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THE THERMAL-MICHAEL REACTION—IV[1]
THE MECHANISM

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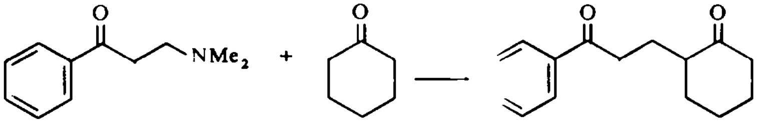
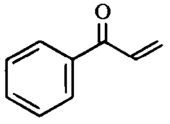
Abstract—The thermal Michael reaction proceeds via an enamine intermediate which is formed directly from the Mannich base by a special mechanism.

A SATISFACTORY mechanism for the thermal-Michael reaction must accommodate the two salient features which have emerged from recent studies, the unusual orientation of the reaction,[2] and the striking range of yields (0–96%) which have been observed.[1]

As an initial postulate, it seemed likely that at the working temperature (ca. 170°) the Mannich base would decompose[3] rapidly into dimethylamine and phenyl vinyl ketone, and on this basis, three possible mechanisms can be considered for the reaction I + II → III; (a) an uncatalyzed condensation of phenyl vinyl ketone (IV) with II; (b) a base catalysed reaction of IV with II; and (c) the reaction of IV with the dimethylamine enamine of II.

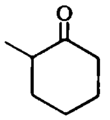


I II III

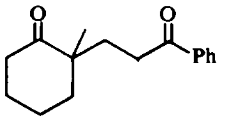


IV

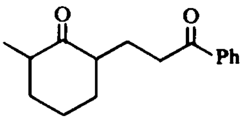
Of these mechanisms, the first can be immediately eliminated, since heating a mixture of II and IV under standard reaction conditions produced polymer but no trace (GLC) of III. Likewise the reaction of β-acetoxypropiophenone with cyclohexanone at 160° yielded the dimer of phenylvinyl ketone, as the only identifiable product. Mechanism (b) is also unsatisfactory on the grounds that it fails to account for the orientation of the product.[2] For reasons which are not understood, a "classical" (i.e. base-catalysed) Michael condensation involving an unsymmetrical ketone (e.g. V) takes place mainly at the more highly substituted C atom[4] giving rise to VI. The distinctive feature of the thermal reaction is the almost exclusive formation[2]



V



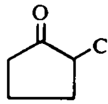
VI



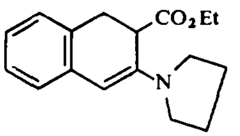
VII

of its isomer, VII. On the other hand the successful thermal-Michael reaction of I with diethyl malonate[1] can *only* be a base catalysed reaction, and there remains the interesting possibility that under the special conditions of the reaction, a very volatile base (Me_2NH) behaves uniquely e.g. in affording kinetically controlled reaction products. This presupposes that in the classical Michael reaction, the orientation of the condensation is equilibrium controlled. In fact, no equilibration took place when VII was subjected to standard Michael conditions, and an attempt to simulate the "unique" behaviour by reacting IV with V in the presence of triethylamine afforded a mixture of VI and VII in the ratio (88:12%) customarily observed in base-catalysed reactions. Thus it is difficult to escape the conclusion that with the exception of the malonic ester case cited above, the thermal reaction is not base catalysed.

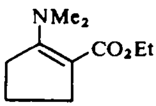
The third mechanism (c), which has already been suggested by House,[5] is particularly attractive. It faithfully accounts for the observed orientation features, it explains the wide range of yields observed and the relative competitive reactivities of II and IV recently noted,[1] in terms of ease of enamine-formation; and in the light of recent Japanese work[6] it explains the formation of bicyclo[2.2.2]octane derivatives from isophorone. The other products obtained[1] from isophorone, and from 10-methyloctalone are also enamine-derived, for the reaction of IV with the morpholine enamines of these unsaturated ketones has yielded the same products. The participation of an enamine intermediate in the thermal reaction of I with VIII[1] deserves special comment. Enamines of cyclic β-keto esters have been prepared from ammonia and some primary amines,[7] but few have been prepared from secondary amines and one such has been shown to have the *non-conjugated* structure IX.[8] We have been unable to prepare the morphine enamine of VIII but the dimethylamine enamine was readily obtained and showed no vinyl absorption in the NMR. Consequently, it must have the structure X, which reflects the smaller steric demands of Me_2N-. The reaction of X with IV afforded the same mixture of products (XI + XII) as the thermal Michael reaction. In instances where enamine formation is impossible (e.g. diethylmalonate) or difficult (e.g. 2,6-dimethylcyclohexanone) it is presumed that the reaction occurs, perforce, by the classical Michael mechanism. However the enamine mechanism leaves two questions unresolved—how is the enamine formed, and how does it condense with the enone? It is inconceivable that a highly volatile amine such as dimethylamine (b.p. 7°), liberated at ca. 170°, would be able to react well nigh quantitatively with II to give a 96% yield of III. Two attempts were made to simulate this stage of the reaction by reacting IV with V in the presence of



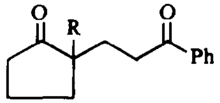
VIII



IX

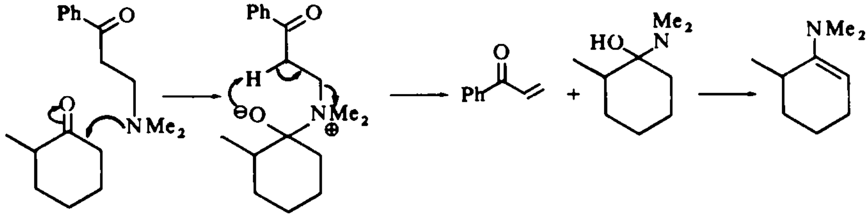


X



XI R = H
XII R = Co_2Et

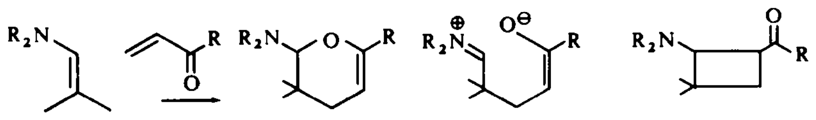
two less volatile amines, diethylamine and pyrrolidine. The former produced a 42% yield of VI + VII in the ratio 62:38% and the latter gave a 34% yield of the same mixture in the ratio 23:77%. Thus in each case the amine functions both as a base and as a nucleophile, the efficiency of the reaction is low and the proportion of enamine-derived product is low. There appears to be justification for a *special* mechanism for the thermal Michael reaction to explain these facts and we propose the following scheme:



a **b** IV XIII

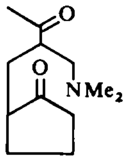
This mechanism accounts for the surprising efficiency of Mannich bases derived from highly volatile amines, since the amine is not liberated until the end of the reaction. It will also account for the behaviour of the Mannich base as a nucleophile rather than a base if we make one assumption. If the first step (**a** → **b**) is fast, *vis à vis* proton abstraction, the resulting oxy-anion is uniquely positioned to promote an intramolecular β-elimination (**b**) which is irreversible. These factors will disfavour proton abstraction and lead to IV and the enamine XIII. The subsequent interaction of these two is interesting only in as much as it affords the 1,5-dione VII rather than its enamine. Although our normal work-up involves aqueous acid, treatment, it is equally possible to isolate the product directly from the reaction mixture, by distillation. Consequently, it is necessary to envisage hydrolysis of the N-containing intermediate, be it enamine or aminodihydropyran, by the H_2O molecule generated in forming XIII.

The condensation of enamines with αβ-enones gives rise to substituted aminodihydropyrans (XIV) in equilibrium with zwitterion (XV) and cyclobutane (XVI) isomers. It may therefore be viewed either as a 4 + 2 cycloaddition or as a Michael addition, and both mechanisms have received support.[9] It was therefore of some interest to examine the thermal condensation of the bis-Mannich base XVII with cyclopentanone. On the basis of the known orientation rules this condensation should yield XIX *via* XVIII, and the mechanisms of this step can *only* be of the Michael type; a cycloaddition leading to a dihydropyran intermediate is sterically impossible.

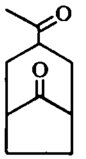


XIV XV XVI

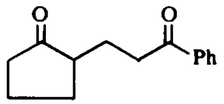
XVII



XVIII



XIX



XX

The condensation afforded a complex mixture from which the two major constituents were isolated in >95% purity, (but only with considerable loss) in overall yields of 3% and 19%. The first proved to be XX, which probably arises via a retro-Mannich process; the second is ascribed structure XIX on the following evidence. Analytical and mass spectral analyses confirm the formula $C_{10}H_{14}O_2$; the compound shows no appreciable UV absorption and its IR spectrum reveals only two bands ($\nu_{CO}^{CCl_4}$ 1748 and 1712 cm^{-1}) in the double bond region. The former is at the top of the accepted cyclopentanone range and typical of a bicyclo[3.2.1]octane-8-one.[10] The NMR spectrum shows a strong 3H singlet at τ 7·85 with broad underlying absorption (τ 6·8–8·4) but no vinyl protons. The mass spectrum showed an ion of *m/e* 43 corresponding to $MeC{\equiv}O^+$. On deuteration, the molecule incorporated only 4 atoms of deuterium, and the ion at *m/e* 43 was replaced by one at *m/e* 46. We can interpret these facts only in terms of the bicyclic dione XIX, and its formation under these reaction conditions represents either a rare intrusion of base catalysis, or more probably, the addition of an enamine to an electrophylic olefin by a true Michael-type mechanism.

EXPERIMENTAL

IR spectra were recorded on a Unicam SP100 double beam instrument, UV spectra on a Unicam SP800 (in EtOH) and NMR spectra on a Perkin–Elmer R10 (60 m/c) spectrometer in $CDCl_3$ with TMS as internal reference. GLC analyses were carried out on a Perkin– Elmer F11 instrument and mass spectra were recorded on an A.E.I., MS 12, but combined GC-MS work was done on an L.K.B. 9000A instrument provided by S.R.C. grant No. B/SR/2398.

Condensation of phenyl vinyl ketone (IV) *and 2-methylcyclohexanone* (V)

(a) *In the absence of base.* A mixture of 2-methylcyclohexanone (8·4 g) and phenyl vinyl ketone (3·3 g) was refluxed for 30 min at 165°. The mixture was cooled, neutralized with glacial AcOH, diluted with ether and extracted with brine. The ethereal soln was dried, the ether and excess ketone removed under reduced press, but only polymeric material was isolated. GLC analysis showed that neither VI nor VII had been formed.

(b) *In the presence of triethylamine.* A mixture of 2-methylcyclohexanone (8·2 g), phenyl vinyl ketone (3·2 g) and Et_3N (2·5 g) was refluxed for 40 min at 160°. The above work-up procedure gave 3·0 g (50%) of product, b.p. 150–155°/0·1 mm. GLC analysis of this showed the presence of the three products, III = 18% and the remainder consisting of VII and VI in the ratio 12:88.

(c) *In the presence of diethylamine.* The above procedure was repeated using 2-methylcyclohexanone (8·7 g) phenyl vinyl ketone (3·4 g) and Et_2NH (1·88 g). After removal of the solvent and excess ketone, this yielded 2·49 g (42%) of an oil, b.p. 160–165°/0·2 mm. GLC analysis showed the ratio of VII to VI to be 38:62 in this case, with III being present in the same proportion as VI.

(d) *In the presence of pyrrolidine.* The above procedure was repeated using 2-methylcyclohexanone (3·36 g) phenyl vinyl ketone (1·32 g) and pyrrolidine (0·71 g). After removal of solvent and excess ketone, this yielded 820 mg (34%) of an oil, b.p. 160–165°/0·25 mm. GLC analysis showed the presence of VII and VI in the ratio 77:23, with III amounting to 40% of VII.

Attempted equilibration. A sample of the diketone VII (378 mg) in dry ether (5 ml) was treated with ethanolic KOH (1 pellet in 1 ml) and the mixture stirred at room temp for 1 hr. The mixture was then poured onto ice, neutralized with conc HCl and extracted with ether. The ethereal extracts were washed with brine and dried. On removal of the solvent this yielded 345 mg material which was shown by GLC analysis to be unchanged starting material.

Attempted condensation of β-*acetoxypropiophenone and cyclohexanone*. A mixture of cyclohexanone (1·12 g) and β-acetoxypropiophenone[11] (730 mg) was refluxed for 1½ hr at 160°. The mixture was diluted with ether, thoroughly washed with brine and dried. Removal of the solvent and excess cyclohexanone left 407 mg (46·5%) material, which was shown by GLC analysis to consist largely of a single product, R_t = 10·6 min on 5% QF 1 at 200° and 45 ml/min. The material could be isolated by preparative TLC as a white solid, m.p. 128° (benzene/petrol). (Found: C, 81·74; H, 5·92. $C_{18}H_{16}O_2$ requires C, 81·79; H, 6·10%). This showed $\nu_{CO}^{CCl_4}$ 1687 cm^{-1} in the IR spectrum, aromatic protons (10 × H) between 2·1 and 2·8 τ, vinyl protons at 4·05 and 4·32 τ (2 × H, singlets), and methylene protons between τ 6·7 and 7·3. This is a dimer of phenyl vinyl ketone.

Reaction of IV *with an enamine of isophorone*. The morpholine enamine of isophorone,[12] was characterized as its picrate m.p. 134–135° (EtOH). (Found: C, 50·89; H, 5·73. $C_{18}H_{34}O_8N_4$ requires: C, 50·94; H, 5·70%).

A mixture of phenyl vinyl ketone (1·5 g) and the enamine (2·5 g) in dry benzene (30 ml) was refluxed for 24 hr in a stream of dry N_2. A buffer soln of glacial AcOH (7·5 ml) water (7·5 ml) and NaOAc (3·75 g) was added and refluxing continued for a further 4 hr. The mixture was cooled and the benzene and aqueous layers separated. The aqueous layer was extracted with benzene and the combined benzene extracts washed with 10% HCl, sat $NaHCO_3$aq, water and dried. Removal of the solvent yielded, on distillation, 2·10 g (69%) of a pale yellow oil, b.p. 155–160°/0·01 mm. GLC analysis on 5% QF 1 at 200° and 45 ml/min showed the presence of one major and three minor products, R_t = 9·8, 12·1, 16·8 and 25·0 min, accounting for 55, 20, and 10 and 10% of the total respectively. These represent four of the five products formed in the thermal Michael reaction[1] the missing one being the bicyclo [2.2.2] octane derivative. Separation was effected by preparative TLC into three fractions. The first, consisting of the first two peaks, showed $\nu_{C=O}^{CCl_4}$ 1665 and 1689 cm^{-1} and a parent ion at *m/e* 270 on gas chromatography/mass spectrometer analysis. In addition the NMR spectrum had Me signals at 9·02 τ (6 × H, singlet) and 7·78 τ (3 × H, s) but no vinyl proton. (Found: C, 79·88; H, 8·23. $C_{18}H_{22}O_2$ requires: C, 79·96; H, 8·20%). The last component by GLC could not be isolated in a pure state, but the NMR spectrum showed three distinct Me signals at 7·65, 8·83 and 9·05 τ. This also showed a parent ion at *m/e* 270. The third GLC product showed $\nu_{C=O}^{CCl_4}$ 1669 and 1686 cm^{-1} in the infra red spectrum and its NMR spectrum showed a vinyl proton at 4·07 τ and Me signals at 7·80 τ (3 × H, s) and 8·98 τ (6 × H, s). Its structure has already been discussed.[1]

2-(N-*Morpholino*) 10-*methyl*-3,4,5,6,7,10-*hexahydronaphthalene*. A mixture of 10-methyl-$\Delta^{1;9}$-2-octalone[13] (2·8 g) and morpholine (4·5 g) in toluene (30 ml) was refluxed in a Dean–Stark apparatus for 36 hr. Removal of the solvent and excess morpholine and distillation of the residue yielded 2·5 g (62%) pale yellow oil, b.p. 110–115°/0·25 mm, which was transparent in the IR carbonyl region. The UV spectrum showed λ max = 263 mμ (ε = 12,000) and a picrate was obtained, m.p. 139–140° (EtOH). GLC analysis showed the presence of two isomers, R_t = 6·3 and 8·8 min on 5% APL at 150° and 55 ml/min in the ratio 6:1.

A mixture of this crude enamine (1·15 g) and phenyl vinyl ketone (700 mg) in dry benzene (20 ml) was refluxed for 24 hr in a stream of dry N_2. The usual acetate buffer soln (4 ml) was added and refluxing continued for a further 2 hr. The mixture was cooled and, following the usual enamine work-up, distillation gave 1·02 g (61%) of a clear viscous oil, b.p. 182–187°/0·35 mm. GLC analysis showed that the predominant product corresponded to that isolated from the thermal reaction. The NMR of a sample, isolated by preparative TLC, again showed no vinyl proton, a Me signal at 8·83 τ (3 × H, s) and aromatic protons between 2·0 and 2·7 τ (5 × H, m).

1-*Dimethylamino*-2-*carbethoxycyclopent*-1-*ene* (X). The literature method[14] was amended, as follows: A steady bubble of MeNH gas, dried over KOH, was passed for 18 hr through a stirred soln of VIII (4·0 g) in dry benzene (5 ml), containing, in suspension, 1 g anhyd K_2CO_3. The soln was diluted with ether and filtered, solvents were removed and the residue was distilled to give 3·75 g (80%) pale yellow oil, b.p. 156–160°/30 mm. This gave a negative $FeCl_3$ test and showed λ max 305 mμ (ε = 10,500) (Lit.[14] 309 mμ (ε = 11,000) in the UV spectrum. Its NMR spectrum showed N-Me's at 7·03 τ (6 × H, s); ester Me at 8·78 τ (3 × H, t, J = 7 c/s) and methylene at 5·89 τ (2 × H, q) but no vinyl proton.

Condensation of the enamine X *and phenyl vinyl ketone* (IV). A mixture of the enamine (750 mg) and phenyl vinyl ketone (600 mg) in dry benzene (15 ml) was refluxed for 24 hr in a stream of dry N_2. Following the addition of 2 ml acetate buffer and a further 2 hr reflux, the normal enamine work-up yielded 670 mg

(59%) product. This gave a negative $FeCl_3$ reaction and no bathochromic shift in the UV spectrum on the addition of base. GLC analysis on 5% QF 1 at 200° and 40 ml/min showed it to consist of two components, corresponding to XI and XII obtained from the thermal reaction, R_t = 7·00 and 20·75 min.

3-Acetylbicyclo[3.2.1]*octan-8-one* (XIX). The Mannich base XVII[15] showed a 3N singlet at τ 7·9, and consequently, the structure ascribed to it by earlier workers, is correct.

The base (12·4 g) dissolved in cyclopentanone (19 g) was refluxed for 2½ hr, cooled, neutralized with AcOH and extracted into ether. After drying, the ether and excess cyclopentanone were removed *in vacuo* and the residue was distilled. The middle fraction (b.p. 98–158°/0·7 min) (5 g) was collected and examined further.

GLC analysis on 5% QF1 at 150° and 40 ml per min detected five components of R_t 0·4, 0·56, 0·81, 1·0, 1·5 and 2·1 min, of which all but Nos. 3 and 5 were in negligible amount. These two principle components were separated by preparative GLC.

The former (400 mg) showed $\nu_{CO}^{CCl_4}$ 1735 and 1714 cm^{-1} and *m/e* 154. Its NMR spectrum showed no olefinic absorption but a 3H singlet (τ 7·9) and a 2H triplet (J = 4 Hz) at τ 7·5, and its identity with XX was proved by GLC comparisons on 5% QF1 at 150° and 1% OV17 at 125° by mixed injections.

The latter (2·2 g) gave the following physical data: $\nu_{CO}^{CCl_4}$ 1748 and 1712 cm^{-1}: *m/e* 166. (Found: C, 71·57: H, 8·56. $C_{10}H_{14}O_2$ requires: C, 72·26: H, 8·49%). A sample (50 mg) was added to a soln of Na (50 mg) in peroxide-free dioxan (2 ml) and D_2O (2 ml). The mixture was warmed at 70° for 15 min under N_2, then the dioxan and D_2O were removed *in vacuo*, a further 1 ml D_2O was added and the mixture was extracted into ether. On evaporation of the solvent, there was left a semi-crystalline product, which was found (GLC) to be a 1:1 mixture. The constituents were separated by preparative TLC yielding,

(i) An oil, $\nu_{CO}^{CCl_4}$ 1754 and 1710 cm^{-1}: *m/e* 170 (parent)

(ii) A colourless solid m.p. 124–125°, $\nu_{CO}^{CCl_4}$ 1728 cm^{-1}: $\nu_{OH}^{CCl_4}$ 3605 cm^{-1}, which is probably the tricyclic, intramolecular aldol product.

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