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THE REACTION OF PHOSGENE WITH ENAMINES

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Abstract—The reaction of phosgene with two equivalents of 1-morpholino-1-cyclopentene afforded 1,3,5-triketone (II) together with γ-pyrone (III). The relative yields of the two products could be controlled by choosing suitable hydrolysis conditions. Four products, 1,3,5-triketone (VI), γ-pyrone (V), hemiketal (VII) and γ-pyrone (VIII) were obtained in the reaction of phosgene with 1-morpholino-1-cyclohexene. The mechanism of the reaction is discussed.

INTRODUCTION

ACYLATION of enamines with acid chlorides of either mono- or dicarboxylic acids have been used in the synthesis of β-diketones and related compounds.[1] Acylation with phosgene, surprisingly enough, has received only limited attention.[2] We have investigated the possibility that phosgene, being formally a dichloride of carbonic acid, may act in the presence of two equivalents of enamine as a "double" acylating agent, and thus may furnish a simple route to 1,3,5-triketones and γ-pyrones. We wish now to report our results regarding this reaction.

RESULTS AND DISCUSSION

When a solution of one equivalent of phosgene was added to a solution of two equivalents of 1-morpholino-1-cyclopentene (I) containing triethylamine, an immediate reaction took place (disappearance of the 1800 cm^{-1} absorption band of the phosgene soon after addition, and the appearance of a new CO band at 1690 cm^{-1}). Mild acid catalysed hydrolysis of the mixture afforded, mainly two products,* which were identified as triketone II and substituted γ-pyrone III (Scheme 1).

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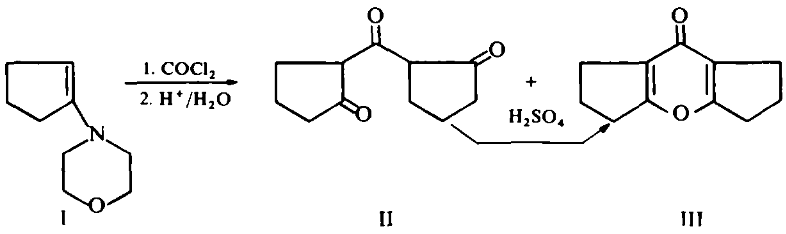

SCHEME 1

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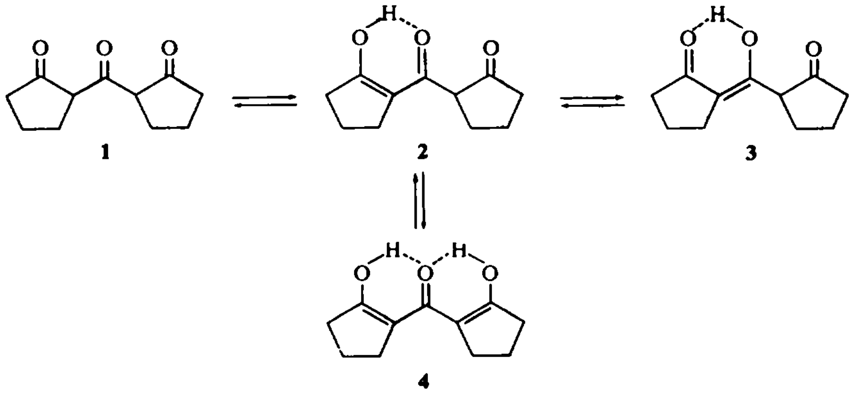
* Small amounts of N,N'-tetraethylurea were present when dry, but not purified with phenylisocyanate, Et$_3$N was used.

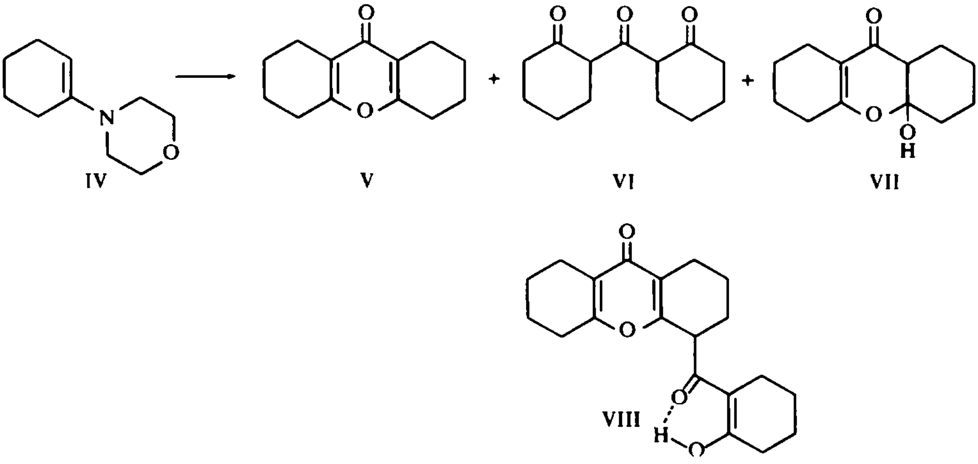
Separation of the two products when both were present in comparable amounts was very tedious (both have a similar R_f value on TLC). It was found, however, that the relative yields of either II or III could be controlled by choosing suitable hydrolysis conditions. Thus, when the hydrolysis was carried out with 15% HCl at 50°, pyrone III, m.p. 121°–3° was the major product, and could be purified either by distillation or by column chromatography. The structure assignment of III was based upon the following evidence: analytical data were in good agreement with a $C_{11}H_{12}O_2$ formulation. The mass spectrum exhibited a parent peak of M^+ 176 (Mol Wt. Calc. 176·22). The IR spectrum ($CHCl_3$) exhibited absorptions at 1645 cm^{-1} and 1605 cm^{-1} which are characteristic of γ-pyrone systems.[3] The NMR spectrum ($CDCl_3$) exhibited 3 multiplets at δ 2·10, 2·71 and 2·82 with area ratios of 1:1:1. The UV spectrum (MeOH) displayed an absorption at $\lambda = 255$ nm ($\varepsilon = 15{,}000$).

When the hydrolysis was carried out at 0° with 5% HCl, triketone II, m.p. 49–52°, was obtained as the major product and was purified by distillation. The structure assignment of II was based on the following evidence: analytical data were in good agreement with a $C_{11}H_{14}O_3$ formulation. The mass spectrum exhibited a parent peak at M^+ 194 (Mol. Wt. Calc. 194·23). II gave a purple colouration when treated with 5% ferric chloride solution. When treated with conc sulphuric acid for $\frac{1}{2}$ hr, II was converted to III in 80% yield. From the IR and NMR data for II it was apparent that II is, in fact, a mixture of several keto-enol tautomers. Thus in the IR spectrum ($CHCl_3$), four strong bands were displayed, at 1745 cm^{-1}, 1700 cm^{-1}, 1655 cm^{-1}, and 1600 cm^{-1}. The same absorptions were displayed when the spectrum was run in KBr pellets. In neither case was it possible to see any absorption in the region of 3500 cm^{-1} indicating the presence of a free OH group. The first two absorptions were assigned to the non-bonded cyclic CO and acyclic CO, respectively. There are two plausible interpretations for the two other absorptions. One is analogous to that advanced for β-keto esters,[4] namely, that the two absorptions are those of the acyclic chelated CO and the enolic double bond, respectively. The other one is analogous to that advanced for β-di-and β-triketones derived from cyclopentanone,[5] namely, that the two bands represent different chelated CO groups. The 1655 cm^{-1} band should then be due to the chelated cyclic CO, and the 1600 cm^{-1} band to that of the chelated acyclic CO. Adoption of the second interpretation would imply that II is a mixture of at least three, possibly four tautomers, represented below:



The NMR spectrum of II ($CDCl_3$) exhibited a complex pattern at δ 1·8–2·8 which was assigned to the twelve methylene hydrogens, three triplets at δ 4·1 ($\sim$0·5H, J 8 c/s), 3·7 ($\sim$0·2H, J 8 c/s), and 3·1 ($\sim$0·5H, J 8 c/s), and a very broad signal at 12·7 ($\sim$0·7H). All the four last signals disappeared when II was treated with D_2O. The significance of the three triplets is not clear. Though **1**, **2** and **3** have different acidic hydrogens, the interconversion of the external tautomers **2** and **3** should be a rapid process outside the NMR time scale and only one average triplet should be seen.[5] Yet **1** can give rise to two triplets as it contains two asymmetric centers, and may be present as two different diastereomers, a DL and a meso. We tentatively suggest that the signal at δ 3·1 is that of **2** and **3** and the two lower ones are those of DL and meso **1**.

Four products were isolated from the reaction between 1-morpholino-1-cyclohexene (IV), and phosgene, when different reaction conditions were used (Scheme 2). When



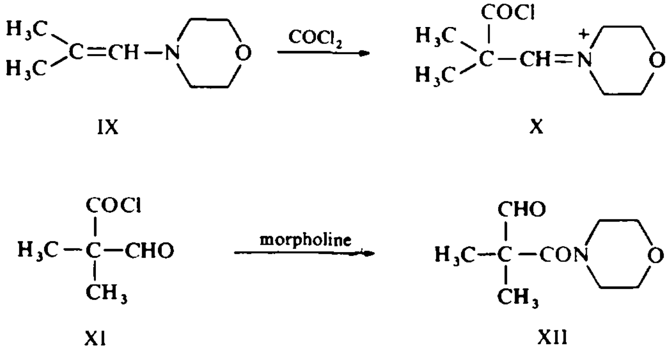
Scheme 2

the hydrolysis was carried out with 15% HCl at 50°, γ-pyrone V, m.p. 131°, was obtained in fair yields. The structure of V was confirmed by analysis and by its spectral properties. In an attempt to obtain the corresponding triketone VI, the hydrolysis was carried out with 5% HCl at 0°. A TLC of the crude product showed three spots, the middle one of which corresponded to V. The two other spots were identified as those of triketone VI and hemiketal VII. On distillation, the crude product afforded mainly V, preceded by an oily fraction, which still displayed the same three spots on TLC. From a column chromatography VI, the upper spot on the TLC, was obtained as an oil, and its structure was confirmed by analysis and by its spectral properties. Yet VI cannot be considered pure, as in a few hours it was found to contain VII, the lower spot on TLC. On standing for some time, VI deposited crystals, m.p. 153°, which were found to be those of VII. The structure assignment for VII was based on the following evidence: analytical data were in accord with a $C_{13}H_{18}O_3$ formulation; ms, M^+ 222 (Mol. Wt. Calc. 222·28); IR ($CHCl_3$) 3540 cm^{-1} (sharp) 3300 cm^{-1} (broad), 1650 cm^{-1}, NMR ($CDCl_3$), (δ) 1·40–1·80 (12H, m), 2·10–2·50 (5H, m), 4·10

(1H, broad s). It was eventually realized that the main product under these conditions was, in fact, VII, rather than V, as an addition of ethyl acetate to the crude product prior to distillation, VII was obtained in high yield. These results should be rationalized in the explanation that under these conditions VI is initially formed, as the main product, which is, however, quickly converted under those acidic conditions to the thermodynamically more stable VII. On distillation, VII loses water, probably by catalysis by traces of acid, and V is obtained. The ease with which VII tends to lose water was also demonstrated when, on 2 hr reflux in benzene in the presence of catalytical amounts of *p*-toluenesulphonic acid, VII was completely transformed to V. Even on heating VII in 20% K_2CO_3 solution, V, rather than VI, was obtained. Although direct evidence is lacking, the ease with which VII tends to lose water seems to indicate a trans fusion of the two rings in VII.

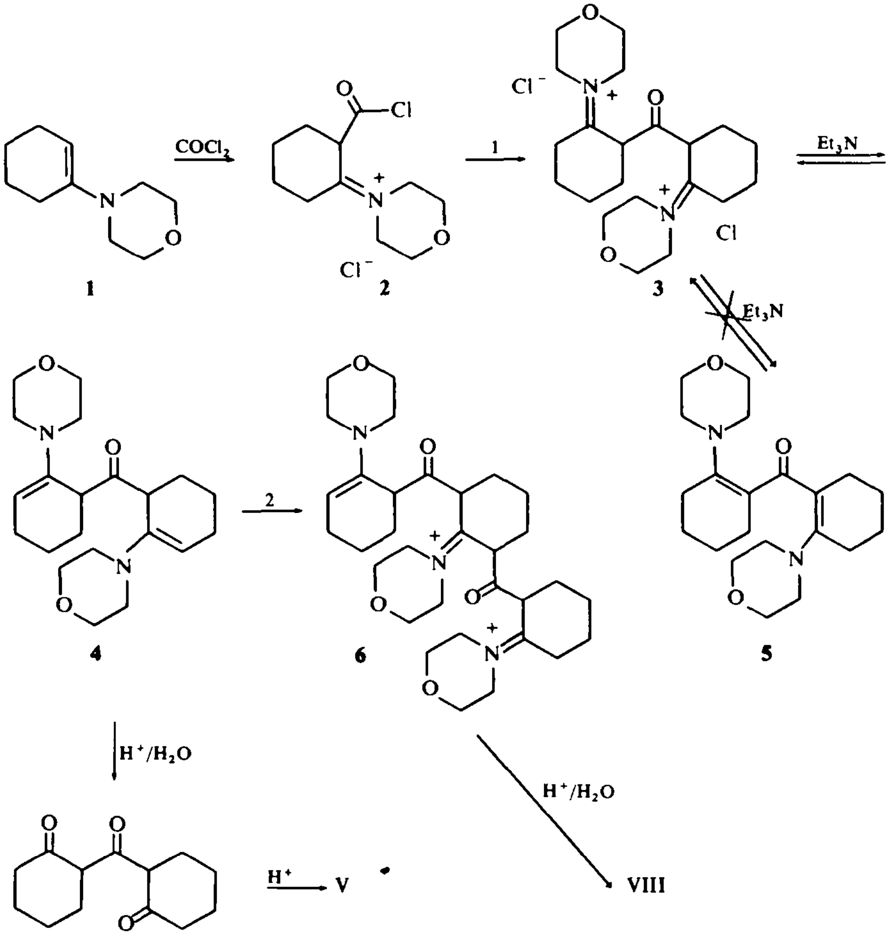
The fourth product, VIII, was obtained in a reaction where an excess of phosgene was used. The structure assignment of VIII was confirmed by analysis and by its spectral properties. The formation of VIII is interesting from a mechanistic point of view, and its formation will be discussed below.

In an attempt to obtain a 1,3,5-tricarbonyl compound that would not cyclize to γ-pyrone, we tried the reaction with 1-morpholino-1-isobutene (IX). In our hands the only product obtained in this reaction was α-formyl-α-methylpropionemorpholide (XII) whose structure was confirmed by analysis and by its spectral properties. A trivial explanation for the formation of XI would be that it arises from the presence of free morpholine in the reaction mixture, prior to the addition of phosgene. We believe, however, in view of the care taken to use only pure freshly distilled batches of IX, another explanation is warranted, namely the one depicted in Scheme 3: Phosgene initially reacts with IX yielding X, which, however, fails to react further with another molecule of IX. On hydrolysis, the azmethynium group reacts faster with water than the COCl group, and the free morpholine obtained reacts with XI to give XII.



MECHANISM

The exact mechanism of the reaction is unknown. A probable one for 1-morpholino-1-cyclohexene is represented below:



It is our belief, supported by evidence, that **5** is not an intermediate in this reaction. We have followed the course of the reaction for 48 hr and have failed to observe any absorption in the UV above 230 nm. In the IR spectra only a strong saturated CO absorption at 1700 cm^{-1} could be seen. We believe, therefore, that **3**, possibly in equilibrium with **4**, is the intermediate in this reaction and in this respect this reaction resembles alkylation of enamines rather than acylation. The presence of **4** is also supported by the isolation of VIII which is probably formed in a reaction between **2** and **4**.

EXPERIMENTAL

M.ps were determined on a Thomas Hoover 'Unimelt" apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer grating spectrometer model 337. UV spectra were recorded on a Perkin-Elmer 137 UV spectrometer. NMR spectra were taken on a Varian HA-100 spectrometer and on a Jeol JNM-C-60HL spectrometer with TMS as an internal standard. Mass spectra were taken with an Hitachi Perkin-Elmer RMU-6 instrument, the samples being introduced directly into the ion source through a vacuum lock, electron energy 70 eV.

General procedure for the reaction of phosgene with enamines

To a stirred soln of enamine (0·1 mole) in CH_2Cl_2 (100 ml) containing Et_3N (0·1 mole), phosgene (0·05 mole: 26 ml of 20% soln in toluene) was added dropwise (30–45 min), at room temp and under dry N_2. Stirring was continued for 4 hr at room temp, and then the mixture was left overnight. HClaq (100 ml: 5 or 15%) was added and the mixture was stirred for 3–5 hr (at 0° or 50°). The layers were separated, the aqueous layer extracted with 2 × 100 ml portions of CH_2Cl_2. The combined CH_2Cl_2 solns were washed with water and dried on $MgSO_4$. Removal of the CH_2Cl_2 and toluene left an oily residue which was further worked up as described below.

γ-Pyrone III. I[6] (0·1 mole) and phosgene (0·05 mole) was used. The hydrolysis was carried out with 15% HCl at 50°. The crude residue was distilled at low pressure, yielding 2·1 g (24%) of III, b.p. 114–120°/0·1 mm, m.p. 121–3° after recrystallization from EtOAc–light petroleum. (Found: C, 74·20: H, 6·83: $C_{11}H_{12}O_2$ requires: C, 74·35: H, 6·86%).

Bis(2-oxycyclopentyl)ketone (II). I (0·1 mole) and phosgene (0·05 mole) was used. The hydrolysis was carried out with 5% HCl at 0°. The crude residue was distilled at low pressure, yielding 2·0 g (20%) of II, b.p. 110–112°/0·01 mm, as a pale oil that slowly solidified, m.p. 49–52° after recrystallization from light petroleum–EtOAc. (Found: C, 68·08: H, 7·09: $C_{11}H_{14}O_3$ requires: C, 68·02: H, 7·26%).

Reaction of II *with sulphuric acid.* II (0·5 g) was dissolved in conc H_2SO_4 (4 ml), and the soln kept for ½ hr at room temp. The soln was poured into 100 ml water, and solid K_2CO_3 was added until pH 5–6. The aqueous soln was extracted thoroughly with ether, and the ether dried on $MgSO_4$. Removal of the ether left 0·36 g (80%) of III m.p. 121–2°, after recrystallization from light petroleum. There was no depression of mixed m.p. with authentic III.

γ-Pyrone V. IV[6] (0·1 mole) and phosgene (0·05 mole) was used. The hydrolysis was carried out with 15% HCl at 50°. The crude residue was distilled at low pressure yielding 4·3 g (42%) of V, b.p. 162–170°/1 mm, m.p. 131° after recrystallization from EtOAc-light petroleum: IR ($CHCl_3$) 1655 cm^{-1}, 1595 cm^{-1}; UV, λ_{max} (MeOH) 256 nm (ε = 13,000): NMR (δ), 1·73 (4H, m), 2·43–2·49 (4H, 2m): ms, M^+ 204 (Mol. Wt. Calc. 204·27): Found: C, 76·78: H, 7·94: $C_{13}H_{16}O_2$ requires: C, 76·92: H, 7·90%).

Hemiketal VII. IV (0·1 mole) and phosgene (0·05 mole) was used. The hydrolysis was carried out with 5% HCl at 0°. Removal of the CH_2Cl_2 left an oily residue to which EtOAc (60 ml) was added. On standing for a few hr in the cold, 3·6 g (32·5%) of VII were separated and collected, m.p. 153° after recrystallization from EtOAc. (Found: C, 70·36: H, 8·02: $C_{13}H_{18}O_3$ requires: C, 70·20: H, 8·11%).

Bis(2-oxycyclohexyl) ketone (VI). IV (0·1 mole) and phosgene (0·05 mole) was used. The hydrolysis was carried out with 5% HCl at 0°. The crude product was distilled at low pressure affording 1·2 g of an oily fraction, b.p. 152–156°/0·5 mm, followed by 3·1 g (30·5%) of V b.p. 163–165°/0·5 mm. The oily fraction was subjected to column chromatography on Kieselgel (0·05–0·20 mm), using EtOAc-light petroleum as eluents. From the 80:20 V/V light petroleum-EtOAc fraction 0·52 g (4·7%) of VI were obtained, one spot on TLC; IR ($CHCl_3$) 1705 cm^{-1}, 1650 cm^{-1}, 1605 cm^{-1}; ms, M^+ 222 (Mol Wt./Calc. 222·28); (Found: C, 69·71: H, 7·96: $C_{18}H_{18}O_3$ requires: C, 70·20: H, 8·11%). After a few hr standing, a TLC of VI showed that it contained VII as well.

γ-Pyrone VIII. IV (0·1 mole) and phosgene (0·06 mole) was used. The hydrolysis was carried out with 15% HCl at 50°. The crude residue was distilled at low pressure, affording 3·9 g (38%) of V. The residue from the distillation flask was subjected to column chromatography on Kieselgel (0·05–0·20 mm) employing EtOAc–light petroleum as eluents. From the 100% EtOAc fraction 0·32 g of VIII were obtained, m.p. 148°, after recrystallization from EtOAc: IR ($CHCl_3$) 1650 cm^{-1}, 1595 cm^{-1}: NMR ($CDCl_3$) (δ) ~1·7 (14H, m), ~2·4 (8H, m), 3·86 (1H, t), 12·5 (1H, broad s); ms, M^+ 328 (Mol Wt. Calc. 328·41). (Found: C, 73·37; H, 7·25: $C_{20}H_{24}O_4$ requires: C, 73·09: H, 7·40%).

Reaction of VII *with p-toluenesulphonic acid.* A soln of VII (0·45 g) and *p*-toluenesulphonic acid (0·01 g) in benzene (20 ml) was refluxed for 4 hr. The benzene soln was washed with 10% K_2CO_3aq and dried over $MgSO_4$. Removal of the benzene left a solid that after recrystallization from EtOAc–light petroleum afforded 0·37 g (90%) of V, m.p. 131°. There was no depression of mixed m.p. with authentic V.

Reaction of VII *with* K_2CO_3. A suspension of VII (0·15 g) in 20% K_2CO_3 (30 ml) was heated to reflux, and EtOH was added until the soln became clear. After 6 hr of reflux, the soln was acidified with HCl to pH 7, extracted with ether and the ether dried over $MgSO_4$. Removal of the ether left an oil which on TLC showed the presence of V and VII. EtOAc was added and VII was filtered off. Evaporation of the EtOAc left 0·06 g of V, m.p. 130°.

α-Formyl-α-methylpropionemorpholide (XII). IX[7] (0·1 mole) and phosgene (0·05 mole) was used. The hydrolysis was carried out with 15% HCl at room temp. The crude residue was distilled at low pressure affording 3·3 g (36%) of XII, b.p. 88–89°/0·3 mm: IR ($CHCl_3$) 1720 cm^{-1}, 1645 cm^{-1}: NMR ($CDCl_3$) (δ), 1·35 (6H, s), 2·50 (4H, m), 2·66 (4H, m), 9·62 (1H, s); ms, M^+ 185 (Mol Wt. Calc. 185·23); (Found: C, 58·03; H, 8·41: N, 7·32: $C_9H_{15}NO_3$ requires: C, 58·36: H, 8·16; N, 7·56%).

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