Registry No.—**4**, 6460-83-9; **5**, 41328-60-3; **6**, 711-78-4; **6**-^{18}O, 41328-63-6; **6**-$^{18}O_2$, 41391-12-2; **6**-$^{18}O_3$, 41328-64-7; **7**, 708-10-1; **7**-$^{18}O_3$, 41328-66-9; **8**, 22118-96-4; **8**-^{18}O, 41328-68-1; **9**, 29769-75-3; **9**-$^{18}O_2$, 41328-70-5; 2,6-dimethylphenylisonitrile, 2769-71-3.

Abnormal Michael Reaction. The Reaction between 2-Cyclohexenone and Diethyl Methylmalonate

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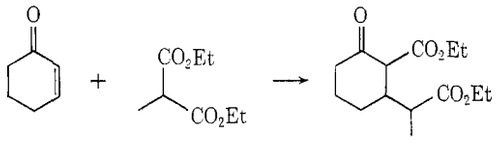
Although the abnormal Michael reaction has been investigated for a number of years, the synthetic aspects of this reaction have not been studied.[1-7] Recently, we have been interested in developing new syntheses of the sesquiterpene series, and thought that the reaction between 2-cyclohexenone and diethyl methylmalonate under these conditions would afford, if successful, the β-keto ester **1**, which could be a potential precursor for the synthesis of the cadalene family.



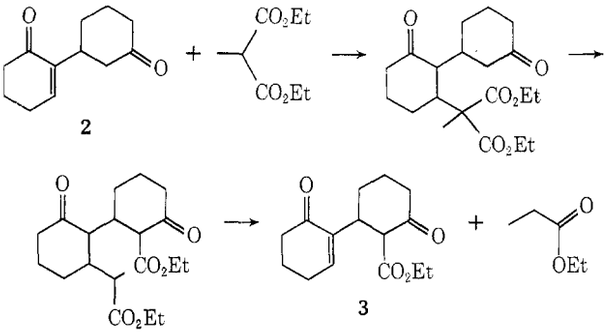
1

On investigating this reaction, we found that the reaction failed under the usual abnormal Michael conditions.[2] Distillation of the reaction mixture afforded only starting materials. Extending the reaction time did not affect the reaction course; however, when the concentrations of both reactants were increased, a reaction did occur. Under these modified conditions, the reaction mixture gave a positive ferric chloride test, and distillation of this mixture afforded ethyl propionate, diethyl methylmalonate, and 2-(3-oxocyclohexyl)-2-cyclohexenone (**2**). We were unable to distill any substance which displayed a positive ferric chloride test from the mixture.

Thick layer chromatographic analysis of the remaining oil afforded a band which gave the enol test. Extraction of this band with methanol and subsequent 2,4-dinitrophenylhydrazone formation yielded a crystalline compound which analyzed for $C_{21}H_{24}N_4O_7$. Based upon nmr analysis, the hydrazone appears to be a derivative of 2-(2-ethoxycarbonyl-3-oxocyclohexyl)-2-cyclohexenone (**3**). In addition to the characteristic signals due to the protons of the 2,4-dinitrophenyl nucleus, the derivative has a complex series of signals at δ 1.5–2.5, a quartet centered at δ 4.05, and a complex multiplet at δ 7.42. The upfield portion of the spectrum and the signal in the vinyl region are very similar to the signals in the spectrum of 2-(3-oxocyclohexyl)-2-cyclohexenone.

(1) A. Michael, *J. Prakt. Chem.*, **35**, 349 (1887).
(2) A. Michael and J. Ross, *J. Amer. Chem. Soc.*, **55**, 1632 (1932).
(3) N. E. Holden and A. Lapworth, *J. Chem. Soc.*, 2368 (1931).
(4) A. Michael, *J. Org. Chem.*, **2**, 303 (1937).
(5) E. D. Bergmann, D. Ginsberg, and R. Pappo, *Org. React.*, **10**, 191 (1959).
(6) G. E. Risinger and H. Dupont Durst, *Chem. Ind. (London)*, 1647 (1967).
(7) R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).

The isolation of **2** and **3** suggests the following conversion.



2

3

In order to test this reaction scheme, we prepared 2-(3-oxocyclohexyl)-2-cyclohexenone[8] and subjected it to abnormal Michael conditions. Analysis of this mixture revealed the presence of the same reaction products as in the 2-cyclohexenone reaction. Distillation afforded ethyl propionate, diethyl methylmalonate, and **2**; thick layer chromatography of the residue yielded a single positive ferric chloride band which gave a 2,4-dinitrophenylhydrazone identical with the one produced from the 2-cyclohexenone sequence.

Thus, it appears that the facile conversion of 2-cyclohexenone into **2** precludes the employment of the abnormal Michael reaction in the synthesis of cyclic terpenoid systems.

Experimental Section

Reaction of Diethyl Methylmalonate with 2-Cyclohexenone with a Minimum of Solvent.—Diethyl methylmalonate (8.7 g, 0.05 mol) and 2-cyclohexenone (4.8 g, 0.05 mol) were refluxed in a solution of sodium (1.15 g, 0.05 mol) in absolute ethanol (25 ml) for 24 hr under nitrogen. The reaction mixture was neutralized, taken up in ether (100 ml), and washed with water (2 × 50 ml). The ether was dried and concentrated to give a crude oil (10.0 g). Distillation of this oil gave ethyl propionate (0.2 g, 22%), diethyl methylmalonate (2.8 g, 32%), and 2-(3-oxocyclohexyl)-2-cyclohexenone (**2**): 1.1 g (23%); bp 132–134° (4 mm); ir (CCl_4) 5.82 (C=O), 5.95 μ (α,β-unsaturated C=O); uv max (95% EtOH) 233 mμ; nmr ($DCCl_3$) δ 6.74 (t, 1). Chromatography of the crude oil (silica; elution with 3% ethyl acetate in heptane) followed by extraction of the enolic band with methanol gave a yellow oil (0.050 g): 2,4-dinitrophenylhydrazone mp 182–184°; nmr ($DCCl_3$) δ 9.11 (d, 1), 8.30 (d, 1), 7.94 (d, 1), 7.42 (m, 1), 4.05 (m, 2).

Anal. Calcd for $C_{21}H_{24}N_4O7$: C, 56.76; H, 5.41; N, 12.61. Found: C, 56.58; H, 5.55; N, 12.97.

Preparation of 2-(3-Oxocyclohexyl)-2-cyclohexenone.—2-Cyclohexenone (9.6 g, 0.1 mol) was treated with a solution of sodium (0.23 g, 0.01 mol, in 100 ml of ethanol) at 0° for 72 hr. Neutralization and concentration gave a crude mixture, which was taken up in diethyl ether (100 ml) and washed with water (2 × 50 ml). The ether layer was dried (Na_2SO_4) and concentrated. The resulting oil afforded 3-ethoxycyclohexanone (0.8 g, 6%) and 2-(3-oxocyclohexyl)-2-cyclohexenone (**2**) (3.2 g, 33%) which was identical with the compound produced in the reaction between diethyl methylmalonate and 2-cyclohexenone.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 75.18; H, 7.99.

Reaction between 2-(3-Oxocyclohexyl)-3-cyclohexenone and Diethyl Methylmalonate.—2-(3-Oxocyclohexyl)-2-cyclohexenone (7.7 g, 0.08 mol) and diethyl methylmalonate (13.9 g. 0.08 mol) in absolute ethanol (20 ml) were refluxed in the presence of sodium (1.8 g, 0.08 mol) for 24 hr under nitrogen. The reaction mixture was neutralized, taken up in ether, and washed with water. The ethereal solution was dried (Na_2SO_4) and concentrated. Subsequent distillation of the oil yielded ethyl propionate, diethyl methylmalonate, and 2-(3-oxocyclohexyl)-2-cyclohexenone. Chromatography of the pot residue and subsequent treatment of the enol component with 2,4-dinitrophenyl-

(8) J. E. Englehart and J. R. McDivitt, *J. Org. Chem.*, **36**, 367 (1971).

hydrazine yielded a 2,4-dinitrophenylhydrazone which was identical with the $C_{21}H_2N_4O_7$ derivative isolated from the 2-cyclohexenone reaction.

Registry No.—**2**, 5216-84-2; **3** dinitrophenylhydrazone, 41008-55-3; diethyl methylmalonate, 609-08-5; 2-cyclohexenone, 930-68-7.

Photochemistry of Diazonium Salts. III. A New and Facile Synthesis of 4-Fluoroimidazoles

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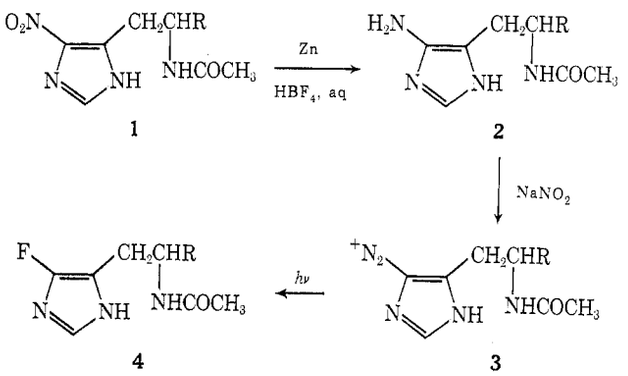
In paper I of this series,[1] we described the synthesis of a variety of 4-fluoroimidazoles, based on the irradiation of 4-diazonium imidazoles in aqueous tetrafluoroboric acid. Since the immediate precursors of the diazonium salts, 4-aminoimidazoles, are often too unstable for isolation, indirect and tedious synthetic routes were found necessary. Thus, 4-aminoimidazole itself was generated, *in situ*, by acid cleavage of its *tert*-butoxycarbonyl derivative; the latter compound was derived from ethyl imidazole-4-carboxylate by a three-step procedure. Other 4-fluoroimidazoles (*e.g.*, 4-fluoro-L-histidine, **4a**) were obtained by converting the stable 4-aminoimidazole-5-carboxylic esters to 4-fluoro analogs, followed by synthetic elaboration of the side chain, as necessary. Thus, the synthesis of 4-fluorohistamine required a sequence of nine steps from the commerically available 4-aminoimidazole-5-carboxamide. Subsequent to our announcement of these compounds,[1,2] extensive interest developed in the synthesis of polypeptide analogs containing 4-fluoro-L-histidine,[3] as well as in the pharmacological and enzymatic properties of the amino acid and the amine. This interest emphasized to us the fact that considerably larger quantities of these compounds would be required than could be obtained practically by our published procedures.

Initial attempts to exploit the readily available 4-nitroimidazoles as precursors were thwarted, repeatedly, by the instability of the amines. For example, catalytic hydrogenation of 4-nitroimidazole, followed by rapid work-up of the product under nitrogen and either in the presence or absence of tetrafluoroboric acid, resulted in extensive decomposition, as evidenced by insoluble dye formation. Diazotization and irradiation of the crude reduction products in tetrafluoroboric acid solution resulted in recoveries of only trace amounts of 4-fluoroimidazole. Catalytic reductions in other solvents, including 50% tetrafluoroboric acid itself, were similarly fruitless; however, the nitroimidazole was rapidly reduced with zinc dust in the same fluoroboric acid system and with little evidence of decomposition of the product. The aminoimidazole so formed can be diazotized and irradiated *in situ*. Thus, 4-nitroimidazole was rapidly reduced to 4-aminoimidazole at −10 to 0° (nitrogen atmosphere), progress of the reduction being monitored by disappearance of the chromophore at 298 nm. When reduction was complete, 1 equiv of sodium nitrite was added, generating a diazonium ion chromophore at 270 nm. The solution was subjected to irradiation at 0°, progress of the reaction being monitored by loss of the diazonium ion chromophore. From the reaction mixture, 4-fluoroimidazole was obtained in 17% yield. Considering the ready availability of 4-nitroimidazole and the fact that no intermediates were isolated, this overall yield is quite acceptable, and compares favorably with that reported previously.[1] With 4-nitro-5-methylimidazole, a 37% yield of the fluoro derivative was obtained by use of the same procedure.

In our earlier synthesis of 4-fluoro-L-histidine, an overall yield of 1.5% was obtained after eight steps, beginning with 4-aminoimidazole-5-carboxamide. 4-Fluorohistamine was obtained in 0.7% yield after nine steps from the same starting point. Recent development of the direct nitration of histidine and histamine (and their derivatives)[4,5] widened the range of accessible nitroimidazoles, and led us to explore the simplified synthetic approach with the more complex compounds. Indeed, α-*N*-acetyl-4-nitro-L-histidine methyl ester (**1a**) was converted into its fluoro analog **4a** in 10% yield, and α-*N*-acetyl-4-nitrohistamine (**1b**) was converted into its fluoro analog **4b** in 18% yield.



a, R = $COOCH_3$
b, R = H

Removal of the blocking groups from these derivatives incurs no losses.

This considerable facilitation of the syntheses of the histidine and histamine analogs removes the principal obstacle to expansion of a wide variety of biochemical and pharmacological studies, either already under way or being planned. A relatively broad spectrum of functional groups can be introduced into the imidazole ring (both at C-2 and at C-4) by photochemical decomposition of the respective diazonium ions.[6] These syntheses are also made more inviting and practical by the

(1) K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **95**, 4619 (1973).

(2) A preliminary report was presented at the Symposium on Fluorine in Medicinal Chemistry, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971; see also K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **93**, 3060 (1971).

(3) See, *e.g.*, B. M. Dunn, C. DiBello, and I. M. Chaiken, *Fed. Proc.*, **32**, 541 (1973). Reports of other studies are in preparation.

(4) W. Tautz, S. Teitel, and A. Brossi, *J. Med. Chem.*, **16**, 705 (1973). We are indebted to these investigators for providing us with experimental details of the nitration procedure prior to publication.

(5) (a) Racemic 4-nitrohistidine has been obtained by synthetic elaboration of the side chain in 4-chloromethyl-5-nitroimidazole: G. E. Trout, *J. Med. Chem.*, **15**, 1259 (1972). (b) Nitration of α-*N*-acetyl-L-histidine, under more vigorous conditions, has been reported to yield a racemic, dinitrated product of unknown structure: N. P. Buu-Hoi and C. Lepoivre, *C. R. Acad. Sci.*, **257**, 3618 (1963).

(6) These studies are in progress and will be reported separately.