The Structure of the Condensation Products of Troponoids and Ethyl Cyanoacetate

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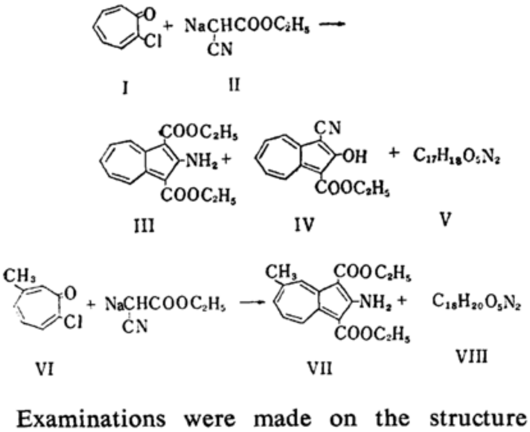
Nozoe and his co-workers have already reported that the condensation of 2-chlorotropone (I) and ethyl sodiocyanoacetate (II) formed 2-amino-1, 3-diethoxycarbonylazulene (III), 1-cyano-2-hydroxy-3-ethoxycarbonylazulene (IV), and a structurally unknown compound (V) of m. p. 137°C, whose analytical values correspond to the molecular formula of $C_{17}H_{18}O_5N_2$[1].

Similar condensation was carried out by Akino[2] on 2-chloro-6-methyltropone (VI) and he observed the formation of 2-amino-1, 3-diethoxycarbonyl-5-methylazulene (VII) and a compound (VIII) of m. p. 103°C, whose analytical values agree with $C_{18}H_{20}O_5N_2$.



Examinations were made on the structure of V and VIII.

The ultraviolet absorption spectra[3] of V and VIII, shown in Fig. 1, are very similar to each other and the two compounds are assumed to have a common skeletal structure.

V and VIII easily form picrates melting at 215 and 196°C, respectively. The infrared ab-

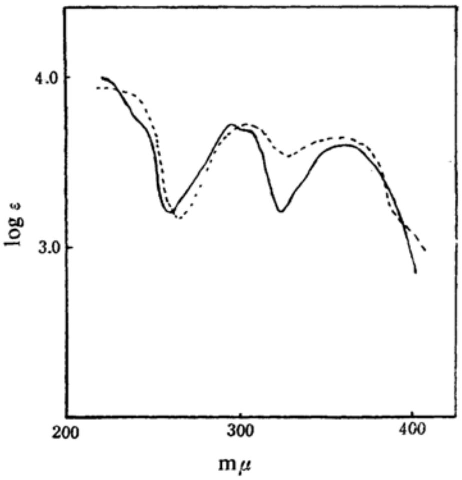


Fig. 1. Ultraviolet absorption spectra in methanol.
—— V, ---- VIII

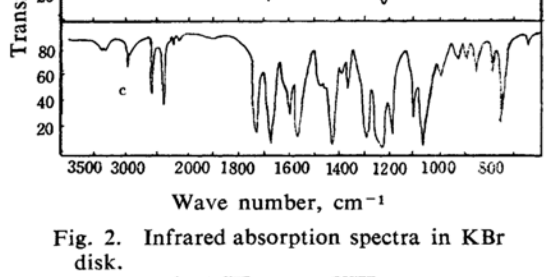


Fig. 2. Infrared absorption spectra in KBr disk.
a V, b VIII, c XIII

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

[2] H. Akino, to be published.

[3] Ultraviolet spectra were measured with a Hitachi EPU-2A spectrophotometer by Mr. F. Sato of this Institute, to whom the author is deeply indebted.

sorption spectra[4] of V and VIII are shown in Fig. 2, a and b.

The infrared spectrum of V exhibits absorption bands at 3455 and 3323 cm^{-1} for the primary amino or hydroxyl and imino group, at 2260 cm^{-1} for cyano group, at 1735 cm^{-1} for ester carbonyl, at 1678 cm^{-1} for ester carbonyl conjugated with unsaturated bond, and at 1635 cm^{-1} for absorption due to the deformation vibration of N–H group. Similar bands are found in the spectrum of VIII.

When V is warmed with dilute hydrochloric acid in ethanol for a short period, colorless crystals (IX), m. p. 93°C, are obtained. IX is also obtained on decomposition of the picrate of V with sodium hydrogencarbonate solution. Analytical values of IX agree with $C_{12}H_{10}O_4$.

The reaction of V with dilute acid for 4 hr. affords colorless crystals (X), m. p. 188°C, which are also formed on treatment of IX with dilute acid. X is an acid substance since it dissolves in sodium hydrogen carbonate solution. Analytical values of X correspond to the molecular formula of $C_{10}H_6O_4$. The ultraviolet absorption spectra of IX and X, shown in Fig. 3, are similar to the absorption curves of coumarin derivatives. Thermal decomposition of X produces colorless crystals (XI), m. p. 68°C, with an aroma. The ultraviolet absorption spectrum of XI (Fig. 3) and its melting point is identical with that of coumarin and on admixture it is confirmed that XI is coumarin.

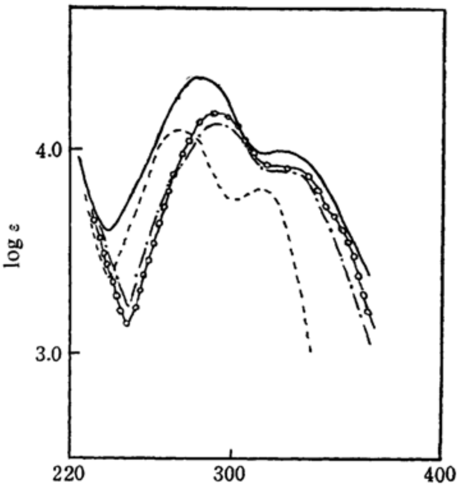
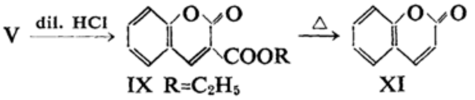


Fig. 3. Ultraviolet absorption spectra in methanol.

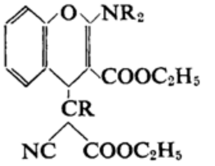
-○-○ IX, -·-·- X, ---- XI, —— XV

Consequently, IX is 3-ethoxycarbonylcoumarin and X is 3-carboxycoumarin. The melting points of IX and X are in good agreement with those reported in the literature.

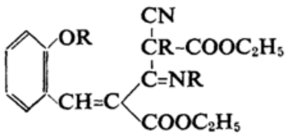


IX $R=C_2H_5$
X $R=H$
XI

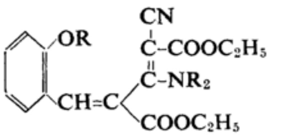
From these experimental results, formulae A, B, C and D are taken into consideration for the structure of V.



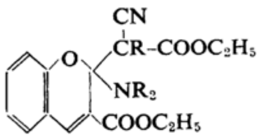
(A) R=H
(A_D) R=D



(B) R=H
(B_D) R=D



(C) R=H
(C_D) R=D



(D) R=H
(D_D) R=D

If formula A is correct, its ultraviolet absorption should be similar to that of *o*-alkylphenol[5]. However, V has absorption maxima at 296 and 365 mμ, differing from those of *o*-alkylphenols, so that the structure of V is not A.

The formulae B, C and D are tautomeric.

Baron[6] prepared a dimer (XII) by condensation of two molecules of ethyl cyanoacetate and gave the ketimine-type structure alone for XII, but it should also take a tautomeric amino-type structure. The infrared spectrum

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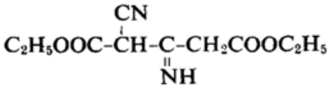
[4] Infrared spectra were measured with a Perkin-Elmer Model 21 double beam spectrophotometer by Mr. S. Aono of this Institute, to whom the author is deeply indebted.

[5] H. F. Hunter, R. A. Morton and A. T. Carpenter, *J. Chem. Soc.*, 1950, 441.

[6] H. Baron, ibid., 85, 1736 (1904).

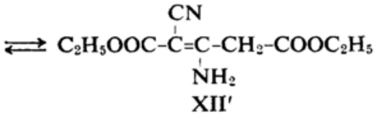
of XII exhibits absorption bands at 3420 and 3300 cm^{-1} for the primary amino group, at 2215 cm^{-1} for the cyano group conjugated with unsaturated bond, at 1710 cm^{-1} for ester carbonyl, and at 1680 cm^{-1} for ester carbonyl conjugated with unsaturated bond.

These facts indicate that the dimer XII takes the amino form XII′ in crystalline state.



$$C_2H_5OOC\text{-}\overset{\overset{\displaystyle CN}{|}}{C}H\text{-}\underset{\underset{\displaystyle NH}{\|}}{C}\text{-}CH_2COOC_2H_5$$

XII



$$\rightleftarrows C_2H_5OOC\text{-}\overset{\overset{\displaystyle CN}{|}}{C}{=}\underset{\underset{\displaystyle NH_2}{|}}{C}\text{-}CH_2\text{-}COOC_2H_5$$

XII′

In analogy with the above, it is more likely that V takes the amino-type C structure rather than the imino-type B. However, the infrared spectrum of V has an absorption for cyano group at 2260 cm^{-1}, but not of a cyano group conjugated with unsaturated bond. Moreover there is an absorption due to ester carbonyl not conjugated with unsaturated bond at 1735 cm^{-1}. It follows, therefore, that V has the structure of D, i.e. 2-amino-2-(cyano-ethoxycarbonylmethyl)-3-ethoxycarbonyl-α-benzopyrane.

VIII is a methyl derivative of V and the position of the methyl is assumed to be at 7-position, since there is absorption of C–H out-of-plane vibration at 820 cm^{-1} 7).

In order to confirm the formula D for V, the deuterated compound XIII of V was prepared and its infrared absorption spectrum was examined. XIII is obtained by recrystallization of V from 50% dioxane-deuterium oxide mixture. Admixture of XIII and V shows no depression in the melting point and the ultraviolet spectra of two compounds are identical.

The infrared spectrum of XIII (Fig. 2c) shows that the absorption bands at 3455, 3323, 2937, 1635, 1528, 1490, 1418, 1280, 1175, 1037 and 1025 cm^{-1} in V disappear in XIII, and new bands at 2576, 2418, 2160, 1565, 1430 and 1000 cm^{-1} appear in XIII. The absorption bands at 940 and 915 cm^{-1} in V shift to 934 and 900 cm^{-1} with slightly increasing intensity in XIII. The fact that no ring-substitution has occurred by deuteration is proved by the absence of any change in the C–H out-of-plane deformation vibration absorption in V and XIII. If all the deuterable functional groups in B, C and D structures assumed for V have been completely deuterated, the structures B_D, C_D or D_D would be possible for XIII. The wave number ratio of 3455 cm^{-1} in V and 2576 cm^{-1} in XIII is 1.34, and that of 3323 cm^{-1} in V and 2418 cm^{-1} in XIII is 1.38. These ratios agree with the usual values of ν(N–H)/ν(N–D).

The disappearance of the absorption band at 2937 cm^{-1} and appearance of a new absorption band at 2160 cm^{-1} gives a wave number ratio of 1.36, which agrees with the usual value of ν(C–H)/ν(C–D).

The absorption band at 2937 cm^{-1} in V is not due to the stretching absorption of C–H in aromatic ring or that in unsaturated double bond. This indicates that the deuterable hydrogen in the methine group of V has undergone an exchange reaction with deuetrium. Consequently, there should be no absorption band of ν(C–D) in formula C_D and this formula is excluded.

Mecke et al.8) examined infrared absorption spectra of phenol and deuterated phenol, and assigned the bands at 1399$\sim$1332 and 1230$\sim$1180 cm^{-1} for characteristic absorption of ν(C–O) and δ(O–H) in phenol. They showed that new absorption bands appeared at 1300 and 980$\sim$920 cm^{-1} in deuterated phenol.

There are absorption band at 1370 and 1175 cm^{-1} in V.

The band at 1175 cm^{-1} is active to deuteration but that at 1370 cm^{-1} is inactive. There is no absorption band due to δ(O–D) at 980$\sim$920 cm^{-1} in XIII. The absorption band at 1635 cm^{-1} in V is active to deuteration and this band may be assigned to δ(N–H). These facts suggest that V takes the formula D and not B.

Bechert9) obtained a compound XIV of m. p. 140°C by condensation of salicylaldehyde and ethyl cyanoacetate with alkoxide.

Knoevenagel et al.10) obtained XIV by the use of piperidine in place of alkoxide. Both workers gave the molecular formula of $C_{17}H_{18}O_5N_2$ for XIV.

Since the melting point of XIV is close to that of V and the molecular formula of the two compounds are identical, XIV was prepared by the method of Knoevenagel and its admixture with V showed no depression of the melting point. Further the ultraviolet absorption spectra of the two compounds were found to be identical.

Bechert and Knoevenagel et al. assigned the structure of diethyl-α,γ-dicyano-β-(2-hydroxyphenyl)-glutarate as XIV, i. e. V, but this structure cannot explain the ultraviolet and infrared spectral data obtained with V.

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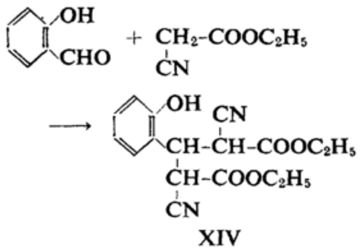
7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", Methuen, London, (1958), p. 65.

8) R. Mecke and G. Rossmy, *Z. Elektrochem.*, **58**, 866 (1955).

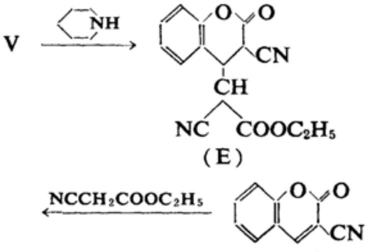
9) C. Bechert, *J. prakt. Chem.*, [2] **50**, 1 (1894).

10) E. Knoevenagel and R. Ornot, *Ber.*, 37, 4496 (1904).



XIV

Seshadri et al.[11] found that on refluxing XIV in ethanol containing piperidine, a compound XV of m. p. 248°C, was obtained. From the identity of XV with the condensation product of 3-cyanocoumarin (XVI) and ethyl cyanoacetate, they gave the structure of ethyl 3-cyano-3, 4-dihydrocoumarin-4-cyanoacetate (E) for XV.



(E)

XVI

If Seshadri's assumption is correct, formation of XV from the proposed structure of α-benzopyrane derivative for V cannot be explained. Therefore, re-examination was made on the structure of XV. The ultraviolet spectrum of XV, shown in Fig. 3, is similar to that of coumarin derivatives. The infrared spectrum of XV, as indicated in Fig. 4, exhibits absorption at 3410 and 3280 cm^{-1} for the primary amino group, at 2210 cm^{-1} for the cyano group conjugated to unsaturated bond, and at 1710 and 1680 cm^{-1} for lactonic carbonyl and ester carbonyl conjugated with unsaturated bond.

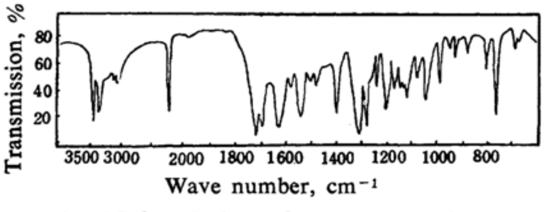
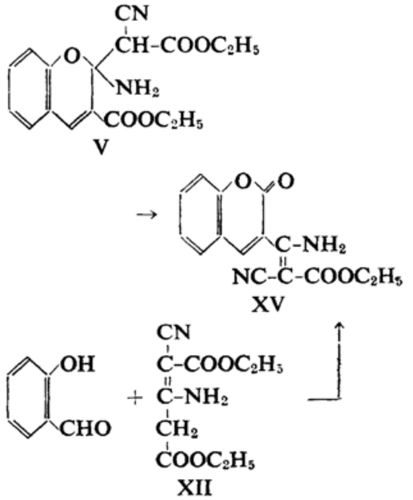


Fig. 4.Infrared absorption spectrum of XV in KBr disk.

These data suggest that the structure of XV is not E as proposed by Seshadri but must be α-amino-α-(3-coumarinyl)-β-cyano-β-ethoxycarbonylethylene.

Condensation of salicylaldehyde and XII, in the presence of potassium hydroxide or piperidine, affords a compound corresponding to XV.



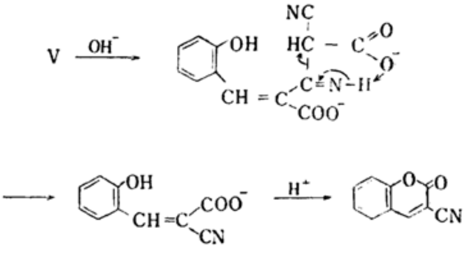
V

XV

XII

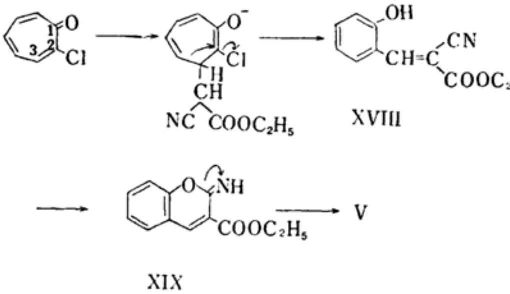
Knoevenagel et al.[10] reported the formation of 2-oxo-β-phenylpropane-α, α, γ-tricarboxylic anhydride (XVII) from V but re-examination of this reaction showed the formation of IX alone and not the compound corresponding to XVII.

It has been found that hydrolysis of V with ethanolic solution of potassium hydroxide produces XVI[9]. This reaction mechanism must be such as is indicated in Scheme 1.



Scheme 1.

This reaction is similar to the mechanism of formation of aromatic nitrile by alkaline hydrolysis of trichloro-aryl-ketimine[12].



XVIII

XIX

Scheme 2.

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[11] V. D. N. Sastry and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **16A**, 29 (1942); *Chem. Abstr.*, **37**, 880 (1943).

[12] J. Houben and W. Fisher, *J. prakt. Chem.*, **123**, 313 (1929); D. T. Mowry, *Chem. Revs.*, **42**, 221 (1948).

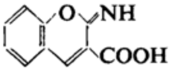
The mechanism for formation of V by the condensation of I and II is illustrated in Scheme 2.

Formation of salicylaldehyde derivatives by nucleophilic attack against tropone derivatives has already been witnessed in the reaction of 2, 7-dihalotropone with alkali[13] or ammonia[14], of 2-halo-7-phenyltropone and 2, 4, 7-tribromotropone[15,16].

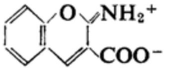
Kitahara[17] assumed a reaction mechanism for this kind of rearrangement reaction in which the nucleophilic reagent attacks the 3-position of the tropone ring.

Formation of V from I is assumed to follow similar rearrangement reaction mechanism.

Formation of an intermediate XIX is supported by the following evidence. Baker et al.[18] found that heating of salicylidenecyanoacetic acid (XX) in ethanol changed it into a substance XXI sparingly soluble in ethanol, and XXI was easily soluble in water and neutralization of its aqueous solution resulted in the formation of X. They therefore assumed for XXI an imino compound like XXIa or an intramolecular salt of imino compound like XXIb.



XXIa



XXIb

Experimental[19]

Picrate of V.—A saturated ethanolic solution of picric acid was added to a solution of 100 mg. of V dissolved in 3 ml. of ethanol and 150 mg. of yellow needles, m. p. 215°C (decomp.), separated out immediately. This picrate undergoes decomposition when heated in ethanol and changes into an easily soluble substance.

Found: C, 49.52; H, 3.91; N, 12.63. Calcd. for $C_{23}H_{21}O_{12}N_5$: C, 49.37; H, 3.75; N, 12.52%.

Picrate of VIII.—Yellow needles, m. p. 195~196°C.

Found: N, 12.53. Calcd. for $C_{24}H_{23}O_{12}N_5$: N, 12.21%.

Reaction of V with Dilute Acids. — a) A solution of 500 mg. of V dissolved in 10 ml. of ethanol, added with 0.2 ml. of 6 N hydrochloric acid, was boiled for 3 min. and evaporation of ethanol left prismatic crystals. The addition of water to this crystalline residue resulted in the melting of the crystals to form an oily substance which crystallized on standing. Recrystallization from ethanol afforded 250 mg. of colorless prisms (IX), m. p. 92~93°C which showed no depression on admixture with 3-ethoxycarbonylcoumarin.

Found: C, 66.38; H, 4.95. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62%.

b) A mixture of 100 mg. of V in 3 ml. of 2 N hydrochloric acid was refluxed at 100~110°C for 1 hr., by which V dissolved gradually. Water was added to the reaction mixture under cooling and colorless crystals precipitated out. Recrystallization from ethanol afforded 40 mg. of IX.

c) A mixture of 100 mg. of V in 1 ml. of 6 N hydrochloric acid was heated on a water bath for 4 hr., water was evaporated, and the precipitate thereby formed was recrystallized from ethanol, affording 20 mg. of X, m. p. 186~188°C, which showed no depression on admixture with 3-carboxycoumarin.

Found: C, 63.02; H, 3.61. Calcd. for $C_{10}H_6O_4$: C, 63.16; H, 3.18%.

Formation of Coumarin (X).—Low-pressure sublimation of 50 mg. of X by heating at 200~230°C produced some crystals with an aroma. Reccystallization of the sublimate from cyclohexane gave colorless plates (X), m. p. 67~68°C, undepressed on admixture with coumarin.

Deuteration of V. — V was recrystallized from 50% mixture of dehydrated dioxane and deuterium oxide.

Formation of α-Amino-α-(3-coumarinyl)-β-cyano-β-ethoxycarbonylethylene (XV).—A suspension of 100 mg. of V in 1 ml. of ethanol, with 3 drops of piperidine added, was refluxed for 4 hr., by which V dissolved once, and colorless needle crystals began to precipitate out as the reaction proceeded. Recrystallization of these crystals from a large volume of ethanol gave 60 mg. of XV, m. p. 245~246°C.

Found: C, 63.12; H, 4.34; N, 9.85. Calcd. for $C_{15}H_{12}O_4N_2$: C, 63.38; H, 4.26; N, 9.86%.

UV. $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (log ε): 280 (4.36), 318 (4.0).

Synthesis of XV.—A solution of 50 mg. of salicylaldehyde and 100 mg. of XII dissolved in 0.5 ml. of absolute ethanol with 1 drop of piperidine added was allowed to stand at room temperature. The crystals that precipitated out were recrystallized from ethanol and 120 mg. of XV was obtained.

The author takes this opportunity to express his deep gratitude to Professor Tetsuo Nozoe and Professor Shuichi Seto for their unfailing guidance and to Mr. Yusaku Ikegami and Mr. Kyozo Ogura for much helpful advice. Also the author expresses his thanks to Mr. S. Ohyama and Miss A. Iwanaga for the microanalyses.

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[13] S. Seto, *Sci. Repts. Tohoku Univ.*, (I), 37, 275 (1953).

[14] T. Nozoe. S. Seto and T. Sato, *Proc. Japan Acad.*, 30, 473 (1954).

[15] T. Mukai, This Bulletin, 32, 272 (1959).

[16] T. Nozoe, K. Doi and S. Endo, This Bulletin, 33, 1285 (1960).

[17] Y. Kitahara, *Sci. Repts. Tohoku Univ.*, (I), 39, 250 (1956).

[18] W. Baker and A. Lapworth, *J. Chem. Soc.*, 127, 560 (1925).

[19] All melting points are uncorrected.