

STUDIES ON REACTIVE INTERMEDIATES. PART VI.¹⁾ SYNTHESIS OF
BENZO[a]QUINOLIZINES VIA METHYLKETENE DIMER

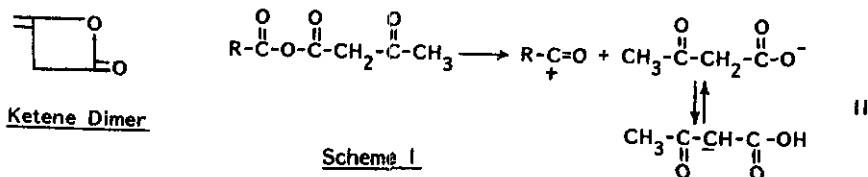
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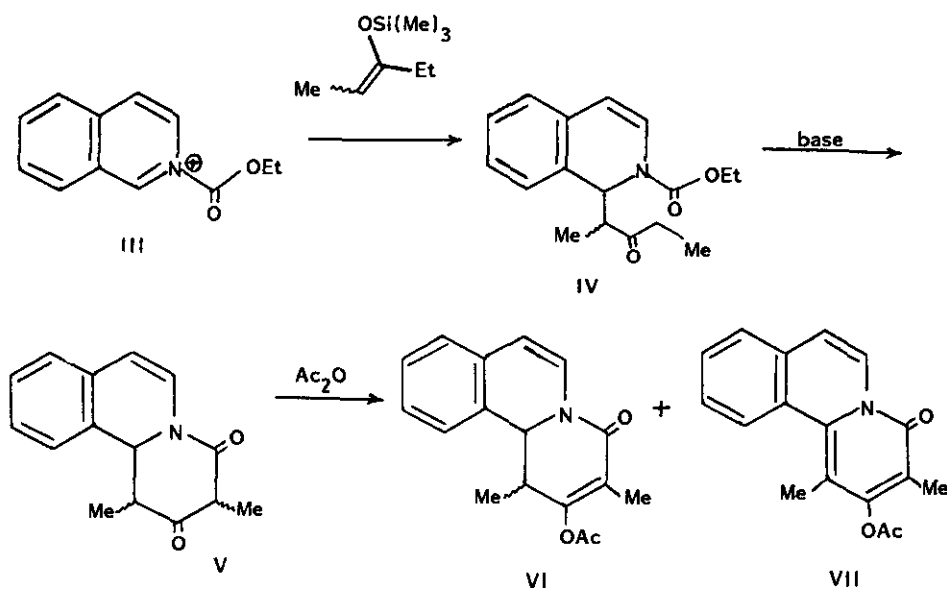
Abstract- Reaction of methylketene dimer with isoquinoline in neat condition or refluxing ether resulted in the formation of 2-hydroxy-1,3-dimethyl-4-oxo-4H-benzo[a]quinolizine (VIII) in 55% yield. The reaction in acetic acid gave rise to 2-acetoxy-1,3-dimethyl-4-oxo-1,4-dihydro-11bH-benzo[a]quinolizine (VI) and 2-acetoxy-1,3-dimethyl-4-oxo-4H-benzo[a]quinolizine (VII) in 40% and 45% yields, respectively. Compound VI has been reported as one of the precursors of emetine type alkaloids.

Since the last decades, ketene dimer, 4-methylene-2-oxetanone, has been used as an acetoacetyl group equivalent synthon in organic synthesis, and hundreds of articles have been published concerning its reactivity and utilization. Depending upon the reaction condition, ketene dimer shows different reactivities toward nucleophiles. For example, in neat condition or non-polar solvents, it acts as an intact molecule, while, in carboxylic acid medium, it is reported to act as an anion of acetoacetic acid through the formation of a mixed anhydride of type II²⁻⁴⁾ (Scheme I).



β -dicarbonyl group equivalent source for the heterocyclic synthesis. In this article, we wish to introduce methylketene dimer, 4-ethylidene-3-methyl-2-oxetanone (III), and report its reactivity toward C=N double bond in aromatic nuclei.

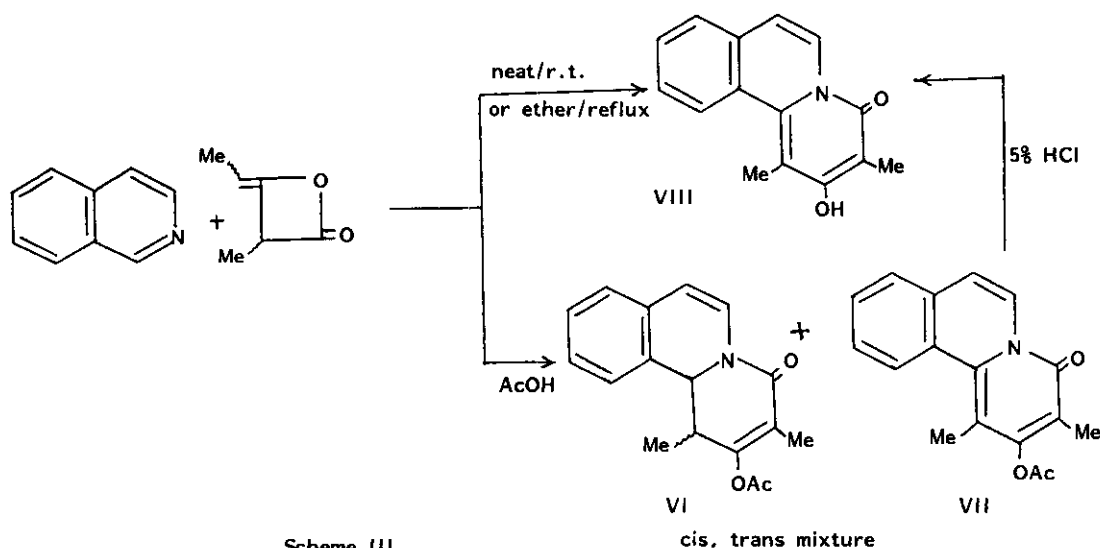
Isoquinoline was selected as a source of C=N double bond, because of its involvement in some alkaloid skeletons. Akiba et al. have reported the synthesis of the benzo[a]quinolizine derivatives V, VI, and VII in a series of their attempts to achieve totally synthetic emetine.⁵⁾ Scheme II.



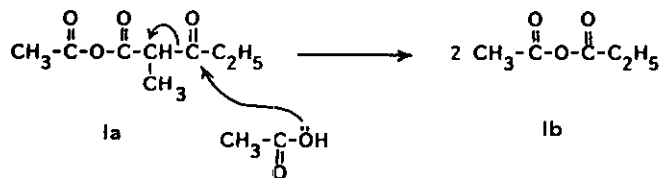
Scheme II

Structural consideration of these compounds revealed that the trimethylsilyl enol ether derivative can be essentially substituted by a β -dicarbonyl group equivalent source, in order to shorten and simplifying the synthetic route. In the course of our studies on the chemistry of methylketene dimer, we found it a good substitute for the trimethylsilyl enol ether. Namely, when an equimolar amount of methylketene dimer and isoquinoline were allowed to react in neat condition at room temperature or refluxing ether, after work up, pale yellow needles were obtained in 55% yield. Structural assignment was carried out upon spectral and analytical data as 2-hydroxy-1,3-dimethyl-4-oxo-4H-benzo[a]-quinolizine (VIII). When the reaction was carried out in acetic acid, using two equivalent methylketene dimer, two products were isolated in 40% (VI) and 45% (VII) yields, respectively. On the basis of elemental analysis, spectral data, and chemical reactions, their structures were determined as 2-acetoxy-1,3-dimethyl-4-oxo-1,4-dihydro-11bH-benzo[a]quinolizine (VI) and 2-acetoxy-1,3-dimethyl-4-oxo-4H-benzo[a]quinolizine (VII). The physical and spectral data of compounds VI and VII are in full agreement with those reported by Akiba et al.⁵⁾ On refluxing with 5% solution of HCl,

compound VII transferred to compound VIII, quantitatively (Scheme III).

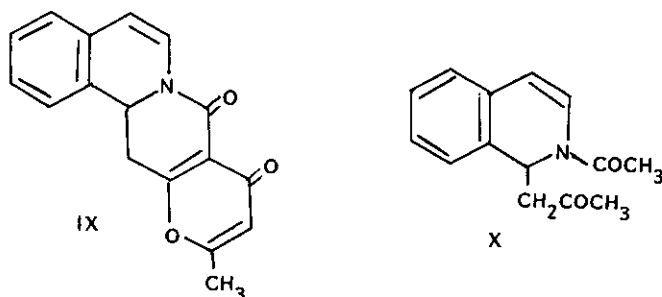


The reaction is considered to proceed through N-acylation of isoquinoline followed by further cyclization to compound V, which consequently oxidized to compound VIII under reaction condition. In acetic acid, a mixed anhydride of type Ia or Ib, which were considered to be formed through the attack of acetic acid to the carbonyl carbon of methylketene dimer followed by the ring opening to form Ia, and/or further attack of acetic acid to the intermediate Ia to form acetyl propionyl anhydride (Ib), are thought to be involved in the acylation of compound V to form compound VI. This fact is proved by the observation of a band at 1820 cm^{-1} in the infra-red spectrum of the reaction mixture.⁶⁾ Compound VII could be considered as an oxidation product of VI during the course of the reaction. Actually, oxidation of VI to VII is also explained by Akiba et al. due to the instability of compound VI toward air-oxidation.⁵⁾



Comparing these results with those of ketene dimer with isoquinoline, which terminated to the formation of the Wollenberg type compound (IX)⁷⁾ or 1,2-dihydroisoquinoline (X)⁴⁾, it is concluded that in contrast to the case of ketene dimer, methylketene dimer acts as an intact molecule in its reaction with isoquinoline regardless to the reaction conditions, and the reaction terminates by the involvement of only one molecule of methylketene dimer. This fact could be explained by the positive inductive effect of the methyl group, substituted on 3- and exo-methylene positions of the ketene dimer

molecule, which confer its stability and less reactivity toward nucleophiles.



EXPERIMENTAL

Melting points were determined on a Kopfler hot stage microscope and are uncorrected. The ^1H -nmr spectra were obtained from a Varian T-60 spectrometer, and chemical shifts (δ) are expressed in ppm relative to tetramethylsilane as an internal standard. Ir spectra were obtained from a Unicam SP 1000 infra-red spectrometer. Mass spectra were determined on a Varian Model Mat CH5 instrument. Methylketene dimer was prepared according to the J.C. Saure's method^{8,9} by dehydrohalogenation of propionyl chloride in the presence of triethylamine-triethylamine HCl, as a cis-trans mixture (1:1), in 66% yield. Bp₃₀ 70° C (lit.^{8,9}) bp₁₂ 57-58° C).

Synthesis of 1-Hydroxy-1,3-dimethyl-4-oxo-4H-benzo[a]quinolizine (VIII)

Method A- Methylketene dimer (1.12 g, 10 mmole) was added to isoquinoline (1.29 g, 10 mmole) while stirring in an ice-bath. A mild exothermic reaction occurred. The reaction mixture was then transferred to room temperature. After 15 min, the mixture turned to orange-yellow, which was then diluted with acetone (10 ml) and allowed to stand at room temperature for two days. The pale yellow crystals thus obtained were purified by recrystallization from EtOH to pale yellow prisms (1.31 g, 55% yield), mp 195-197° C. Ms: 239 (M^+). ^1H -Nmr (CF_3COOH) δ : 2.40 (3H, s), 2.70 (3H, s), 6.40 (1H, d, $J=8\text{Hz}$), 7.80-8.50 (4H, m), 8.95 (1H, d, $J=8\text{Hz}$). Ir (KBr) cm^{-1} : 3200, 1635, 1580. Anal. calcd. for $\text{C}_{15}\text{H}_{13}\text{NO}_2$ (VIII): C, 75.30; H, 5.48; N, 5.85. Found: C, 75.55; H, 5.38; N, 5.50.

Method B- Methylketene dimer (1.12g, 10 mmole) was added dropwise to a solution of isoquinoline (1.29 g, 10 mmole) in ether (10 ml) at room temperature. The resulting solution was refluxed on a water-bath. A colorless precipitate was formed gradually, which disappeared later. After 30 min, the reaction mixture turned to orange-yellow. Ether was removed from the reaction mixture, and acetone (10 ml) was added to the residue. The resulting solution was kept at room temperature for

2 days, and the pale yellow needles formed were purified by recrystallization from EtOH to pale yellow needles of mp 195-197°C. Physical and spectral characteristics of this compound were identical, in every respect with those of compound VIII obtained from the method A. Yield: 1.43 g(60%).

Synthesis of 2-Acetoxy-1,3-dimethyl-4-oxo-1,4-dihydro-11bH-benzo[a]quinolizine (VI) and 2-Acetoxy-1,3-dimethyl-4-oxo-4H-benzo[a]quinolizine (VII)

Methylketene dimer (4.48 g, 40 mmole) was added dropwise to a solution of isoquinoline (2.58 g, 20 mmole) in glacial acetic acid (10 ml). An exothermic reaction occurred, and the mixture turned to yellow. The reaction mixture was kept at room temperature for 4 days. Acetic acid was removed at reduced pressure, and the residue was chromatographed on silica gel using ether as an eluant. The first fraction was collected and concentrated. The residual oil was dissolved in EtOH (10 ml) and kept at room temperature overnight. The pale yellow prisms (VI) obtained were collected and dried (2.264 g, 40% yield). Mp 45°C (cis-trans mixture). Ms : 283 (M⁺). ¹H-Nmr (CDCl₃) δ : 1.20 (3H, d, J=7Hz), 1.80 (3H, s), 2.20 (3H, s), 2.80-3.85 (1H, m), 4.35-5.18 (1H, m), 5.78 (1H, d, J=8Hz), 6.85-7.25 (4H, m), 7.35 (1H, d, J=8Hz). Ir (KBr) cm⁻¹ : 2190, 1756, 1635. Anal. Calcd. for C₁₇H₁₇NO₃ (VI) : C, 72.06; H, 6.05; N, 4.94. Found : C, 71.86; H, 6.15; N, 4.85.

The filtrate was kept at room temperature for 2 days, and the pale yellow crystals obtained were collected and purified by recrystallization from EtOH to pale yellow needles (VII)(2.50 g, 45% yield). Mp 170-174°C. Ms: 281 (M⁺). ¹H-Nmr (CDCl₃) δ : 2.20 (3H, s), 2.42 (3H, s), 2.52 (3H, s), 6.95 (1H, d, J=8Hz), 7.30-7.82 (3H, m), 8.10-8.46 (1H, m), 8.75 (1H, d, J=8Hz). Ir (CHCl₃) cm⁻¹ : 1755, 1650, 1635. The physical and spectral characteristics of compound VII, obtained in this reaction, is identical in every respect with that reported by Akiba et al.⁵⁾

Acid Hydrolysis of Compound VII to Compound VIII

A mixture of compound VII (0.281 g, 1 mmole) in 5% HCl (5 ml) was refluxed for 1 h. After cooling, the reaction mixture was neutralized by a saturated solution of NaHCO₃. The resulting mixture was extracted by CHCl₃ (3x20 ml), and the extract was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give pale yellow crystals of mp 195-197°C, undepressed on admixture with a sample of compound VIII, obtained from the above reaction, in quantitative yield. The spectral data of this compound was in full agreement with those of compound VIII.

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