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Alkylation and Isomerization of 2-Carboxamido-3-ethyl-1-indenone and 2-Carboxamido-3-ethylidene-1-indanone[1]

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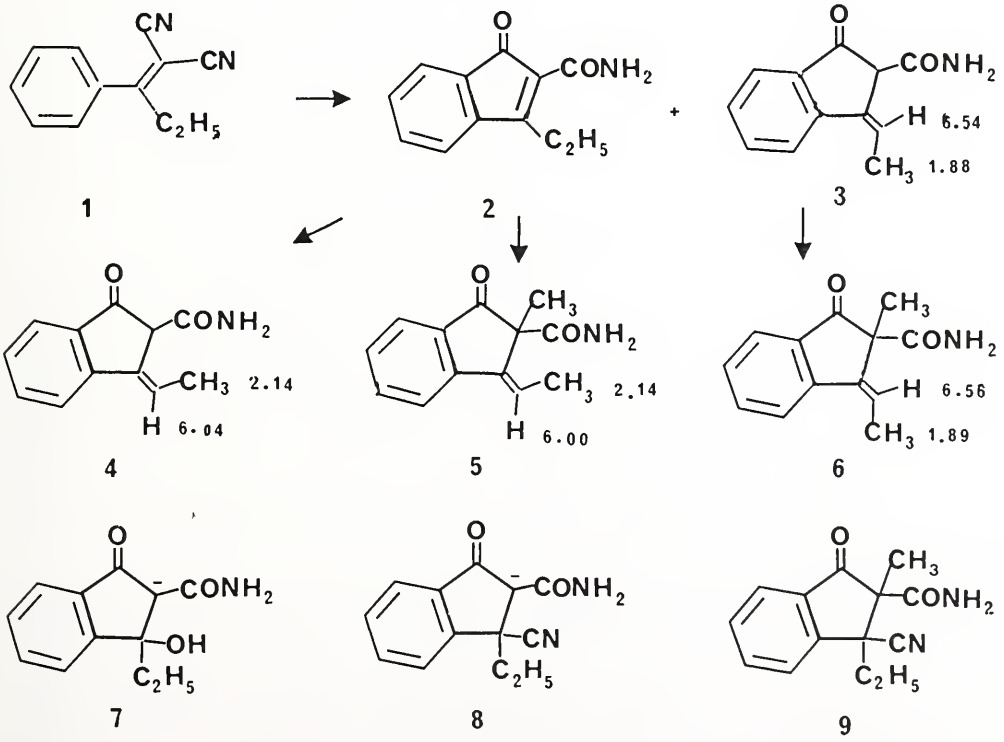
Introduction

We have recently reported on the Michael addition to indenones (4) and on the isomerization and alkylation of 2-carboxamido-3,4-trimethyleno-1-indenone (5). This compound is the only example in which the indenone isomer is the sole product from the acid cyclization of an ylidenemalononitrile having a gamma-hydrogen (13). The isomeric indanone has been obtained as an unstable white product which reverts to the parent indenone on melting or attempted recrystallization (5). Generally, the cyclization of an ylidenemalononitrile having a gamma-hydrogen, such as 2-cyano-3-ethylcinnamonitrile (1, Scheme 1) yields a mixture of the yellow indenone (2) and white indanone (3) in a ratio of about one part of 2 to two or three parts of 3 (1). These isomers can be separated by different solubilities in ether. The yellow indenone 2 melted at 150°, turned white and solidified, and melted again near the melting point of indanone 3, indicating the indanone isomer is the more stable of this pair.

Scheme 1



Discussion

Our previous study (5) would indicate that treatment of either 2 or 3 with sodium hydride and methyl iodide would give the same methylated indanone. However, treat-

ment of 2 in this way gave a product which melted 40° higher than the product for similar treatment of 3. The elemental analyses of these two products were the same, consistent with a methylated derivative, and the ultraviolet spectra were similar and typical of comparable unsaturated indanones (1,5). The infrared spectra were similar, but showed distinct differences in the finger-print region.

The difference in structure of these two isomeric indanones was established by pmr spectroscopy. Although both compounds exhibited aromatic and amide multiplets centered at δ 7.5 and a singlet for the C_2 methyl group at δ 1.43, the difference was in the chemical shifts of the vinyl hydrogen and methyl groups. The product derived from 2 had a methyl doublet (J = 7.5 cps) at δ 2.14 and a vinyl quartet (J = 7.5 cps) at δ 6.00. The product from 3 had a methyl doublet (J = 7.5 cps) at δ 1.89 and a vinyl quartet (J = 7.5 cps) at δ 6.56. The difference between the two isomers is in the configuration around the ethylidene double bond. The isomer derived from 2 has the methyl group deshielded, compared to the methyl group in the isomer derived from 3, and the reverse is true for the vinyl hydrogens. The configuration of the two isomers was assigned assuming that the substituent that is *cis*-oriented to the carboxamide group at C_2 would be deshielded more than the corresponding *trans*-isomer (7). Consequently the product from 2 is assigned as Z-2-carboxamido-2-methyl-3-ethylidene-1-indanone (5), and that derived from 3 is E-2-carboxamido-2-methyl-3-ethylidene-1-indanone (6).

Now that the chemical shifts of the vinyl hydrogen and methyl protons are known for both geometric isomers of the ethylidene group, the configuration of indanone 3, obtained by cyclization of 1, can be assigned. The chemical shift of the vinyl hydrogen is at δ 6.56 and the methyl group at δ 1.88. These values are almost identical to those of 6. Therefore the configuration of 3 is that shown on Scheme 1, E-2-carboxamido-3-ethylidene-1-indanone. The formation of only one indanone isomer from acid cyclization is surprising, but may depend on steric repulsion between the C_2 substituents and the ethyl group in the transition state. However, a more reasonable explanation involves coordination of one of the acidic methylene protons of the ethyl group with the negative carbonyl group of the amide in the protonated intermediate. Thus elimination of a methylene proton with electron migration and hydrolysis of the resulting vinylamine leads to 3. Since indanone 3 and the methylated indanone 6 have the same configuration, the formation of 6 from 3 must proceed by simple abstraction of the acid C_2 proton by sodium hydride followed by alkylation.

The reason for the formation of the more hindered Z-isomer 5, when indenone 2 is isomerized and alkylated, is not obvious. The base-catalyzed allylic rearrangements of 1-alkenes to either or both *cis* and *trans*-2-alkenes have been discussed by Cram (6), and the same logic can be applied to the base-catalyzed isomerization of 2. It has been found that in kinetically controlled processes the less stable *cis*-isomer is the preferred product, while the more stable isomer is formed in thermodynamically controlled processes. Since proton abstraction from 2 by sodium hydride is an irreversible process, the expected product would be the kinetically controlled product. Proton abstraction would occur most easily from that rotomer of 2 having the gamma-protons most exposed, which is this case leads to the Z-isomer 5.

Since the non-nucleophilic base sodium hydride produced the less stable Z-isomer on rearrangement and alkylation, it was interesting to examine the rearrangement of 2 with the nucleophilic base sodium hydroxide, previously reported (1). Isomerization of 2 in the presence of one equivalent of sodium hydroxide in ethanol, followed by dilution and acidification gave an isomeric white indanone not identical to 3. The pmr spectrum of this substance, obtained in 45% yield, showed a vinyl quartet at δ 6.04 and a methyl doublet at δ 2.14. These chemical shifts are almost identical to the values for the methylated Z-indanone 5, and we have therefore assigned the structure as Z-2-carboximade-3-ethylidene-1-indanone (4, Scheme 1).

Compound 4 exhibited unusual melting point behavior. The white compound melted at 130°, turned yellow and resolidified, melted again at 145°, turned white and resolidified, and melted again at 190°. This behavior is similar to that of 2. Apparently the less stable Z-isomer 4, on heating, isomerizes to the yellow indenone 2, which then isomerizes when melted to form the more stable E-isomer 3.

The mother liquor from the sodium hydroxide isomerization yielded about 20% of 3 contaminated with a trace of yellow 2. Purification gave 3 as shown by congruent infrared spectra and mixture melting point. However, treatment of 3 with sodium hydroxide, as above, for 100 hr led to about 80% recovery of 3, indicating that the E-isomer does not isomerize, or isomerizes only slightly, under basic conditions.

The formation of both the E- and Z-isomers, 3 and 4, from the sodium hydroxide catalyzed isomerization of 2 suggests that a different mechanism than that proposed for sodium hydride isomerization may be involved. Sodium hydroxide is both a base and a nucleophile, so that in addition to proton abstraction, hydroxide may add to the conjugated double bond of 2, followed by elimination of water, which could produce both 3 and 4. Addition of hydroxide to indenones has been shown to occur (4).

Table 1
Principal Ultraviolet Absorption Peaks, in mμ.

A	B	C	D	E
Compound 2				
		229	223	
248	236	236		234
254	258	258	264	254
		274	274	
331	319	320	319	327
Compound 3				
242	225	225	222	225
264	264	264	264	264
273	273	273	273	275
332	318	318	318	318

A. In 95% ethanol. B. In 95% ethanol containing 100 molar excess sodium hydroxide, after 1 hour. C. Same as B after 24 hours. D. Same as B after 120 hours. E. In 95% ethanol containing 10 equivalents of sodium cyanide, after 24 hours.

If sodium hydroxide is abstracting a proton from 2, causing rearrangement to the reasonanced stabilized carbanions of 3 and/or 4, then the ultraviolet spectra of 2 and 3 in ethanolic sodium hydroxide should be identical. However, if hydroxide ion added to the conjugated double bond, a discreet intermediate 7 would be formed, and should be detectable by ultraviolet spectroscopy. The result of ultraviolet spectroscopy studies of 2 and 3 in ethanol, in ethanolic sodium hydroxide over time, and in ethanolic sodium cyanide solution, are summarized in Table 1. The set of data for 3 is relatively simple. The spectrum of 3 in neutral solution (Column A) is slightly changed on the addition of base, causing a hypsochromic shift of the principal peak at 242 to the 225-222 region, and a slight hypsochromic shift of the peak at 332 to 318-320 (Columns B and C). The mid peaks at 264 and 273 are unchanged, even after 120 hours in basic solution (Column D). When 3 is treated with sodium cyanide in alcohol (Column E), the U.V. spectrum

is nearly identical to that in alcoholic hydroxide solution. This indicates that cyanide is a sufficiently strong base to abstract the proton at C_2 to form the anion of 3. The spectrum of this solution after acidification was the same as 3.

The changes in the ultraviolet spectra of 2 in base with time, shown at the top of Table 1, were more complex. The initial change from the neutral indenone (Column A) to that after one hour in basic solution (Column B) is a hypsochromic shift of the 248 and 331 peaks to 236 and 319, and a slight bathochromic shift of the 254 peaks to 258. As time increases from one to 120 hours, the spectrum of 2 changes with two new peaks appearing at 264 and 274 mμ. After 120 hours in hydroxide solution, spectra of 2 and 3 are identical, that of the anion of 3. Column E (Table 1) shows that the U.V. spectrum of 2 with cyanide is quite similar to that of 2 after one hour in base (Column B). Cyanide is known to add readily to similar indenones (2,5), and the U.V. spectrum of anion 8 (Scheme 1) should be very similar to that of 7.

Final and conclusive evidence for the formation of the hydroxide adduct 7 was obtained from the pmr spectra of 2 and 3 in sodium deuteroxide-deuterium oxide solution. The pmr spectrum of the anion of 3 would be expected to exhibit a vinyl quartet and a methyl doublet, whereas the hydroxide adduct 7 would be expected to show a methyl triplet and a methylene quartet. The desired information could be obtained using the aromatic multiplets of 2 and 3, not affected by the base, as internal standards. The spectrum of 3 in sodium deuteroxide-deuterium oxide shows a vinyl proton, which was 1.28 ppm upfield from the aromatic multiplet, and a methyl doublet 5.15 ppm upfield. The integral trace gives a correct ratio (6:1:3) of the combined aromatic-amide protons, vinyl and methyl protons. The spectrum of 2 in sodium deuteroxide-deuterium oxide solution exhibited a broad methylene region 5.2 ppm upfield from the aromatic protons, and a broad methyl triplet, which was 6.92 ppm upfield, with the correct ratio of 6:2:3 for combined aromatic-amide, methylene and methyl protons. The expected pattern for hydroxide adduct 7 was obtained from 2 in base, confirming the initial formation of 7 as an intermediate in the hydroxide catalyzed rearrangement of 2 to 3 and 4.

When 2 was allowed to rearrange in alcoholic sodium hydroxide, a mixture of 3 and 4 was obtained, in a ratio of about 1:2, with a trace of unrearranged 2 present. However, when 3 was treated similarly, no evidence of rearrangement to 2 or 4 was observed. The possibility of microscopic reversibility was further examined by the use of a trapping experiment. Sodium cyanide abstracts the C_2 proton from 3 to form the anion, as shown by the ultraviolet spectrum (Table 1, Column E), but if a reversible rearrangement occurs, then cyanide will add to the indenone intermediate, forming anion 8 in solution, and this anion can be trapped. A solution of 3 in dimethylsulfoxide was treated with a two-fold excess of sodium cyanide, and after eight hours the mixture was treated with methyl iodide. Work-up of the reaction gave a low yield of the methylated cyanide adduct 9, showing that there is a finite, though small, reversibility in the rearrangement of indenone 2 to 3.

Experimental

All melting points were determined in open capillary tubes with a Mel-Temp heating block and are corrected. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, IN. Infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 137 Infracord, and were calibrated with polystyrene. Ultraviolet spectra were determined in 95% ethanol with a Bausch and Lomb Spectronic 505 Recording Spectrophotometer. Proton magnetic resonance spectra were obtained with a Varian A-60 spectrometer in indicated solvents using tetramethylsilane as an internal standard, except when hexadeuteriodimethyl-sulfoxide was the solvent, sodium2,2-dimethyl-2-silapentane 5-sulfonate (DDS) was used as the standard.

2-Carboxamido-3-ethyl-1-indenone (2) and 2-Carboxamido-3-ethylidene-1-indanone (3).

A solution of 2-cyano-3-ethylcinnamonitrile (1) (46 g, 0.252 mole) in 400 mL of concentrated sulfuric acid was heated on a steam bath for 30 min. The deep red solution was poured into 4 L. of ice; after 24 hr the solid was collected by filtration, washed thoroughly with water and dried to give 42 g (83%) of a mixture of indenone 2 and indanone 3. The two isomers were separated by the difference in their solubility in diethyl ether, using a Soxhlet apparatus. The yellow ether solution was concentrated to dryness at reduced pressure and the solid was recrystallized twice from 95% ethanol to give a pure sample of indenone 2 (5.06 g, 10%) as evidenced by tlc on silica gel using benzene:acetic acid (50:1), which exhibited one spot, R_f 0.06: mp 147-149°, solidified and turned white and remelted 190-192° (lit (1) 148-150°); ir 2.95 and 3.18 (NH_2), 5.90 (CO), 6.00 ($CONH_2$), and 6.20-6.35 μ (aromatic); uv (λ max) 248 (ϵ 40,800) and 254 mμ (ϵ 40,700), originally reported (1) 244 (ϵ 36,300) and 249 mμ (ϵ 35,300); pmr ($CDCl_3$) δ 7.75 (1H, broad singlet, amide), 7.37 (4H, multiplet, aromatic), 6.10 (1H, broad singlet, amide), 3.21 (2H, quartet, J = 7.5 cps, methylene), and 1.31 (3H, triplet, J = 7.5 cps, methyl).

The solid remaining in the Soxhlet cup was rinsed with ether to remove the last traces of 2 and recrystallized twice from 95% ethanol to give 11.95 g (22%) of indanone 3 as evidenced by tlc on silica gel using benzene:acetic acid (50:1), which exhibited one spot, R_f 0.14: mp 197-199° (lit (3) 199-200°); ir 2.97 and 3.12 (NH_2), 5.82 (CO), 6.06 ($CONH_2$), and 6.25 μ (aromatic); uv (λ max) 242 (ϵ 32,200), 264 (ϵ 17,000), 271-274 (ϵ 14,200), and broad band centered at 330 mμ (ϵ 2,250); pmr (DMSO-d_6) δ 7.6 (6H, complex multiplet, aromatic and amide), 6.54 (1H, quartet, J = 7 cps, further split into 1 cps doublets by long range coupling, vinyl), 4.21 (1H, broad singlet long range coupling, C_2H), and 1.88 (3H, couplet, J = 7 cps, methyl).

Z-2-Carboxamido-2-methyl-3-ethylidene-1-indanone (5).

Sodium hydride (0.27 g of 50% NaH in mineral oil, 5.4 mmoles) was added to a flask, fitted with a drying tube (Drierite), containing 1.08 g (5.0 mmoles) of indenone 2 in 25 mL of dry tetrahydrofuran. After stirring at room temperature for 4 hr methyl iodide (2.5 mL) was added and the reaction was maintained at room temperature for 55 hr. The reaction mixture was diluted with 200 mL of water, the excess methyl iodide was removed on a steam bath, and the solution extracted twice with 250 mL portions of chloroform. The chloroform solution was dried (magnesium sulfate), decolorized (Norit), and evaporated to dryness at reduced pressure. The residue was triturated with cyclohexane and collected to give 5 (0.42 g, 39%). An analytical sample of white plates was prepared by recrystallization from benzene: mp 180-182°; ir 2.90 and 3.14 (NH_2), 5.84 (CO), 6.01 ($CONH_2$), 6.24 (aromatic), and 13.0 μ (alkene); uv (λ max) 241 (ϵ 31,700), 265 (ϵ 16,500), 271-274 (ϵ 14,800) and 333 mμ (ϵ 3,100); pmr (DMSO-d_6) δ 7.5 (6H, complex multiplet, aromatic and amide), 6.00 (1H, quartet, J = 7 cps, vinyl), 2.14 (3H, doublet, J = 7 cps, methyl), and 1.42 (3H, singlet, methyl).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.56; H, 6.05; N, 6.51. Found: C, 72.35; H, 6.19; N, 6.46.

E-2-Carboxamido-2-methyl-3-ethylidene-1-indanone (6).

Compound 6 was synthesized in 50% yield from indanone 3 following the procedure described above for 5. An analytical sample of white plates was prepared by recrystallization from benzene: mp 142-143.5°; ir 2.91 and 3.18 (NH_2), 5.85 (CO), 5.98 ($CONH_2$), 6.25 (aromatic), and 13.3 μ (alkene); uv (λ max) 241 (ϵ 29,000), 265 (ϵ 16,100) 271-274 (ϵ 13,400), and 334 mμ (ϵ 2,400); pmr (DMSO-d_6) δ 7.5 (6H, complex multiplet,

aromatic and amide), 6.56 (1H, quartet, J = 7.5 cps, vinyl), 1.89 (3H, doublet, J = 7.5 cps, methyl), and 1.43 (3H, singlet, methyl).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.56; H, 6.05; N, 6.51. Found: C, 72.43; H, 6.23; N, 6.50.

Isomerization of Indenone 2 with Sodium Hydroxide to Indanones 3 and 4.

Indenone 2 (1 g, 5 mmoles) was added to a solution of sodium hydroxide (0.2 g, 5 mmoles) to 50 mL of 95% ethanol and 2 mL of water. The solution was maintained at room temperature for 120 hr, diluted with 150 ml of water and acidified to pH 3 with 10% hydrochloric acide. The off-white precipitate was collected by filtration to give 0.45 g of 4 (45%). Recrystallization from 95% ethanol and washing with diethyl ether afforded an analytical sample of white powder, which showed one spot of tlc (benzene:acetic acid, 50:1), R_f 0.14: mp 129-130°, the sample turned yellow, solidified, remelted 145°, turned white, solidified and melted again at 190°; ir 2.95 and 3.12 (NH_2), 5.85 (CO), 6.01 ($CONH_2$), and 6.15-6.30 μ (aromatic); uv (λ max) 242 (ϵ 31,500), 255 inflection (ϵ 19,000), 261-264 (ϵ 15,800), 271-274 (ϵ 12,500), and 326 mμ (ϵ 4,200); pmr (DMSO-d_6) δ 7.5 (complex aromatic), 6.04 (quartet, J = 8 cps further split into 2 cps doublets, vinyl), 4.17 (broad singlet, C_2H), and 2.14 (doublet, J = 8 cps further split into 2cps doublets, methyl). The compound, after solution in DMSO, turned slightly yellow indicating isomerization to 2, and minor peaks were observed at δ 1.31 and 3.21 for the methyl and methylene protons of 2.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.64; H, 5.47. Found, C, 71.58; H, 5.69.

The mother liquor was extracted with three 200 mL portions of chloroform; the chloroform solution was dried with magnesium sulfate, and evaporated to dryness at reduced pressure. The residue was recrystallized from 95% ethanol to give 0.2 g (20%) of indanone 3 contaminated with a trace of 2 as evidenced by tlc (benzene:acetic acid, 50:1), major spot R_f 0.14 and minor spot R_f 0.06. The yellow indenone 2 was removed by treating the solid with diethyl ether to give pure 3 as evidenced by congruent infrared spectrum and melting point. The isomerization was also carried out using a five-fold excess of sodium hydroxide to give 37% of 4 and 30% of 3.

Treatment of 3 with Sodium Hydroxide.

Indanone 3 was added to a solution of 50 mL of 95% ethanol and 50 mL of 10% sodium hydroxide. After 100 hr at room temperature the solution was diluted with 200 mL of water and acidified to pH 2 with sulfuric acid. The resulting solid (40%) was collected and proved to be 3 by congruent infrared spectrum and melting point. The mother liquor was extracted with chloroform, and the chloroform phase was dried (magnesium sulfate), concentrated to dryness at reduced pressure, and the solid was triturated with hexane, and collected to give an additional 45% of 3 as evidenced by congruent infrared spectrum and melting point.

2-Carboxamido-2-methyl-3-cyano-3-ethyl-1-indanone (9).

A solution of 3 (2 g, 10 mmoles) and sodium cyanide (1g, 20 mmoles) in 20 mL of dimethyl sulfoxide was stirred at room temperature for 8.5 hr and then methyl iodide (5 mL) was added. After an additional 24 hr the solution was diluted with 250 mL of water and the excess methyl iodide was removed on a steam bath. The cooled solution precipitated 0.46 g (20%) of 9. The mother liquor was extracted with chloroform, but work-up of the chloroform solution only produced an oil which resisted further purification. Analytical sample of 9 (white plates) was prepared by recrystallization from 50% ethanol: mp 197-199°; ir 2.90 and 3.10 (NH_2), 3.35 (CH), 4.44 (CN), 5.83 (CO), 5.93 ($CONH_2$), and 6.30 μ (aromatic).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.79; N, 11.58. Found: C, 69.52; H, 6.02; N, 11.50.

Ultraviolet Studies. A 2.0×10^{-5} M solution of 2 or 3 in 95% ethanol was prepared by dissolving 4 mg of either 2 or 3 in 100 mL of 95% ethanol and diluting 5 mL of this solution to a volume of 50 mL. The solutions of 2 and 3 in base were prepared by adding 10 drops of 10% sodium hydroxide (ca. 2.5×10^{-2} M) to a 2.0×10^{-5} M solution of 2 or 3 in 50 mL of 95% ethanol. The solutions for the sodium cyanide spectra were prepared by dissolving 5 mg of 2 or 3 and 10 mg of sodium cyanide in 100 mL of 95% ethanol and diluting 5 mL of this solution to a volume of 50 mL to give solutions that were 2.5×10^{-5} M in indenone or indanone and 2.0×10^{-4} M in sodium cyanide. The acidified spectra were run after adding enough 1N hydrochloric acid to the cell to lower the pH to 1. All spectra were run against the appropriate blank on a Bausch and Lomb 505 spectrophotometer.

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Note

[1] Taken in part from a thesis submitted to Indiana University by D.A.T. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, September, 1968.