Reactions of Enamines. V. The Acylation of Enamino Ketones[1]

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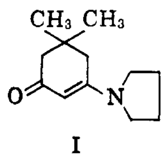
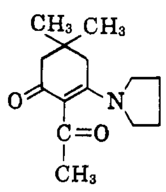
The acylation of 5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (I) and 5,5-dimethyl-3-N-morpholylcyclohex-2-en-1-one (V) with aromatic acid chlorides gives C-acylated products. Aliphatic acid chlorides react similarly except when they are capable of undergoing dehydrohalogenation to a ketene. Ketene or diketene does not react with I and V. 2-Nitrobenzenesulfenyl chloride with I afforded the 2-substituted sulfide (VII). The criteria for O- *vs.* C-acylation of enamino ketones are discussed.

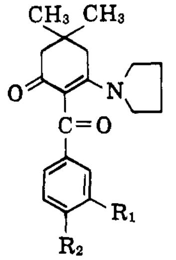
The O- and C-alkylation of enamino ketones is well-established.[2] The only reported acylation of an enamino ketone must have involved O-acylation as shown by hydrolysis of the intermediate iminium salt to the enol ester of a 1,3-diketone.[3] Indirect evidence for O-acylation is provided by the formation of chloroiminium salts from enamino ketones.[1] On this basis, O-acylation would be expected in the reaction of enamino ketones with acid chlorides. Surprisingly, reaction of 5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (I) with acetyl chloride gave exclusively the C-acylated, 2-acetyl-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (II) with concomitant formation of an equimolar amount of the hydrochloride of I. The structure of II follows from the elemental analysis, the ultraviolet spectrum, and the n.m.r. spectrum which did not show a vinyl proton. Similar results were obtained by reaction of I with benzoyl, 3,4-dichlorobenzoyl, and *p*-nitrobenzoyl chlorides. In each case the C-acylated product (IIIa, IIIb, IIIc, respectively) was obtained together with an equimolar amount of I hydrochloride. The formation of the hydrochloride of I rather than that of the C-acylated products (II or III) reflects the fact that enamino ketone I is a stronger base than II or III.



I



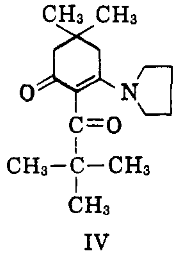
II



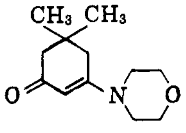
IIIa, $R_1 = R_2 = H$
b, $R_1 = R_2 = Cl$
c, $R_1 = H$; $R_2 = NO_2$

It has been reported[3] that the addition of triethylamine in the acylation of enamines avoids the loss of starting material as the hydrochloride. In the reaction of the enamino ketone I with acetyl chloride in the presence of triethylamine, a quantitative yield of triethylamine hydrochloride was obtained. However, no C-acylated product was isolated and I was recovered unchanged. This result is readily understood by allowing for the dehydrohalogenation of acetyl chloride by triethylamine to ketene which is rapidly converted to dimer under the reaction conditions.[4] In a control experiment it was shown that diketene does not react with I under the same conditions.[5]

For similar reasons reaction of propionyl chloride and I did not give the C-acylated product. A quantitative yield of I hydrochloride together with unchanged I was obtained. Thus, the enamino ketone I is a strong enough base to dehydrohalogenate propionyl chloride to methylketene before C-acylation can take place. Pivalyl chloride, which cannot undergo dehydrohalogenation, reacted normally to give C-acylated IV.

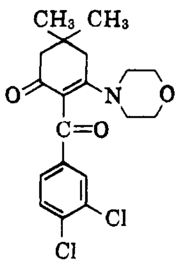


IV

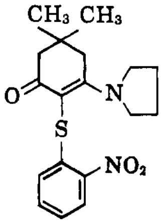


V

Reaction of 5,5-dimethyl-3-N-morpholylcyclohex-2-en-1-one (V) with 3,4-dichlorobenzoyl chloride afforded the C-acylated product (VI). However, a quantitative yield of the V hydrochloride and unchanged compound V were the only products from the reaction of V with acetyl chloride. Evidently dehydrohalogenation of acetyl chloride by the enamino ketone V had taken place. The difference in the behavior of I and V



VI



VII

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[1] Part IV: G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 794 (1964).

[2] *Cf.*, *inter alia*, (a) N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.*, **81**, 595 (1959); (b) N. K. Kochetkov, *Izv. Ak. Nauk SSSR Otd. Khim. Nauk*, 47 (1954).

[3] S. Hünig, E. Benzing, and E. Lücke, *Ber.* **90**, 2833 (1957).

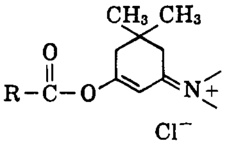
[4] J. C. Sauer, *J. Am. Chem. Soc.* **69**, 2444 (1947); see also W. E. Hanford and J. C. Sauer, "Organic Reactions," Coll. Vol. III, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 124.

[5] The reaction of enamines with ketene and diketene is well-known. See (a) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **26**, 4775 (1961); (b) G. A. Berchtold, G. R. Harvey, and G. E. Wilson, Jr., *ibid.*, **26**, 4776 (1961); (c) S. Hünig, E. Benzing, and K. Hübner, *Ber.*, **94**, 486 (1961); (d) G. Opitz and F. Zimmermann, *Ann.*, **622**, 178 (1963).

towards acetyl chloride must lie in the basicities of the amines as well as in the greater ease of formation of a trigonal atom in a five-membered ring compared with one in a six-membered ring in the transition state.[6] Thus, the more reactive (*i.e.*, in the acylation reaction) pyrrolidine enamino ketone reacts to give C-acylated product while the morpholine enamino ketone, which is less reactive, is nevertheless a strong enough base to effect the dehydrohalogenation of acetyl chloride. This difference in reactivity is well-illustrated by the reaction of I and V with acetic anhydride. The pyrrolidine enamino ketone (I) reacts with boiling acetic anhydride to give II while the morpholine enamino ketone (V) is recovered unchanged under the same conditions.[7]

The enamino ketone I also reacted smoothly with *o*-nitrobenzenesulfenyl chloride to give a compound (VII) having the *o*-nitrophenylthio group substituted in the 2-position. Again the equivalent of C-acylation had taken place.

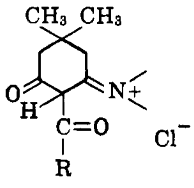
Since initial O-acylation must have taken place in the formation of chloroiminium salts,[1] it seems reasonable that in the present cases, O-acylation[8] also occurs, but does not lead to stable products. The O-acylated intermediate (VIII) can collapse to starting materials by attack of chloride ion at the carbonyl carbon.



VIII

In the formation of chloroiminium salts[1] (*e.g.*, VIII, R = $-CCl_3$) the inductive effect of the trichloromethyl group, although rendering the carbonyl carbon more positive, would also strengthen the bond to the ester oxygen. Hence, attack by chloride ion occurs at C-1 of the ring,[9] leading to chloroiminium salt and expulsion of trichloroacetate ion.

When C-acylation does occur, the intermediate IX can stabilize itself by loss of a proton from C-2 to give the observed product.



IX

Experimental[10]

2-Acetyl-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (II). A. Reaction of I with Acetyl Chloride.—To a solution of 5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (I)[1,2a] (4.9 g., 0.025 mole) in benzene (70 ml.) was added acetyl chloride (1.0 g., 0.013 mole) in benzene (20 ml.). The reaction mixture was heated under reflux for 3 hr. during which time a solid precipitated. After cooling the solid was filtered giving 2.9 g. (100%) of the hydrochloride of the starting enamino ketone I, m.p. 225–228° (no depression with authentic I hydrochloride).[1] The filtrate was evaporated to dryness *in vacuo* giving 2.8 g. of sticky crystals, m.p. 140–146°, which on several recrystallizations from benzene or ethyl acetate–hexane mixture gave pure II (2.1 g., 72% based on enamino ketone reacted), m.p. 158–159°; $\lambda_{\max}^{\mathrm{EtOH}}$ 274 mμ (ε 13,300), 310 (16,000); n.m.r. spectrum, τ 8.92 singlet, 8.05 multiplet, 7.75 singlet, 7.50 multiplet, 6.75 multiplet, no vinyl proton, with intensity ratios 6:4:2:5:4, respectively.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00. Found: C, 71.47; H, 8.73.

Treatment of 400 mg. of II in 5 ml. of water with perchloric acid gave II perchlorate. Recrystallization from ethyl acetate–ethanol gave 200 mg., m.p. 164–165°; $\lambda_{\max}^{\mathrm{EtOH}}$ 274 mμ (ε 12,700), 310 (17,000).

Anal. Calcd. for $C_{14}H_{22}ClNO_6$: C, 50.07; H, 6.61; Cl, 10.56. Found: C, 49.89; H, 6.50; Cl, 10.80.

In the reaction of I with 0.5 mole of acetyl bromide, I hydrobromide and unchanged I were the only products. If an excess of acetyl bromide (>1.0 mole) was used, II was isolated in low yield.

B. Reaction of I with Acetic Anhydride.—The enamino ketone I (2.45 g., 0.013 mole) in acetic anhydride (30 ml.) was refluxed for 3 hr. The acetic anhydride was removed by distillation *in vacuo*. The residue was recrystallized from benzene–hexane to give II (1.7 g., 59%), m.p. 157–159°, not depressed in admixture with authentic material above.

Reaction of I with Acetyl Chloride in the Presence of Triethylamine.—To a solution of the enamino ketone I (4.9 g., 0.025 mole) and triethylamine (3 g., 0.03 mole) in benzene (70 ml.) was added acetyl chloride (2.0 g., 0.0255 mole) in benzene (20 ml.), and the reaction mixture heated at 60–65° for 6 hr. On cooling, triethylamine hydrochloride (3.5 g., 0.0252 mole ≡ 100%) was removed by filtration, and the benzene filtrate was evaporated to give 6 g. of a very viscous oil. Chromatography or several recrystallizations from benzene–methylcyclohexane gave I (3.8 g.), m.p. 129–131°, not depressed in admixture with authentic starting material.

Attempted Reaction of I with Diketene.—The enamino ketone I (4.9 g., 0.025 mole) and freshly distilled diketene (2.2 g., 0.026 mole) in benzene (70 ml.) were heated at the reflux temperature for 5 hr. On evaporation, 7 g. of a solid mixed with tar were obtained. Recrystallization from benzene–methylcyclohexane gave I (3 g.), m.p. 130–132°, identical with authentic starting material.

Attempted Reaction of I with Propionyl Chloride.—The enamino ketone I (4.9 g., 0.025 mole) in benzene (70 ml.) was heated with propionyl chloride (1.2 g., 0.013 mole) in benzene (20 ml.) at 70° for 3 hr. On cooling, I hydrochloride (3.0 g., 0.013 mole ≡ 100%), m.p. 224–228°, was removed by filtration. Evaporation of the filtrate gave 3.0 g. of a yellow oil. Chromatography over alumina and crystallization from benzene–methylcyclohexane gave I (1.5 g.), m.p. 129–131°, not depressed in admixture with authentic material.

2-Benzoyl-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (IIIa).—To a solution of the enamino ketone I (4.9 g., 0.025 mole) in benzene (50 ml.) was added benzoyl chloride (1.9 g., 0.0135 mole) in benzene (25 ml.), and the reaction mixture heated at 80° for 3 hr., during which time a solid precipitated. On cooling, filtration gave the hydrochloride of the starting enamino ketone (2.8 g., 98%), m.p. and m.m.p. 228–230°. The filtrate

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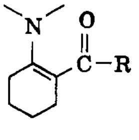
[6] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

[7] A. W. Crossley and J. Renouf [*J. Chem. Soc.*, **101**, 1525 (1912)] report that 5,5-dimethylcyclohexane-1,3-dione may be C-acylated with acetic anhydride in the presence of sodium acetate and O-acylated by rigid exclusion of base. In the reaction of I with acetic anhydride under the above conditions only C-acylation was observed.

[8] The O-acylation by Hünig, *et al.*,[3] is readily understood in view of the absence of a vinyl hydrogen in the enamino ketone involved.



Thus, C-acylation in this case would be equivalent to the disubstitution of this enamine at the same carbon, which has not been observed.[6]

[9] Attack at C-1 cannot be attributed to steric effects at the carbonyl carbon, because pivalyl chloride and I afford C-acylated product IV.

[10] Melting points were taken with a Mel-Temp capillary melting point apparatus and are uncorrected. Ultraviolet spectra were taken on a Beckman DK2A spectrometer in ethanol solution. N.m.r. spectra were taken with a Varian A60 instrument in deuteriochloroform solution using tetramethylsilane as internal standard.

evaporated *in vacuo* gave 3.7 g. (98%) of oily IIIa which was recrystallized from benzene–methylcyclohexane to give m.p. 164–165°, $\lambda_{\max}^{\text{EtOH}}$ 299 mμ (ϵ 23,000). The compound showed no carbonyl absorption in the infrared spectrum below 6.0 μ; n.m.r. spectrum, τ 8.85 singlet, 8.20 multiplet, 7.75 singlet, 7.48 singlet, 6.78 multiplet, 2.62 multiplet, no vinyl proton, with intensity ratios 6:4:2:2:4:5, respectively.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79; N, 4.71. Found: C, 76.32; H, 7.85; N, 4.20.

2-(3,4-Dichlorobenzoyl)-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (IIIb).—To a solution of the enamino ketone I (4.9 g., 0.025 mole) in 50 ml. benzene was added 3,4-dichlorobenzoyl chloride (5.3 g., 0.025 mole) in 40 ml. of benzene. The reaction mixture was refluxed for 2.5 hr., during which time a solid precipitated. On cooling, filtration gave 7.3 g. of solid. The solid was boiled with 50 ml. of water when filtration gave 3.85 g. of yellow solid, m.p. 225–230°. Recrystallization from aqueous ethanol gave pure IIIb, m.p. 228–230°; $\lambda_{\max}^{\text{EtOH}}$ 298 mμ (ϵ 28,000); n.m.r. spectrum, τ 8.90 singlet, 8.17 multiplet, 7.80 singlet, 7.50 singlet, 6.82 multiplet, 2.60 multiplet, no vinyl proton, with intensity ratios of 6:4:2:2:4:3, respectively.

Anal. Calcd. for $C_{19}H_{21}Cl_2NO_2$: C, 62.29; H, 5.78; N, 3.82; Cl, 19.36. Found: C, 62.03; H, 6.03; N, 3.89; Cl, 18.9.

The yield was 40% calculated on the starting enamino ketone or 80% if allowance is made for the enamino ketone used to take up hydrochloric acid. The aqueous filtrate above was evaporated to dryness, and the residue taken up in a minimum amount of water. Addition of perchloric acid gave a precipitate which, on crystallization from ethyl acetate–ethanol, had m.p. 179–181°, not depressed in admixture with the perchlorate of the starting enamino ketone of the same melting point.[2a]

2-(4-Nitrobenzoyl)-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (IIIc).—To a solution of the enamino ketone I (4.9 g., 0.025 mole) in benzene (70 ml.) was added a solution of *p*-nitrobenzoyl chloride (2.3 g., 0.0125 mole) in benzene (10 ml.). The reaction mixture was heated at 50–60° for 4 hr. during which time a solid precipitated. Cooling and filtration gave the hydrochloride of the starting enamino ketone (2.8 g., 98%), m.p. and m.m.p. 228–230°. Evaporation of the filtrate gave crude IIIc (3.0 g., 70%), which recrystallized from ethanol as orange needles, m.p. 203–205°, $\lambda_{\max}^{\text{EtOH}}$ 300 mμ (ϵ 17,000). The compound showed no carbonyl absorption in the infrared spectrum below 6 μ; n.m.r. spectrum, τ 8.85 singlet, 8.08 multiplet, 7.75 singlet, 7.42 singlet, 6.75 multiplet, 1.95 quadruplet, no vinyl proton, with intensity ratios of 6:4:2:2:4:4, respectively.

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.71; H, 6.66; N, 7.97.

2-Pivalyl-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (IV).—The enamino ketone I (3.9 g., 0.02 mole) and pivalyl chloride (2.5 g., 0.021 mole) in xylene (50 ml.) were heated under reflux for 4 hr. After cooling, the precipitated I hydrochloride (2.7 g., 0.0118 mole), m.p. 228–230°, not depressed in admixture with authentic material, was filtered. The filtrate was evaporated to dryness *in vacuo* and the residue chromatographed over alumina. Elution with benzene afforded crude IV (0.9 g., 30%), m.p. 138–142°. Recrystallization from chloroform–methylcyclohexane gave pure IV, m.p. 144–146°, as needles; $\lambda_{\max}^{\text{EtOH}}$ 305 mμ (ϵ 23,000); n.m.r. spectrum, τ 8.80 singlet, 8.72 singlet, 8.10 multiplet, 7.80 singlet, 7.58 singlet, 6.77 multiplet, no vinyl proton, with intensity ratios of 6:9:4:2:2:4, respectively.

Anal. Calcd. for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.52; H, 10.00; N, 5.18.

2-(3,4-Dichlorobenzoyl)-5,5-dimethyl-3-N-morpolycyclohex-2-en-1-one (VI).—5,5-Dimethyl-3-N-morpholylcyclohex-2-en-1-one[1] (V, 4.2 g., 0.02 mole) and 3,4-dichlorobenzoyl chloride (2.1 g., 0.01 mole) in benzene (70 ml.) were heated under reflux for 3 hr. After cooling, the precipitated V hydrochloride (2.3 g., 98%), m.p. 234–236°, not depressed in admixture with authentic material,[1] was filtered. Evaporation of the filtrate gave a residue, which on recrystallization from chloroform–methylcyclohexane gave pure VI (2.0 g., 53%), m.p. 216–218°; $\lambda_{\max}^{\text{EtOH}}$ 302 mμ (ϵ 26,000), 255 (13,000).

Anal. Calcd. for $C_{19}H_{27}Cl_2NO_3$: C, 59.69; H, 5.54; N, 3.66; Cl, 18.55. Found: C, 59.29; H, 5.78; N, 3.58; Cl, 18.88.

Attempted Reaction of V with Acetyl Chloride.—The enamino ketone V (5.2 g., 0.025 mole) and acetyl chloride (1.0 g., 0.013 mole) in benzene (70 ml.) were heated under reflux for 2 hr. The precipitated V hydrochloride (3.1 g., 100%), m.p. 234–236°, not depressed in admixture with authentic material, was filtered after allowing the reaction mixture to cool. The filtrate was evaporated to dryness *in vacuo*, and the residue was recrystallized from benzene–methylcyclohexane to give V (2.0 g.), m.p. 127–128°, not depressed in admixture with authentic starting enamino ketone.

Attempted Reaction of V with Acetic Anhydride.—The enamino ketone V (2.1 g., 0.01 mole) in acetic anhydride (10 ml.) was heated under reflux for 1 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was crystallized from benzene–methylcyclohexane to give starting material V, m.p. 126–128°, not depressed in admixture with an authentic sample.

2-(2-Nitrophenylthio)-5,5-dimethyl-3-N-pyrrolidylcyclohex-2-en-1-one (VII).—The enamino ketone I (1.95 g. 0.01 mole) and 2-nitrobenzenesulfenyl chloride (2.0 g., 0.0105 mole) in benzene (50 ml.) were heated at reflux temperature for 4 hr. After cooling, the precipitated solid (consisting of the product and I hydrochloride, 3.1 g.) was filtered. Recrystallization from aqueous methanol gave VII as orange needles (1.6 g., 92%), m.p. 176–178°; $\lambda_{\max}^{\text{EtOH}}$ 242 mμ (ϵ 11,500), 306 (19,500); n.m.r. spectrum, τ 8.85 singlet, 8.17 multiplet, 7.62 singlet, 7.47 singlet, 6.30 multiplet, 2.75 multiplet, no vinyl proton, with intensity ratios of 6:4:2:2:4:4, respectively.

Anal. Calcd. for $C_{18}H_{22}N_2O_3S$: C, 62.40; H, 6.40; N, 8.09; S, 9.26. Found: C, 62.13; H, 6.34; N, 7.81; S, 9.09.

Treatment of a methanolic solution of VII with 70% perchloric acid gave a crystalline perchlorate as yellow needles, m.p. 212° dec.; $\lambda_{\max}^{\text{EtOH}}$ 242 mμ (ϵ 16,000), 309 (22,000).

Anal. Calcd. for $C_{18}H_{23}ClN_2O_7S$: C, 48.37; H, 5.19; N, 6.27; Cl, 7.93; S, 7.17. Found: C, 48.26; H, 5.16; N, 6.13; Cl, 7.81; S, 7.23.

Acknowledgment.—Our sincere thanks are due to Professor N. J. Leonard for many helpful and stimulating discussions.