Condensation Reaction of Troponoids and Ethyl α-Cyano-β-aminoglutaconate. I

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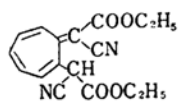
Nozoe and others have studied the reaction mechanism whereby azulene derivatives are formed by condensation of troponoids and cyanoacetic ester, and have considered the formation of an intermediate A during the course of this reaction[1]. There is also a possibility, in addition to the above mechanism,



(A)

of formation of a dimer of cyanoacetic ester followed by its condensation with troponoids in the formation of 2-aminoazulene derivatives.

This paper describes some results obtained on examination of this point.

Reaction of 2-chlorotropone (I) and a dimer[2] of ethyl cyanoacetate, i. e. ethyl α-cyano-β-aminoglutaconate (II) in absolute ethanol, in the presence of sodium ethoxide, affords red needles (III), m. p. 165°C, orange scales (IV), m. p. above 260°C, and colorless scales (V), m. p. 197°C. The use of a tertiary amine as the condensation agent results in the formation of III and IV but not of V.

1) T. Nozoe, S. Seto, S. Matsumura and T. Asano, *Proc. Japan Acad.*, 32, 339 (1956).

2) S. Matsumura, This Bulletin, in press.

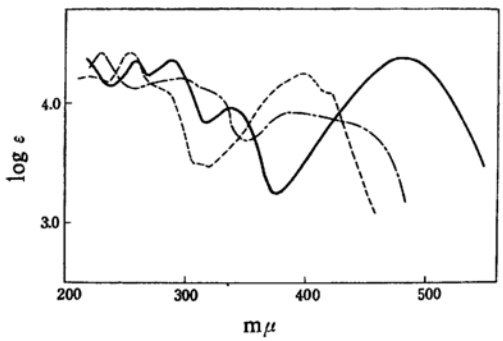
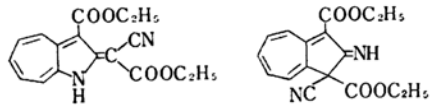


Fig. 1. UV absorption spectra of III, IV and V in methanol.
—— III, ---- IV, -·-· V

Examinations were made on the structure of these products. The ultraviolet absorption spectra[3] of III, IV and V are given in Fig. 1.

These absorption spectra indicate that these products are not 2-aminoazulene derivatives. The analytical values of III correspond to molecular formula of $C_{17}H_{16}O_4N_2$ and structures like IIIa and IIIb may be assumed from this molecular formula.



The infrared absorption spectrum[4] of III, as indicated in Fig. 2a, exhibits absorption bands at 3220 cm^{-1} for the imino or hydroxyl group, at 2200 cm^{-1} for the cyano group conjugated with unsaturated bond, at 1688 cm^{-1} for ester carbonyl conjugated with unsaturated bond, and at 1650 cm^{-1} for stretching vibration of ester carbonyl conjugated with unsaturated bond or that due to NH deformation vibration.

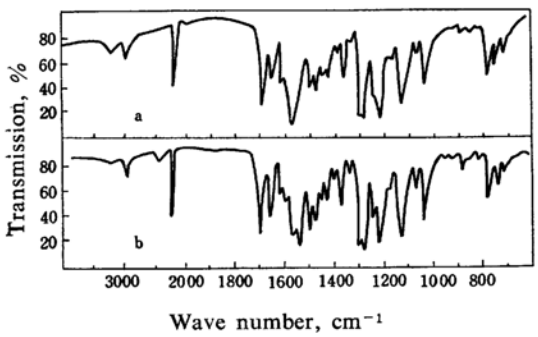


Fig. 2. IR absorption spectra of III (a) and III_D (b) in KBr.

3) Measured by a Beckman Model DU spectrophotometer.

4) IR spectra are measured using a Perkin-Elmer Model 21 double beam spectrophotometer by Mr. S. Aono of this Institute, to whom the author is deeply indebted.

The structure of III which satisfies these infrared spectral results is the formula IIIa.

III undergoes reaction with sodium alkoxide to form a red substance (VI) which is decomposed by water or dilute acid to revert to III. This shows that VI is a sodium salt of III.

III does not form a picrate on addition of an ethanolic solution of picric acid but a prolonged heating of such a solution produces a picrate of m. p. 156°C (decomp.), sparingly soluble in ethanol. III easily reacts with dilute hydrochloric acid to form a labile product of red needles (VII), m. p. 155°C.

Other structurally unknown substances of various colors are obtained but they are all unstable and cannot be isolated in pure form. VII forms a picrate of m. p. 156°C.

The passage of dry hydrogen chloride gas through dehydrated benzene solution of III gives yellow needles (VIII) assumed to be the hydrochloride of III. VIII is extremely labile and decomposes when left in the air. The neutralization of VIII with sodium hydrogen carbonate solution liberates VII, whose ultraviolet absorption spectrum, as indicated in Fig. 3, is similar to that of 1-azaazulene derivatives.

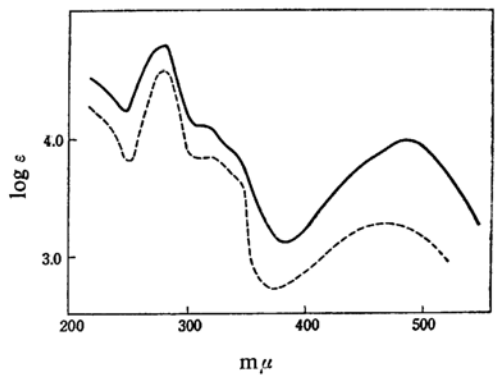


Fig. 3. UV absorption spectra of VII (——) and 3-ethoxycarbonyl-2-(diethoxycarbonylmethyl)-1-azaazulene (----) in methanol.

III is insoluble in water but dissolves in an aqueous solution of potassium hydroxide, from which it is extracted with an organic solvent. These foregoing facts show that III is an amphoteric substance and its behavior resembles that of pyrrole or indole to acids and alkalis.

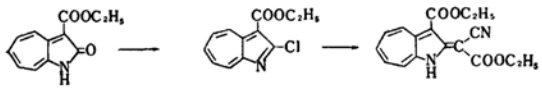
These experimental results support the structure of IIIa for III.

Recently, Seto and others[5] prepared 2-chloro-3-ethoxycarbonyl-1-azaazulene (X) from 3-ethoxycarbonyl-1-azaazulan-2-one (IX) and

5) S. Seto et al., to be published.

obtained corresponding condensates by condensation of X with diethyl malonate and ethyl cyanoacetate.

Comparative examination of III with the condensate, m. p. 165°C, of X with ethyl cyanoacetate showed that they are the same substances. Consequently, III was proved to have IIIa structure, i. e. 2-(cyano-ethoxycarbonylmethylene)-3-ethoxycarbonyl-1-azaazulane.



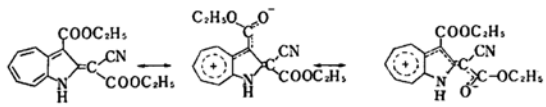
IX X III

Further examination was made on the absorption band at 1650 cm^{-1} in the infrared spectrum of III to see whether it is due to the ester carbonyl conjugated with unsaturated bond, stretching vibration of C=C, or to deformation vibration of N–H group. In order to confirm this point, a deuterated compound (III_D) of III was prepared.

III_D was easily obtained on decomposition of VI with deuterium oxide. Admixture of III_D with III showed no depression in the melting point and the ultraviolet absoption spectrum of III_D in anhydrous cyclohexane agreed with that of III. The infrared spectrum of III_D, indicated in Fig. 2b, shows that the absorption bands at 3220, 1225 and 710 cm^{-1} in III have disappeared and new bands have appeared at 2420, 1533 and 1186 cm^{-1} in the spectrum of III_D, with decreased intensity of the absorption band at 1563 cm^{-1}.

The wave number ratio of 3220 cm^{-1} in III and 2420 cm^{-1} in III_D is 1.330, which approximately agrees with the usual value of ν(N–H)/ν(N–D)[6]. Since the absorption band at 710 cm^{-1} in III is active to deuteration, this absorption can be assigned to the out-of-plane deformation vibration of the N–H group. The absorption band at 1650 cm^{-1} in III is still present in III_D so that it is not due to any deformation vibration of the N–H group but should be the stretching vibration of ester carbonyl or the exo-methylene group. If it were due to the carbonyl, the absorption has a very much lower frequency for that of unsaturated ester carbonyl. This fact indicates that there is a large contribution of ionic structures such as those shown in Scheme 1 in III.

In oder to determine the assignment of absorption bands at 1688 and 1650 cm^{-1}, 2-(dicyanomethylene)-3-ethoxycarbonyl-1-azaazulane (XI) and 2-(cyano-ethoxycarbonylmethylene)-3-cyano-1-azaazulane (XII) were prepared and their infrared spectra were measured. Condensation of X and sodiomalononitrile in dry dioxane afforded lustrous red crystals XI, m. p. above 260°C.



Scheme 1.

Condensation of 2-chloro-3-cyano-1-azaazulene (XIII) and ethyl sodiocyanoacetate in dehydrated dioxane produced dark red crystals (XII), m. p. 230°C. The ultraviolet absorption spectra of XI and XII are indicated in Fig. 4 and the infrared spectra of XI and XII are shown respectively in Fig. 5a and b. These infrared spectra exhibit an absorption band due to ester carbonyl at 1690 cm^{-1} in XI and at 1645 cm^{-1} in XII.

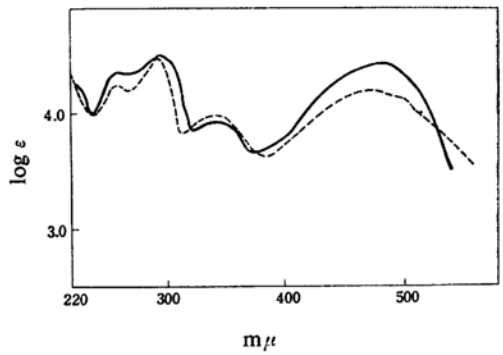


Fig. 4. UV absorption spectra of XI and XII in methanol.
—— XI, ---- XII

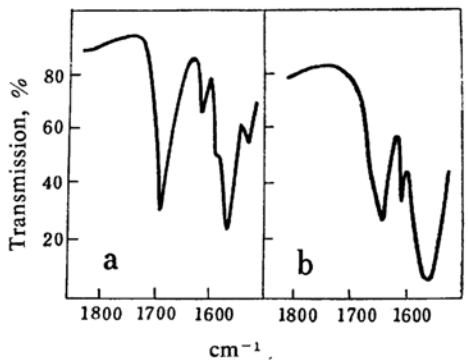


Fig. 5. IR absorption spectra of XI (a) and XII (b) in KBr disk.

These facts prove that the absorption band at 1688 cm^{-1} in III is due to the carbonyl group in the ester at 3-position and that at 1650 cm^{-1} is the absorption of the ester carbonyl group bonded to the methylene group

6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", Methuen (1958), p. 257.

and that it is not due to the stretching vibration of exo-methylene.

Analytical values of IV correspond to the molecular formula of $C_{15}H_{12}O_4N_2$ and its ultraviolet spectrum is similar to the absorption curve of 1-oxaazulan-2-one or 1-azaazulan-2-one derivatives. The infrared spectrum of IV, as indicated in Fig. 6a, exhibits the absorptions at 3380 and 3278 cm^{-1} for primary amino group, at 2205 cm^{-1} for cyano group conjugated with unsaturated bond, at 1740 cm^{-1} for carbonyl in unsaturated γ-lactone, and at 1675 cm^{-1} for ester carbonyl conjugated with unsaturated bond. From these results, IV is assumed to be a 1- oxaazulan-2-one derivative.

Seto obtained 1-oxaazulan-2-one (XIV), by decomposition of 3-ethoxycarbonyl-1-oxaazulan-2-one or 3-acetyl-1-oxaazulan-2-one with concentrated sulfuric acid.[7]

The same decomposition of IV with concentrated sulfuric acid afforded XIV, m. p. 69°C, and this has proved that IV is α-amino-α-(1-oxaazulan-2-on-3-yl)-β-cyano-β-ethoxycarbonyl-ethylene.

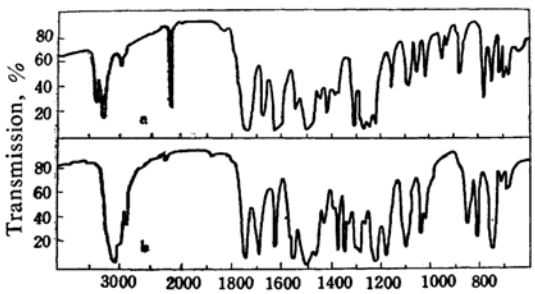
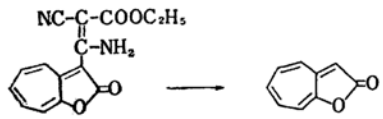


Fig. 6. IR absorption spectra of IV(a) and V(b) in KBr disk.



IV XIV

Analytical values of V correspond to the molecular formula of $C_{17}H_{18}O_5N_2$ and the infrared spectrum of V, indicated in Fig. 6b, exhibits a strong and broad absorption band at around 3100 cm^{-1}, absorption of cyano group at 2260 cm^{-1}, that of ester carbonyl at 1740 cm^{-1}, and that due to ester carbonyl conjugated with unsaturated bond at 1688 cm^{-1}.

Sometimes V is not obtained by condensation of I and II and the yield of V is generally poor. Further examination of this product was not made.

7) S. Seto, *Sci. Repts. Tohoku Univ.* (*I*), 37, 367 (1953).

Reaction of 2-methoxytropone (XV) and II in the presence of an alkoxide results in almost complete recovery of XV and III, IV and V are not obtained.

From the foregoing results, it was shown that 2-aminoazulene derivative was not formed in the condensation of troponoids with II.

Experimental

Reaction of 2-Chlorotropone (I) and Ethyl α-Cyano-β-aminoglutaconate (II).—a) To a solution of sodium ethoxide, prepared from 250 mg. of metallic sodium and 10 ml. of absolute ethanol, 2.45 g. of II was added and a solution of 1.5 g. of I dissolved in 30 ml. of absolute ethanol was added to it with stirring under ice-cooling. The solution colored red immediately. The mixture was allowed to stand at room temperature for 3 hr. and the red crystals that separated out were collected by filtration. The collected crystals were dissolved in benzene to separate them from colorless inorganic salt and evaporation of benzene left red crystals of m. p. 155~159°C. Repeated recrystallization from ethanol afforded 800 mg. of red needles (III), m. p. 163~165°C.

The reaction mixture left after the removal of the above crystals was evaporated to dryness under reduced pressure and the residue separated into crystalline and oily substances. This residual mixture was dissolved in benzene to be separated into benzene-soluble and insoluble portions.

The benzene-soluble portion afforded 350 mg. of III.

Found: C, 65.52; H, 5.38; N, 8.56. Calcd. for $C_{17}H_{16}O_4N_2$: C, 65.37; H. 5.16; N, 8.97%.

UV λ_{max}^{MeOH} mμ (log ε): 260 (4.32), 289.5 (4.37), 340 (3.98), 490 (4.37).

Addition of water to the benzene-insoluble portion precipitated 200 mg. of orange crystals insoluble in water. This substance is extremely sparingly soluble in various organic solvents. Its recrystallization from a large quantity of chloroform afforded orange-yellow scales (IV), m. p. above 260°C.

Found: C, 63.58; H, 4.01; N, 9.85. Calcd. for $C_{15}H_{12}O_4N_2$: C, 63.38; H, 4.26; N, 9.86%.

UV λ_{max}^{MeOH} mμ (log ε): 254 (4.43), 282 (4.14), 399 (4.27).

The water-soluble portion of this mixture produced, upon neutralization with dilute nitric acid, 750 mg. of brown precipitate and five recrystallizations from ethanol afforded 150 mg. of colorless scales V, m. p. 195~197°C.

Found: C, 61.85; H, 5.71; N, 8.83. Calcd. for $C_{17}H_{18}O_5N_2$: C, 61.81; H, 5.49; N, 8.48%.

UV λ_{max}^{MeOH} mμ (log ε): 230 (4.43), 300 (4.21), 388 (3.92).

b) To a solution of 1 g. of I and 1.7 g. of II dissolved in 30 ml. of absolute ethanol, 1.4 g. of tributylamine was added under ice-cooling and the solution changed from orange to red. After allowing the mixture to stand for 5 hr. at room

8) All melting points are uncorrected. The microanalyses were carried out by Mr. S. Ohyama and Miss. Y. Endo of this Institute, to whom the author is deeply indebted.

temperature, the red leaflet crystals that separated out were collected by filtration and treated with chloroform to be separated into chloroform-soluble and insoluble portions.

Red needle crystals separated from the chloroform-soluble portion and recrystallization from ethyl acetate gave 550 mg. of III. The solid sparingly soluble in chloroform was recrystallized from a large quantity of chloroform to 420 mg. of orange-yellow crystals IV.

The reaction mixture after separation of the above products was evaporated, the residue was dissolved in chloroform, and the solvent was evaporated to dryness from the chloroform extract. The red crystalline residue thereby obtained was recrystallized from ethanol to 140 mg. of III.

Sodium Compound (VI) of III.—A solution of sodium ethoxide, prepared from 10 mg. of metallic sodium and 1 ml. of absolute ethanol, was added to the solution of 100 mg. of III dissolved in 1 ml. of dehydrated benzene by which 100 mg. of amorphous orange-red solid (VI), m. p. above 260°C, formed immediately. The solid was collected, washed with benzene, and dried.

VI was dissolved in water and extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate and evaporation of benzene left 70 mg. of III. The residual aqueous solution was adjusted to pH 7 and extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate and evaporated, leaving 20 mg. of III.

Found: N, 8.46. Calcd. for $C_{17}H_{15}O_4N_2Na$: N, 8.35%.

Reaction of III and Picric Acid.—a) A mixture of 50 mg. of III and saturated solution of picric acid in ethanol was warmed on a water bath to effect solution and the solution was allowed to stand at room temperature. The red needle crystals that separated out were recrystallized from ethyl acetate and 40 mg. of III was recovered.

b) A mixture of 50 mg. of III and 100 mg. of picric acid was placed in a test tube and the tube was heated in a water bath at 90°C to effect solution. Addition of ethanol to this solution separated 120 mg. of orange-yellow crystals, m. p. 156~158°C (decomp.), sparingly soluble in ethanol.

Found: N, 12.81. Calcd. for $C_{23}H_{19}O_{11}N_5$: N, 12.79%.

Action of Aqueous Alkali Solution on III.—A solution of 20 mg. of III dissolved in 1 ml. of 10% potassium hydroxide aqueous solution was heated on a water bath for 1 hr., cooled, and adjusted to pH 7. The red crystals thereby produced were recrystallized from ethanol and ca. 15 mg. of III was recovered.

Action of Acetic Anhydride on III.—A solution of 50 mg. of III dissolved in 1 ml. of acetic anhydride to which was added 1 drop of pyridine was heated at 120°C for 3 hr. Acetic anhydride was evaporated and the residue was recrystallized from ethanol, by which 30 mg. of III was recovered.

Action of Diazomethane of III.—The excess of ether solution of diazomethane was added to the solution of 20 mg. of III dissolved in 30 ml. of ether and the mixture was allowed to stand at room temperature for 4 hr. Evaporation of ether left crystals which were recrystallized from ethyl acetate and III was recovered.

Action of Acid on III.—a) Dropwise addition of 0.2 ml. of 2 N hydrochloric acid to a solution of 50 mg. of III dissolved in 1 ml. of ethanol by application of heat resulted in yellowing of the solution. Ethanol was evaporated from this mixture, the residue was neutralized with sodium hydrogencarbonate solution, and the dark red precipitate that formed was extracted with benzene. The benzene extract was dried over anhydrous sodium sulfate and passed through a column of alumina, by which the product separated into red, blue and green bands.

Elution of the red band with benzene afforded ca. 5 mg. of red leaflets VII, m. p. 153~155°C.

Elution of the green band with ethyl acetate failed to give any crystalline product.

VII formed a picrate of m. p. 156~158°C on addition of saturated ethanol solution of picric acid.

Found: N, 13.02. Calcd. for $C_{23}H_{19}O_{11}N_5$: N, 12.79%.

b) Dry hydrogen chloride gas was passed through a solution of 50 mg. of III dissolved in dehydrated benzene and the yellow needle crystals (VIII) that separated out were collected by filtration. This product underwent a change by atmospheric moisture. The product was dissolved in water, neutralized with sodium hydrogencarbonate, and the precipitate was extracted with benzene from which 10 mg. of a substance agreeing with VII, m. p. 153~155°C, was obtained.

Deuterated Compound (III_D).—A solution of 100 mg. of VI dissolved in 1 ml. of deuterium oxide to which was added 1 drop of acetic anhydride was allowed to stand at room temperature for 1 hr. The red needle crystals that separated out were recrystallized from dehydrated benzene-cyclohexane mixture and 60 mg. of III_D, m. p. 163~164°C, undepressed on admixture with III, was obtained.

Synthesis of 2-(Dicyanomethylene)-3-ethoxycarbonyl-1-azaazulane (XI).—To a sodium ethoxide solution prepared from 50 mg. of metallic sodium and 2 ml. of absolute ethanol, 250 mg. of malononitrile was added to form its sodio compound and ethanol was evaporated completely. The residue was suspended in 2 ml. of dehydrated dioxane, 250 mg. of 2-chloro-3-ethoxycarbonyl-1-azaazulene (X) was added to it, and the mixture was heated at 90°C for 1 hr. The reaction mixture colored dark red and orange precipitate separated gradually. Dioxane was evaporated from this mixture, the residue was dissolved in water, and the solution was acidified with acetic acid by which a lustrous crystalline precipitate was produced. Recrystallization from acetone gave 120 mg. of lustrous red crystals XI, m. p. above 260°C.

Found: C, 67.74; H, 4.08; N, 15.98. Calcd. for $C_{15}H_{11}O_2N_3$: C, 67.91; H, 4.18; N, 15.84%.

UV λ_{max}^{MeOH} mμ (log ε): 259 (4.23), 295 (4.47), 340 (3.92), 483 (4.43).

Synthesis of 2-(Cyano-ethoxycarbonylmethylene)-3-cyano-1-azaazulane (XII).—To a suspension of 50 mg. of sodium in 2 ml. of dehydrated dioxane,

400 mg. of ethyl cyanoacetate was added and the mixture was warmed to form the sodio compound. A mixture of this sodio compound and 200 mg. of 2-chloro-3-cyano-1-azaazulene (XIII) was heated at 90°C for 1 hr., by which the solution became dark red and a reddish orange precipitate began to separate out. Dioxane was evaporated, the residue was dissolved in water, and the aqueous solution was acidified with acetic acid. The dark red precipitate thereby formed was recrystallized from acetone and 280 mg. of dark red needles XII, m. p. 230°C (decomp.), was obtained.

Found: C, 67.83; H, 4.26; N, 15.67. Calcd. for $C_{15}H_{11}O_2N_3$: C, 67.91; H, 4.18; N, 15.84%.

UV λ_{max}^{MeOH} mμ (log ε): 256 (4.21), 293 (4.46), 340 (3.80), 490 (4.18).

Formation of 1-Oxaazulan-2-one (XIV). — A solution of 100 mg. of IV dissolved in 0.2 ml. of concentrated sulfuric acid was heated on a water bath for 1 hr. and the brownish orange solution that formed was diluted with water. This was extracted with benzene, the extract was washed thoroughly with water, and dried over anhydrous sodium sulfate. Evaporation of benzene left an oily substance with aroma.

This residue was digested with hot cyclohexane, the orange crystals thereby obtained were sublimed in reduced pressure, and the sublimate was recrystallized from cyclohexane, affording XIV, m. p. 69~71°C.

The author takes this opportunity to express his sincere gratitude to Professor Tetsuo Nozoe and Professor Shuichi Seto for their kind guidance throughout the course of this work, and to Mr. Fumio Sato for his cooperation in carrying out the experiments.

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