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AZIRIDINYL COMPOUNDS AS INTERMEDIATES IN PYRROLIDINE SYNTHESIS

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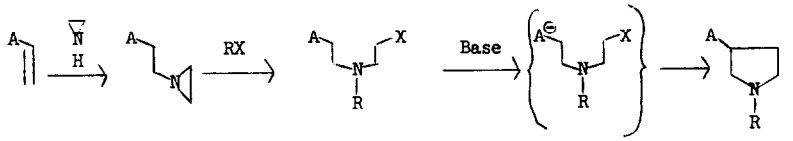
The conversion of electrophilic olefins (I) to substituted pyrrolidines (IV) may be made possible through the intermediacy of N-substituted aziridines (II) which are readily accessible by Michael addition of aziridine to a variety of electrophilic olefins.(1) Reaction of the tertiary aziridines with a suitable quaternizing agent would then provide by ring cleavage, a molecule (III) which upon treatment with base would undergo a cyclization to the pyrrolidine structure (IV).



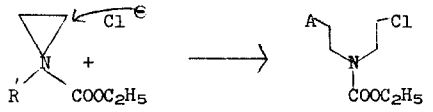
I II III IV

A = $\overset{O}{\overset{\|}{C}}CH_2R$; -CN; -$\overset{O}{\overset{\|}{C}}$OR, etc.

R = alkyl, acyl.

This heteroannulation sequence of an olefin serves very conveniently since the individual steps prove to be operationally uncomplicated and of excellent yield in most cases.

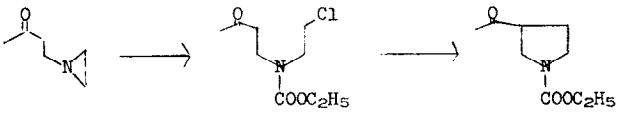
It was found that ethyl chloroformate rapidly and quantitatively converts tertiary aziridines to N,N-disubstituted urethanes, the envisaged quaternary salt (V), due to the high degree of ring strain of the incipient aziridinium ion, spontaneously cleaving in the presence of a nucleophilic



R' = CH_2CH_2A V VI

chloride ion to produce the acylic form (VI). While this is a facile, irreversible method for cleaving tertiary aziridine compounds, it also furnishes a product with a nonbasic nitrogen, thus precluding the possibility of product instability due to intermolecular reactions. In addition the ester grouping may be easily removed hydrolyticly if desired after completion of ring formation.

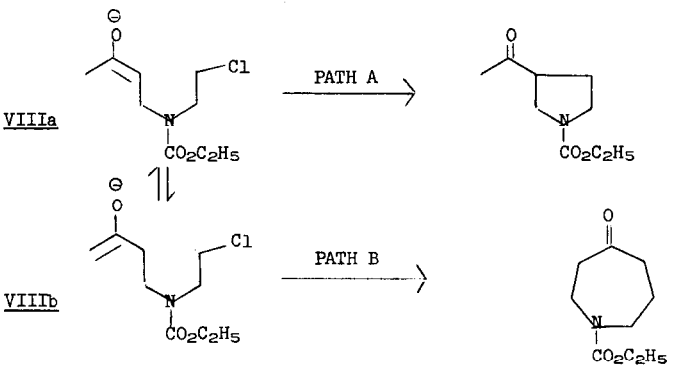
We applied the complete sequence of heteroannulation to the formation of 3-acetyl-1-carbethoxypyrrolidine (IX). The addition of aziridine to



VII VIII IX

methyl vinyl ketone in benzene solution at room temperature for 14 hours gave the 1-(1-aziridinyl)butanone-3 (VII) in 72% yield. (1a) A benzene solution of (VII) was added to an equivalent of ethyl chloroformate in benzene at below 25°C. After the addition the solvent was removed, the intermediate (VIII) was obtained as a colorless oil, b.p. 105-107°C./0.1 mm., (Anal: % Found: C, 49.13; H, 7.20; N, 6.39; Cl, 15.73). The substituted urethan (VIII) was taken up in dimethyl sulfoxide and treated with an equivalent of potassium t-butoxide at 25°C. for 14 hours under nitrogen. After work-up a 73% yield of 3-acetyl-1-carbethoxypyrrolidine (IX, b.p. 94-96°C./0.05 mm., (Anal: % Found: C, 57.78; H, 8.04; N, 7.55) was obtained. The cyclization process is considered to be independent of

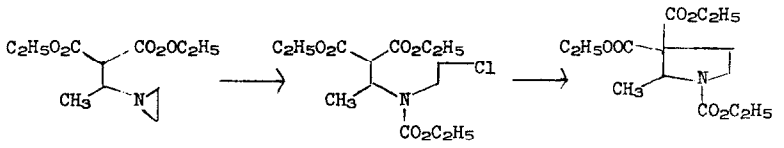
the equilibrium between enolates VIIIa and VIIIb, which probably provides approximately identical amounts of the respective enolates, this being inferred from the case of methyl-n-pentyl-ketone in which the enolate mixture does not greatly favor either α-ketone position. (2) Although the cyclization of the acyclic material can produce either a five or a seven membered ring (path A and path B respectively) the formation of the former is usually considered to be more favorable on a probability basis. (3) A certain indication of structure was available from examination of the p.m.r. spectrum which showed in particular the presence



of a methyl ketone absorption as a singlet (three protons) positioned at 2.20 p.p.m. (from T.M.S.), as expected for the five membered system.

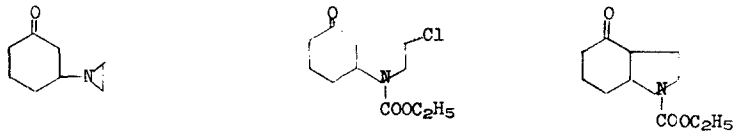
Diethyl ethylidenemalonic ester was adaptable to this sequence. Addition of aziridine to this compound gave 14% of the aziridinyl ester (X), b.p. 80-83°C./0.1 mm., (Anal: % Found: C, 57.47; H, 8.19; N, 6.13), which reacted with an equivalent of ethyl chloroformate in benzene. The intermediate urethane (XI) was not isolated, but was treated with an equivalent of sodium hydride for 14 hours to yield the 1,3,3-tricarbethoxy-3-methylpyrrolidine (XII) in 71% conversion, b.p. 126-129°C./0.15 mm., (Anal: % Found: C, 56.05; H, 7.59; N, 4.50).

The perhydroindole nucleus is readily accessible when a cyclohexenone is employed in the annulation sequence. Thus cyclohexenone itself was



X XI XII

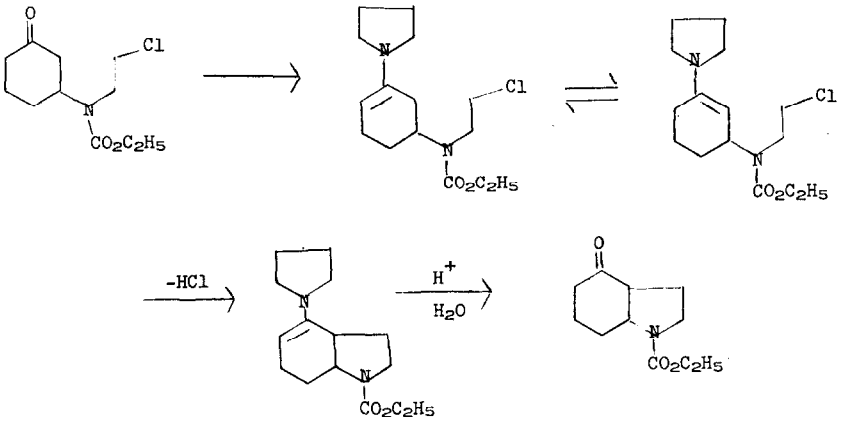
converted to 3-(1-aziridinyl)cyclohexanone (XIII) in 65% yield, b.p. 60-64°C./0.2 mm., (Anal: % Found: C, 68.88; H, 9.43; N, 10.16). A benzene solution of the aziridinylketone (XIII) was treated with an



XIII XIV XV

equivalent of ethyl chloroformate; the intermediate urethane (XIV) proved to be unstable to attempted distillation; however the infrared and p.m.r. spectra were in accord with the proposed structure. Subjection of a benzene solution of this intermediate to reflux with an equivalent of potassium t-butoxide under nitrogen for one hour led to the formation of 1-carbethoxy-4-ketoperhydroindole (XV) in 25% yield, b.p. 111°C./0.1 mm., (Anal: % Found: C, 62.61; H, 8.04; N, 6.89).

A major improvement in the cyclization of the haloketones was based on the formation and intramolecular alkylation of an intermediate enamine. When the haloketone (XIV) was refluxed with two equivalents each of pyrrolidine and of triethylamine in benzene for two hours, with the water formed being removed via a Dean-Stark trap, followed by warm, dilute 10% hydrochloric acid hydrolysis the perhydroindole compound (XV) was obtained in 66% yield, the following steps being operative:



A similar sequence performed on the chloroethylurethane derivative of methyl vinyl ketone (VIII) gave a 57% yield of the corresponding pyrrolidine (IX).

This method of pyrrolidine and perhydroindole ring formation appears to be reasonably general and the enamine modification establishes an excellent method for the heteroannulation of unsaturated ketones. We plan to examine this sequence in more detail with respect to generality and with respect to the nature of the cyclization process as a function of the activity of the anionic species undergoing alkylation and the effect of product strain as reflected in the transition state.

This procedure for preparing 3-substituted pyrrolidines serves as a useful complement to the Michael-alkylation method for preparing 3-substituted piperidines. (4)

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