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THE REACTION OF ENAMINES WITH ACTIVATED CYCLOPROPANES

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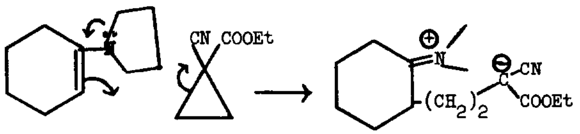
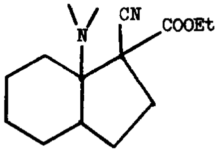
The susceptibility of cyclopropanes such as II and VIII toward nucleophilic ring-opening reactions by carbanions such as malonate(1) and cyanoacetate(2) has been known for some time. Recently, Stewart and Westberg demonstrated that amines can function as nucleophiles in this type of reaction.(3) Another extension in the nortricyclenone series has also been reported.(4) As part of a continuing study of the efficacy of enamines in various cycloaddition reactions,(5,6) we have been studying their interaction with activated cyclopropanes. The purpose of this communication is to report some of the preliminary results of this work.(7,8)

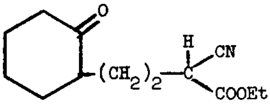
Some of the considerations which prompted this study are shown below for the pyrrolidine enamine of cyclohexanone (I):



I II III



IV



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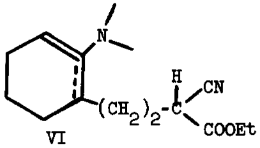

VI

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It will be noted that these envisaged processes are homologously related to those which have been realized in the electrophilic olefin series.(9,10) No appreciable reaction was observed after heating I and II in benzene or ethanol under reflux for prolonged periods of time, conditions more than adequate to effect complete reaction of I with electrophilic olefins such as ethyl acrylate or acrylonitrile. Thus, conjugate addition to an olefin, resulting in the formation of an anion stabilized by a single carboalkoxyl or cyano grouping is a process which requires greater thermal activation than homo-conjugate addition although the latter process leads to the relief of considerable ring strain, accompanied by the formation of a doubly delocalized (COOEt + C≡) anion.

By conducting the reaction in xylene[*] solution under reflux for 4 hr., utilizing a 2:1 molar ratio of enamine to cyanoester, a product was obtained whose combustion analysis (Calcd. for $C_{17}H_{16}N_2O_2$: C, 70.32; H, 9.02; N, 9.65%. Found: C, 70.55; H, 8.97; N, 9.93%) established it to be a 1:1 adduct of the starting materials. The compound, b.p./0.2 mm. 139-143°, $\lambda_{max}^{CHCl_3}$ 4.45, 5.78 μ, could be obtained in a maximum of 41% yield (based on starting ester by fractional distillation of the reaction mixture or, in 26% yield by a workup procedure involving extraction of the xylene solution with aqueous acid, neutralization of the aqueous layer, extraction of this with benzene followed by fractional distillation of the benzene solution. That the adduct could be obtained by the latter procedure, eliminates VI from consideration as its structure since VI would almost surely have afforded the ketone, V, by this procedure. This proposition gains experimental support from our results in the diester series. Structure IV which is in accord with these data is thus tentatively assigned to the adduct.

Acidic hydrolysis of IV afforded the known(11) 4-(2-ketocyclohexyl) butyric acid XIII in 37% (crude) yield. This type of hydrolysis, presumably involving an acid-catalyzed retro-Mannich reaction is well precedented.(10) All efforts to deaminate IV with maintenance of the indane skeleton were unsuccessful.

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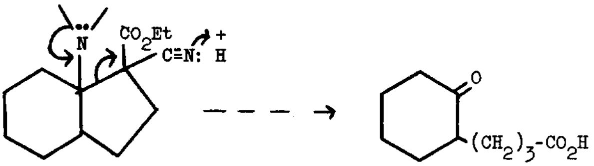
[*] Similar forcing conditions were required in the N-carbethoxyaziridine series (ref. 5).



IV VII

A study of the reaction of the diester, VIII* with the same enamine soon revealed that it is even less reactive than the cyanoester, II. Thus heating a 2:1 molar ratio of enamine to diester in xylene solution for prolonged periods of time under reflux led to virtually complete recovery of starting materials. Similar results were obtained from runs in boiling diglyme and bis(2-ethoxyethyl) ether solutions. From the small amount of tarry residues after distillation of the starting materials were isolated traces of crystalline compounds. While the structures of these can not yet be assigned with confidence, their formulae, $C_{25}H_{36}N_2O_2$ and $C_{21}H_{27}NO_2$ (established from combustion and mass spectral analysis) indicate that they arise from the interaction of two moles of enamine per mole of diester. Hence, conditions were sought to promote more complete reaction of the starting components, and to minimize the reaction of the product thus formed with unreacted enamine.

These objectives were partially realized by heating a two fold molar ratio of diester, VIII, to enamine in p-cymene as solvent, for 63 hrs. under reflux. Extraction with dilute HCl,† neutralization of the aqueous layer, and re-extraction with ether, afforded XII, b.p. 120-122/0.1 mm in 36% yield. Fractional distillation of the neutral layer afforded an additional 4%.

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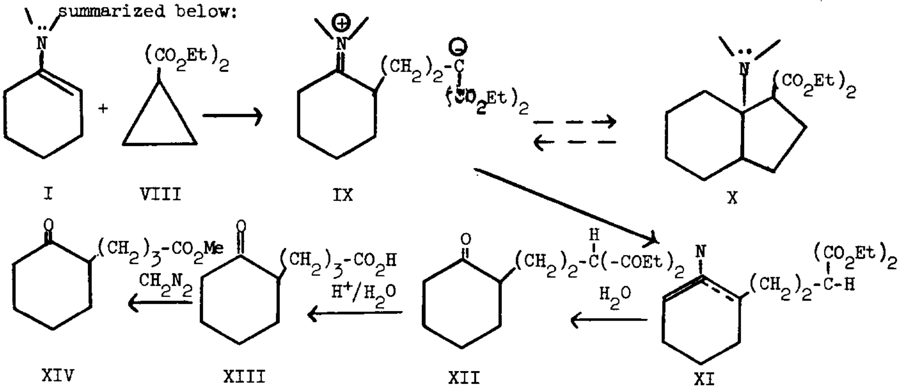
*A commercial sample of this cpd. (City Chem. Corp.) was less than half of VIII, admixed with diethyl malonate and ethylene dibromide. We also encountered serious difficulty in repeating published procedures for its preparation. The sodium ethoxide ethanol method, resulted in extensive dehydrohalogenation of the ethylene dibromide with concominantly high recovery of diethylmalonate. We found that by using dimethoxyethane as solvent and sodium hydride as base, VIII could be prepared reproducably in 34% yield contaminated only by traces of diethylmalonate.

†Efforts to obtain a pure product by direct distillation of the reaction mixture were unsuccessful.

The structure assignment of XII is dictated by its combustion analysis (Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51%. Found: C, 63.50; H, 8.60%) infrared [$\lambda^{CHCl_3}_{max}$ 5.72 (sh), 5.80, 5.86 (sh)] n.m.r. [τ^{CDCl_3} 5.88 (4) quartet, J = 7 c.p.s., 6.84 (1) poorly resolved triplet, 7.62-8.60 (13) complex, 8.75 (6) triplet, J = 7 c.p.s.] and mass (m/e$_{70\ e.v.}$ = 284, 187, 160, 124, 97) spectra. The compound also formed a semicarbazone derivative, m.p. 122-123, $C_{16}H_{27}N_3O_5$ (Calcd. C, 56.29; H, 7.97; N, 12.31%. Found: C, 56.43; H, 8.01; N, 12.09%). Acidic hydrolysis of XII afforded the acid, XIII in 75% yield (after distillation) which in turn gave a semicarbazone derivative, m.p. 183-183.5, lit.[11] 185-187°. Although only ca. 33% of the oily acid could be crystallized (m.p. 55-56° lit.[11] 56-58°), the infrared spectra of the solid and oily material were very similar. A more reliable estimate of the purity of the acid, obtained in 75% yield, could be made from its conversion to the ester, XIV in 80% yield by treatment with diazomethane. The purity of the ester [$\lambda^{CHCl_3}_{max}$ = 5.75, 5.86 μ, τ^{CDCl_3} 6.40 (3) singlet, 7.5-8.8 (15) complex] was ca. 93% as judged by g.l.c. on an S.E. 30 column. The ester is best characterized by its 2,4-dinitrophenylhydrazone m.p. 110-110.5°, lit.[12] 112°. The overall results are summarized below:



That the cyanoester route afforded the formal cycloaddition product IV, while the diester route leads to the ketodiester (presumably *via* the proton transfer product XI) may be ascribed to several factors. Thus, structure X, the analog of the cycloaddition product in the diester series necessarily entails a *cis*, highly eclipsed relationship of the carbethoxy and pyrrolidine functions. This source of instability need not be present in IV if it exists in the *cis* cyano-pyrrolidine relationship. Also, the more stringent conditions which were necessary for appreciable product formation in the diester case may well provoke an equilibrium (Mannich-retro Mannich) IX $\rightleftharpoons$ X which may be irreversibly displaced by the proton transfer process IX → XI. In this view, IV in the cyanoester series, might constitute a kinetic product. Experiments which bear on this question are planned. Support for this postulate is found in the reaction of enamines with nitro olefins.(13) In polar solvents the open chain products isolated arise from a proton transfer step while in non-polar solvents the aminocyclobutane is the only product found. Since these showed no tendency to interconvert, it was felt that the products were kinetically controlled and do not arise from equilibration.

Regardless of the reason for the difference, it might prove to be useful synthetically. Thus, use of the cyanoester leads to the elaboration of a 5-membered carbocyclic system while the diester route leads to the introduction of a 3,3-dicarbethoxypropyl grouping which could prove valuable in various intramolecular processes. Efforts to improve the yields of these reactions, delineate their scope, and capitalize on their promise are planned.

Acknowledgment

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