Condensation Reaction of Troponoids with Ethyl α-Cyano-β-aminoglutaconate. II. Reaction of Alkyl Derivatives of 2-Chlorotropone with Ethyl α-Cyano-β-aminoglutaconate

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It has already been found[1] that the condensation of 2-chlorotropone (I) with ethyl α-cyano-β-aminoglutaconate (II) results in the formation of 2-(cyano-ethoxycarbonylmethylene)-3-ethoxycarbonyl-1-azaazulane (III) and α-amino-α-(1-oxaazulan-2-on-3-yl)-β-cyano-β-ethoxycarbonylethylene (IV).

It has also often been found that the substitution occurs in the 7-position and not in the position previously occupied by the halogen in the amination of 2-halotropones with ammonia[2], and the same sort of abnormal substitution was also observed in the formation of 1-oxaazulan-2-one derivatives by reaction with acetoacetic ester or malonic ester[3], and in the formation of azulene or 1-azaazulan-2-one derivatives by reaction with cyanoacetic ester[4] or cyanoacetamide[5].

In order to determine whether or not such an abnormal reaction took place in the condensation reaction of 2-halotropones with II, the present series of experiments was carried out.

The reaction of 2-chloro-4-isopropyltropone (V) with II in benzene, in the presence of triethylamine, affords red crystals (VI) of m. p. 147°C and orange crystals (VII) of m. p. 184°C. A similar condensation of 2-chloro-6-isopropyltropone (VIII) gives a reddish oily product (IX), while the reaction with 2-chloro-4-methyltropone (X) gives red crystals (XI) of m. p. 190°C and orange crystals (XII) of m. p. 250°C. The same reaction of 2-chloro-6-methyltropone (XIII) affords an orange oily product (XIV).

The ultraviolet absorption spectra*1 of VI and XI (Fig. 1) are similar to that of the 2-methylene-1-azaazulane derivative[1]. The analytical values of VI correspond to those of the isopropyl derivative of III, and those of XI, to those of the methyl derivative of III.

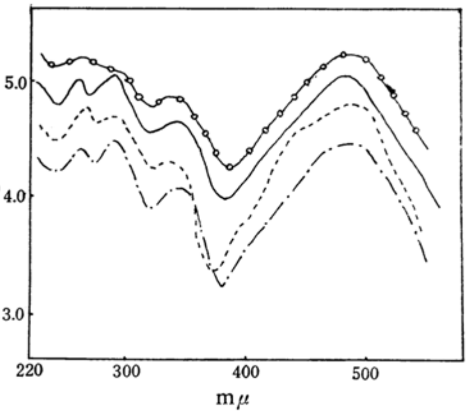

Fig. 1. UV absorption spectra of VI, XI, XVII and XX in methanol.
------ VI: $Y=\log \varepsilon+0.3$
——— XVII: $Y=\log \varepsilon+0.6$
—○— XI: $Y=\log \varepsilon+0.7$
—·—· XX: $Y=\log \varepsilon+0$

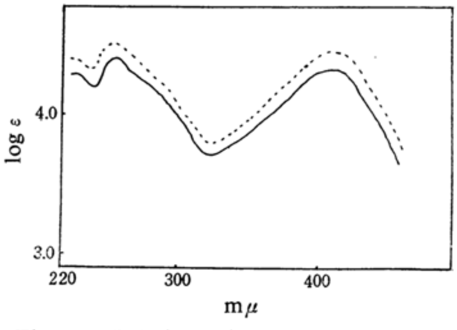

Fig. 2. UV absorption spectra of VII and XII in methanol.
——— VII: $Y=\log \varepsilon+0$
------ XII: $Y=\log \varepsilon+0.1$

The ultraviolet absorption spectra of VII and XII (Fig. 2) are similar to that of the 1-oxaazulan-2-one derivative. The analytical values of VII correspond to those of the isopropyl derivative of IV, and those of XII, to those of the methyl derivative of IV. The ultraviolet spectra of IX and XIV (Fig. 3) are similar to that of the starting 2-chlorotropone derivative except for the absorption at around

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[1] S. Matsumura, This Bulletin, **34**, 1361 (1961).

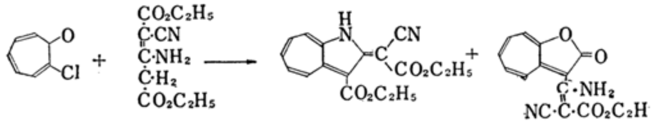
[2] T. Sato, *J. Chem. Soc. Japan*, *Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1056, 1173 (1959).

[3] T. Sato, ibid., **80**, 1342 (1959).

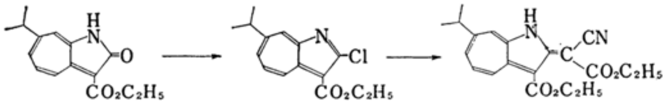
[4] T. Nozoe, S. Seto, S. Matsumura and T. Asano, *Proc. Japan Acad.*, **32**, 339 (1956).

[5] T. Nozoe, S. Seto and S. Nozoe, ibid., **32**, 479 (1956); S. Seto and S. Nozoe, ibid., **32**, 765 (1956).

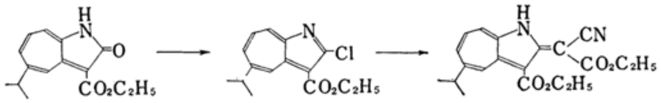
*1 The ultraviolet absorption spectra were measured with a Hitachi EPS-2 Type recording spectrophotometer.



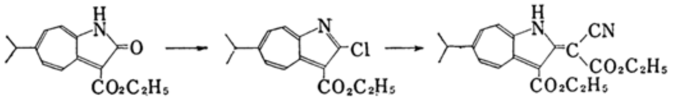
I II III IV



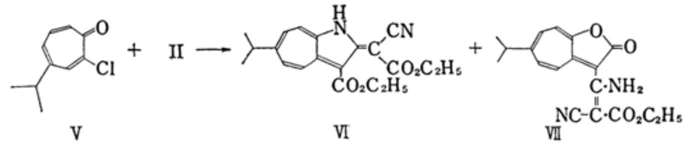
XV XVI XVII



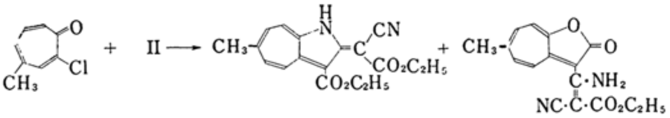
XVIII XIX XX



XXI XXII XXIII = VI



V VI VII



X XI XII

280 mμ. These facts suggest that IX and XIV are tropone derivatives, but their structure still remains undetermined.

In order to determine the position of the isopropyl group in VI, the following experiment was carried out. The application of phosphoryl chloride to 3-ethoxycarbonyl-7-isopropyl-1-azaazulan-2-one (XV) gives 2-chloro-3-ethoxycarbonyl-7-isopropyl-1-azaazulene (XVI), m. p. 79°C, and the condensation of XVI with ethyl sodiocyanoacetate affords 2-(cyano-ethoxycarbonylmethylene)-3-ethoxycarbonyl-7-isopropyl-1-azaazulane (XVII), m. p. 134°C. The ultraviolet absorption spectrum of XVII is shown in Fig. 1.

The application of phosphoryl chloride to 3-ethoxycarbonyl-5-isopropyl-1-azaazulan-2-one (XVIII) affords 2-chloro-3-ethoxycarbonyl-5-isopropyl-1-azaazulene (XIX), m. p. 101°C, whose condensation with ethyl sodiocyanoacetate gives 2-(cyano-ethoxycarbonylmethylene)-3-ethoxycarbonyl-5-isopropyl-1-azaazulane (XX), m. p. 84°C. The ultraviolet absorption spectrum of XX is given in Fig. 1.

The treatment of 3-ethoxycarbonyl-6-isopropyl-1-azaazulan-2-one (XXI) with phosphoryl chloride gives an orange-yellow oily product (XXII) whose condensation with ethyl sodiocyanoacetate affords 2-(cyano-ethoxycarbonylmethylene)-3-ethoxycarbonyl-6-isopropyl-1-azaazulane (XXIII), m. p. 147°C. The mixed fusion of XXIII and VI failed to show any depression of the melting point, and the ultraviolet absorption spectra of these two substances were identical.

As will be clear from the infrared spectra*2 of VI and XI (Fig. 4), the absorptions in the region of the C–H out-of-plane deformation vibrations are very similar in these two compounds, so the position of methyl substitution in XI should be the 6-position.

The absorption band due to the C–H out-of-plane deformation vibration appears at 850 cm^{-1} in VII, while this absorption is present

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*2 The infrared spectra were measured with a Perkin-Elmer Model 21 double beam spectrophotometer by Mr. S. Aono of this Institute; the author is deeply indebted to Mr. S. Aono.

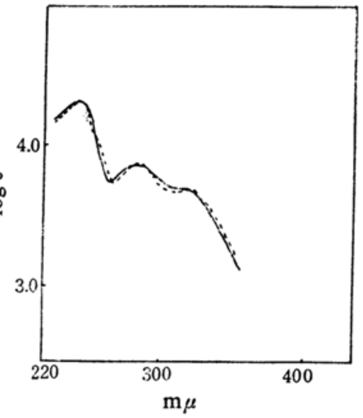


Fig. 3. UV absorption spectra of IX and XIV in methanol.

—— IX ---- XIV

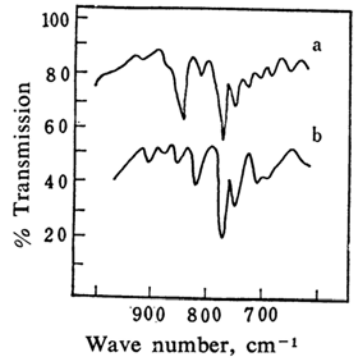
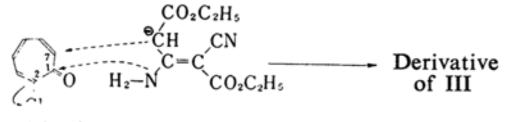


Fig. 4. IR absorption spectra of VI and XI.

a: VI b: XI

at 834 cm⁻¹ in XII. These wave numbers agree with that of the 6-substituted derivatives of 1-oxaazulan-2-one⁶⁾. This evidence shows that VII is a 6-isopropyl derivative of IV and that XII is its 6-methyl derivative.

It has become clear from these experiments that an abnormal reaction occurred also in the condensation reaction of 2-halotropones with II. In this reaction, the carbanion formed from II attacks the 7-position in the tropone ring, and this is followed by a dehydrative cyclization reaction between the amino group and the carbonyl in the 1-position to form a 2-methylene-1-azaazulane derivative.



This is the same mode of reaction as that reported already by Seto and others⁵⁾ for the formation of 1-azaazulan-2-one derivatives by the condensation of 2-halotropones with cyanoacetamide.

Experimental[*3]

Reaction of 2-Chloro-4-isopropyltropone (V) and Ethyl α-Cyano-β-aminoglutaconate (II).—To a solution of 260 mg. of V and 350 mg. of II dissolved in 2 ml. of dehydrated benzene, 200 mg. of triethylamine was added dropwise at room temperature; the solution thereby turned red and a precipitate was gradually deposited. After the mixture had been allowed to stand for 5 hr., the precipitate was collected by filtration, washed thoroughly with water, and recrystallized from acetone to give 250 mg. of VII as orange needles, m. p. 183~184°C.

Found: C, 66.51; H, 5.38; N, 8.67. Calcd. for $C_{18}H_{18}O_4N_2$: C, 66.24; H, 5.56; N, 8.53%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 230 (4.29), 254 (4.44), 410 (4.32).

The reaction solution, separated from the precipitate, was washed thoroughly with water, the benzene was evaporated, and the residue was purified by passage through an alumina column. The reddish crystals thereby obtained were recrystallized from ethanol to afford 120 mg. of VI as red needles, m. p. 145~147°C.

Found: C, 67.84; H, 6.15; N, 7.62. Calcd. for $C_{20}H_{22}O_4N_2$: C, 67.78; H, 6.26; N, 7.91%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 263 (4.46), 290 (4.39), 338 (3.98), 489 (4.48).

Reaction of 2-Chloro-6-isopropyltropone (VIII) and II.—A solution of 730 mg. of VIII and 890 mg. of II dissolved in 4 ml. of dehydrated benzene, with 400 mg. of triethylamine added, was allowed to stand for 2 days at room temperature; colorless needle crystals, easily soluble in water, thereby separated out. The benzene solution was washed with water, dried, and concentrated. The residue was purified by passage through an alumina column, and the column was eluted with benzene. The evaporation of the solvent from the effluent afforded 960 mg. of IX as a reddish oil.

Reaction of 2-Chloro-4-methyltropone (X) and II.—A solution of 320 mg. of X and 470 mg. of II dissolved in 2 ml. of dehydrated benzene, with 240 mg. of triethylamine added, was allowed to stand at room temperature for 5 hr. The precipitate thereby formed was collected by filtration and recrystallized from acetone to give 240 mg. of XII as orange-needles, m. p. 250°C (decomp.).

Found: C, 64.51; H, 4.85; N, 9.56. Calcd. for $C_{16}H_{14}O_4N_2$: C, 64.42; H, 4.73; N, 9.39%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 230 (4.35), 254 (4.46), 410 (4.36).

The solvent was evaporated from the filtrate, and the residue was purified by passage through an alumina column. The crystals thereby obtained were recrystallized from ethanol to afford 60 mg. of XI as red needles, m. p. 189~190°C.

Found: C, 66.52; H, 5.53; N, 8.46. Calcd. for $C_{18}H_{18}O_4N_2$: C, 66.28; H, 5.56; N, 8.58%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 264 (4.48), 289 (4.37), 340 (4.12), 490 (4.53).

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6) T. Sato, *Bull. Chem. Research Inst. Non-Aq. Soln., Tohoku Univ.*, 8, 47 (1959).

[*3] All melting points are uncorrected.

Reaction of 2-Chloro-6-methyltropone (XIII) and II.—A solution of 160 mg. of XIII and 240 mg. of II dissolved in 1 ml. of dehydrated benzene and with 120 mg. of triethylamine added was allowed to stand at room temperature for 2 days, and the reaction mixture was treated as in the reaction of VIII and II; 200 mg. of XIV was thereby obtained as an orange oil.

2-Chloro-3-ethoxycarbonyl-7-isopropyl-1-azaazulene (XVI). — A solution of 200 mg. of 3-ethoxycarbonyl-7-isopropyl-1-azaazulan-2-one (XV) dissolved in 1.5 ml. of phosphoryl chloride was sealed in a glass tube and heated at 150~160°C for 5 hr. The phosphoryl chloride was removed from the reaction mixture, water was added to decompose the residual phosphoryl chloride, and the mixture was neutralized with sodium hydrogencarbonate. This was extracted with benzene, and the extract was dried and passed through a column of alumina. The product thereby obtained was recrystallized from petroleum ether to give 110 mg. of XVI as orange-yellow prisms, m. p. 77~79°C.

Found: C, 64.81; H, 5.75; N, 5.32. Calcd. for $C_{15}H_{16}O_2NCl$: C, 64.98; H, 5.77; N, 5.05%.

2-Chloro-3-ethoxycarbonyl-5-isopropyl-1-azaazulene (XIX). — A mixture of 500 mg. of 3-ethoxycarbonyl-5-isopropyl-1-azaazulan-2-one (XVIII) and 5 ml. of phosphoryl chloride was treated as in the preceding case; 350 mg. of XIX was obtained thereby as orange prisms, m. p. 99~101°C.

Found: C, 64.76; H, 5.38; N, 5.13. Calcd. for $C_{15}H_{16}O_2NCl$: C, 64.98; H, 5.77; N, 5.05%.

2-Chloro-3-ethoxycarbonyl-6-isopropyl-1-azaazulene (XXII). — A mixture of 200 mg. of 3-ethoxycarbonyl-6-isopropyl-1-azaazulan-2-one (XXI) and 1 ml. of phosphoryl chloride was treated as in the preceding cases, obtaining XXII as an orange oil.

2-(Cyano-ethoxycarbonylmethylene)-3-ethoxycarbonyl-7-isopropyl-1-azaazulane (XVII). — To the sodio compound prepared from 30 mg. of sodium granulated in dehydrated dioxane and heated with 260 mg. of ethyl cyanoacetate, 150 mg. of XVI was added and the mixture was heated at 90°C for 1 hr.; an orange-red precipitate thereby gradually formed. The dioxane was evaporated from the mixture, and the residue was dissolved in water, neutralized with dilute acetic acid, and extracted with benzene. The extract solution was dried and passed through a column of alumina. The reddish oily product so obtained solidified when allowed to stand after petroleum ether (b. p. 50~60°C) had been added; the product was then recrystallized from the benzene-petroleum ether mixture to give 80 mg. of XVII as red needles, m. p. 132~134°C.

Found: C, 67.65; H, 6.59; N, 7.84. Calcd. for $C_{20}H_{22}O_4N_2$: C, 67.78; H, 6.26; N, 7.91%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 260 (4.41), 290 (4.45), 340 (4.02), 489 (4.43).

2-(Cyano-ethoxycarbonylmethylene)-3-ethoxycarbonyl-5-isopropyl-1-azaazulane (XX). — Treatment of 30 mg. of sodium, 200 mg. of XIX, as in the preceding case, afforded 120 mg. of XX as red needles, m. p. 82~84°C.

Found: C, 67.53; H, 6.12; N, 8.05. Calcd. for $C_{20}H_{22}O_4N_2$: C, 67.78; H, 6.26; N, 7.91%.

UV $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 262 (4.41), 290 (4.48), 334 (4.05), 489 (4.44).

2-(Cyano-ethoxycarbonylmethylene)-3-ethoxycarbonyl-6-isopropyl-1-azaazulane (XXIII=VI). — A mixture of 30 mg. of sodium, 200 mg. of ethyl cyanoacetate, and 200 mg. of XXII was treated as in the preparation of XVII; 100 mg. of XXIII was thereby obtained as red needles, m. p. 145~147°C. Mixed fusion of XXIII with VI failed to show any depression of the melting point.

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