β-unsaturated esters and to acrylonitrile was studied. Azetidine was condensed with ketones to give the corresponding enamines.

The azetidines have not been as thoroughly investigated as their homologs—aziridines and pyrrolidines.[3] This is probably due, in part, at least, to the difficulty encountered in preparing these compounds. Nevertheless, they are important members in the series of saturated cyclic nitrogen compounds, in view of the fact that they occupy a position between the highly strained aziridines and the pyrrolidines; the latter may be regarded as normal secondary amines. In the present communication, we wish to report on the addition reactions of azetidine to activated double and triple bonds, and on the condensation reactions of azetidine to ketones; both of these reactions have been extensively investigated with other amines, but have been little studied with azetidines. The only report on the reaction of azetidine and unsaturated compounds is one on that with benzoquinone,[4] which gave 2, 5-diazetidinylbenzoquinone and 2, 5-diazetidinylhydroquinone. The reaction of azetidine and carbonyl compounds has been studied only with formaldehyde[5] and has been reported to give, among other products, both the 1- and 2-carbinol derivatives.

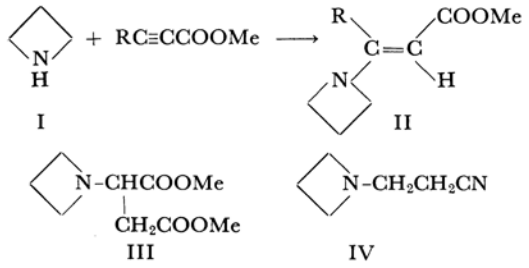
Results and Discussion

The addition of azetidine (I) to dimethyl acetylenedicarboxylate proceeded exothermally to give dimethyl (1-azetidinyl)maleate (II; R=COOMe) as a crystalline solid. The infrared spectrum of this product shows bands of an enamine double bond at 1570 cm^{-1} and two carbonyl groups at 1740 and 1680 cm^{-1}, which may be assigned to the ester carbonyl groups on the carbon atoms which are alpha and beta to the azetidinyl group respectively. The NMR spectrum of this compound agrees with the proposed structure (see Experimental Section); the appearance of the vinylic proton in a high magnetic field (5.90 τ) supports the maleate and not fumarate structure.[6] Better information as to the stereochemical aspect of this addition could be obtained by the inspection of the spectrum of the reaction product with methyl propiolate. The NMR spectrum of this reaction product (II; R=H) shows a pair of doublets arising from the vinylic protons at 2.93 and 5.91 τ with

1) For a preliminary communication, see T. Chen, H. Kato and M. Ohta, This Bulletin, **39**, 1618 (1966).
2) On leave of absence from National Tsing Hua University, Taiwan, The Republic of China.
3) For leading references, see J. A. Moore, "Heterocyclic Compounds with Three- and Four-membered Rings," Part Two, ed. by A. Weissberger, Interscience Publishers, New York, N. Y. (1964), p. 885; E. Testa, A. Wittgens, G. Maffii and G. Bianchi, *Research Progress in Organic, Biological and Med. Chem.*, **1**, 477 (1964).
4) A. Marxer, *Helv. Chim. Acta*, **38**, 1473 (1955).
5) Ya. M. Yanbikov, *J. Gen. Chem. (U. S. S. R.)*, **8**, 1470 (1938); *Chem. Abstr.*, **33**, 4197 (1939).
6) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).

a large coupling constant (J=13 cps), indicating that these two hydrogen atoms are *trans* to each other.

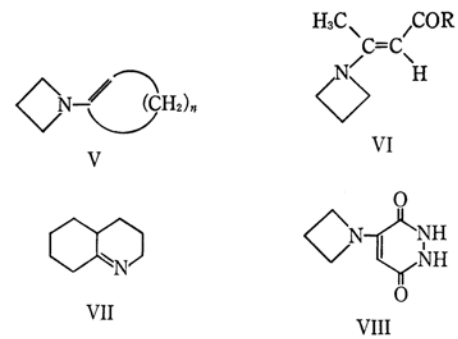
In order to see whether the type of solvent



would influence the stereospecificity of the addition, azetidine was allowed to react with methyl propiolate in a variety of solvents, and the crude product was then used for the NMR measurements. In aprotic solvents—cyclohexane, benzene, ether, and dimethyl sulfoxide, only the *cis* addition occurred, giving the *trans*-acrylate, irrespective of the polarity of the solvents involved. In methanol, however, the *trans* addition competed to some degree with the *cis* addition to give the corresponding *cis*-acrylate. The NMR spectrum of the crude product of the reaction in methanol exhibits two doublets, at 5.49 and 5.73 τ, with a coupling constant of 8 cps, in addition to those for the *trans* ester. The relatively small coupling constant is consistent with the *cis*-structure of this reaction product. The effect of solvents on the stereospecificity of the addition reaction reported above is in agreement with that with usual secondary amines,[7] but it is in contrast with aziridine, where the *trans* addition competes to some degree with the *cis* addition even in aprotic solvents.[6,8]

The reaction of azetidine with dimethyl fumarate and maleate occurred smoothly to give an identical product, dimethyl (1-azetidinyl)succinate (III). Similarly, β-(1-azetidinyl)propionitrile (IV) was formed by the addition of azetidine to acrylonitrile.

The enamine-type azetidinyl derivatives could also be obtained by the reaction of azetidine and ketones; the treatment of azetidine with cyclohexanone and cyclopentanone in benzene and in the presence of potassium carbonate at room temperature afforded 1-(1-azetidinyl)cyclohexene (V; n=4) and 1-(1-azetidinyl)cyclopentene (V; n=3) respectively. The condensation product with cyclohexanone shows an absorption at 1660 cm^{-1} which is attributable to an enamine double bond. Its NMR exhibits a one-proton triplet of the vinylic proton at 6.08, a four-proton triplet of the azetidine ring at 6.70, and a broad multiplet of the



remaining protons between 7.75—8.70 τ. A similar condensation took place with ethyl acetoacetate in ether and in the presence of sodium sulfate to give β-(1-azetidinyl)crotonate (VI; R=OEt). The NMR peak of this product shows the vinylic proton at 6.05 τ, suggesting that the compound formed is (*cis*)-crotonate. The corresponding condensation product (VI; R=Me) could be obtained from acetylacetone.[9] Ethyl benzoylacetate and dibenzoylmethane, however, did not react with azetidine under the same reaction conditions.

It has recently been reported that *N*-acylazetidines are converted, though less readily than *N*-acylaziridines, by acidic catalysts to ring-enlargement products.[10] The attempted ring enlargement of II (R=COOMe) with picric acid did not give an identifiable product. Also unsuccessful was an attempted thermal reorganization of V (n=4) to octahydroquinoline VII, it was unchanged at 254°C and an extensive decomposition and/or polymerization occurred at 340°C.

When II (R=COOMe) was treated with hydrazine hydrate, an extremely hygroscopic substance was formed; this substance gave a deep wine-red color with ferric chloride. These results suggest that the expected pyridazinedione VIII was indeed formed, but we have not been successful in isolating that substance in a pure form.

Experimental

All melting and boiling points are uncorrected. The melting points were measured on a micro hot stage. The infrared spectra were taken on neat liquid or on KBr tablets, and the NMR spectra were determined on a JEOLCO Model C-60 apparatus at 60 Mc in carbon tetrachloride, tetramethylsilane being used as the internal standard.

Dimethyl (1-Azetidinyl)maleate (II; R=COOMe). A solution of 1g (0.018 mol) of azetidine in 10 m*l* of ether was added, with cooling, to a stirred solution of 2.5 g (0.018 mol) of dimethyl acetylenedicarboxylate in 10 m*l* of ether; the resulting solution was allowed to stand

7) R. Huisgen, K. Herbig, A. Siegl and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).
8) E. Winterfelt and H. Prenss, *Angew. Chem.*, **77**, 679 (1965).
9) In a preliminary report,[1] we presumed this substance to be a salt of acetylacetone. This misassignment is highly regretted and should now be corrected.
10) Y. Iwakura, A. Nabeya, T. Nishiguchi and Y. Ichikawa, *J. Org. Chem.*, **30**, 3410 (1965).

overnight. The solvent was then evaporated off, and the residue was recrystallized from hexane to give 2 g (Yield 57%) of yellow green crystals, mp 65.5—67°C. IR: 1740, 1680 and 1570 cm^{-1}. NMR: 5.90 (1H, singlet); 6.20 (4H, triplet); 6.35 (3H, singlet); 6.60 (3H, singlet) and 7.75 (2H, quintet).

Found: C, 54.35; H, 6.85; N, 7.04%. Calcd for $C_9H_{13}NO_4$: C, 54.27; H, 6.53; N, 7.03%.

By similar treatments, the following products were prepared.

Methyl β-(1-Azetidinyl)acrylate (II; R=H). (From I and methyl propiolate). White crystals (from hexane), bp 100—103°C/5 mmHg, mp 46.5—47°C. (Yield 5.2% after distillation and recrystallization). IR: 1680 and 1590 cm^{-1}. NMR: 2.93 (1H, doublet); 5.91 (1H, doublet); 6.21 (4H, triplet); 6.63 (3H, singlet) and 7.78 (2H, quintet).

Found: C, 59.95; H, 8.06; H, 10.19%. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92%.

Dimethyl (1-Azetidinyl)succinate (III). (From I and dimethyl fumarate). Bp 89—90°C/3 mmHg, (Yield 57%), n_D^{25} 1.4500. IR: 1740 cm^{-1}.

Found: C, 53.90; H, 7.82; N, 7.05%. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96%. (From dimethyl maleate). Bp 92—96°C/3 mmHg, (Yield 48%), n_D^{25} 1.4497. The infrared spectrum of this compound was identical with that of III prepared from I and dimethyl fumarate.

Found: C, 53.98; H, 7.65; N, 7.05%.

β-(1-Azetidinyl)propionitrile (IV). (From I and acrylonitrile). Bp 85—91°C/20 mmHg, (Yield 56%), n_D^{25} 1.4467. IR; 2250 cm^{-1}.

Found: C, 65.39; H, 9.17; N, 25.36%. Calcd for $C_6H_{10}N_2$: C, 65.42; H, 9.15; N, 25.43%.

Effect of Solvents on the Addition of I to Methyl Propiolate. A solution of 0.0018 mol each of azetidine and methyl propiolate in 4 m*l* of the solvents described below was allowed to stand overnight. After the solvent had been removed *in vacuo*, the residue was dissolved in carbon tetrachloride and was submitted to NMR measurement. The NMR spectrum of the crude product of the reaction in ether, benzene, cyclohexane, or dimethyl sulfoxide was identical with that of the pure methyl *trans*-β-(1-azetidinyl)acrylate described above. The NMR spectrum of the product of the reaction in methanol, however, exhibited two doublets, at 5.49 and 5.73 τ, with a coupling constant of 8 cps, in addition to those for *trans*-β-(1-azetidinyl)acrylate. The ratio of *cis*- and *trans*-addition products, as judged from the NMR peak height, was *ca.* 2 : 1.

1-(1-Azetidinyl)cyclohexene. A mixture of 1 g (0.018 mol) of azetidine, 1.7 g (0.018 mol) of cyclohexanone, and 2 g of potassium carbonate in 5 m*l* of benzene was kept standing at room temperature for three days. Distillation *in vacuo* after the removal of the potassium carbonate afforded 0.8 g (Yield 22%) of a colorless liquid boiling at 51—53°C/4 mmHg, n_D^{25} 1.4840. IR: 1660 cm^{-1}. NMR: 6.08 (1H, triplet); 6.70 (4H, triplet); 7.75—8.70 τ (10H, multiplet).

Found: C, 78.67; H. 11.35; N, 10.63%. Calcd for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21%.

1-(1-Azetidinyl)cyclopentene. This was similarly formed in a 15% yield from I and cyclopentanone, it was a rather unstable liquid which turned brown fairly rapidly at room temperature. Bp 60—66°C/15 mmHg, n_D^{25} 1.4835. IR: 1630 cm^{-1}.

Found: C, 76.00; H, 10.62; H, 11.12%. Calcd for $C_8H_{13}N$: C, 77.99; H, 10.64; N, 11.37%.

Ethyl β-(1-Azetidinyl)crotonate. A mixture of 1 g (0.018 mol) of azetidine, 2.3 g (0.018 mol) of ethyl acetoacetate, and 2 g of sodium sulfate in 20 m*l* of ether was kept standing overnight. The mixture was then filtered and distilled *in vacuo* to give 2 g (Yield 68%) of a colorless liquid boiling at 110—113°C/2 mmHg, n_D^{25} 1.5068. IR: 1680 and 1585 cm^{-1}. NMR: 6.05 (1H, singlet); 6.22 (2 H, quartet); 6.27 (4H, triplet) (These three peaks are superimposed upon one another); 7.81 (2H, quintet); 8.05 (3H, singlet) and 8.91 τ (3H, triplet).

Found: C, 63.58; H, 9.23; N, 8.59%. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28%.

2-(1-Azetidinyl)pent-2-en-4-one (VI; R=Me). This was similarly prepared from I and acetylacetone as a highly hygroscopic solid, mp 52—57°C.[11] IR: 1540 and 1620 cm^{-1}.

Found: C, 68.53; H, 9.39; N, 10.37%. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06%.

The treatment of I and ethyl benzoylacetate or dibenzoylmethane under similar conditions gave only the starting materials.

Reaction of Dimethyl (1-Azetidinyl)maleate with Hydrazine Hydrate. A solution of 0.3 g of dimethyl (1-azetidinyl)maleate and 0.31 m*l* of 80% hydrazine hydrate in 2 m*l* of ethanol was sealed in a tube and then heated on a boiling water bath for ten hours. The residue obtained after the removal of the solvent was washed repeatedly with acetone to give an extremely hygroscopic solid which could not be purified. It gave a deep wine-red color when alcoholic ferric chloride was added.

We are indebted to Miss Mizuko Yoshida for the measurement of the NMR spectra.

11) Due to the extremely hygroscopic nature of this substance, its melting point could not be measured with accuracy.