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Structure and Properties of the Condensation Product of 2-Amino-3-ethoxycarbonyl-1-azaazulene and Formamide[1]

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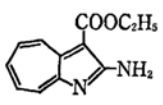
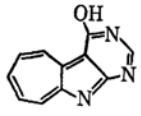
The structure of the condensation product of 2-amino-3-ethoxycarbonyl-1-azaazulene and formamide is proved not to be the expected cyclohepta[2, 3]pyrrolo[5, 4-*d*]pyrimidine derivative, but 5, 6-pentamethylene-7*H*-pyrrolo[2, 3-*d*]pyrimidin-4(3*H*)-one. The chemical properties of the obtained pyrrolo-pyrimidine are investigated, and then the tautomerism of the above compound is discussed.

Many heterocyclic compounds containing pyrimidines and purines are physiologically very important substances. Therefore, it is interesting to synthesize unsaturated seven-membered ring systems (such as tropolones and azulenes) which condensed with such heterocyclic nuclei, and to investigate the chemical and physiological properties of the resulting new heterocyclic compounds.

For this purpose, we attempted the condensation reaction of 2-amino-3-ethoxycarbonyl-1-azaazulene (I) with formamide, expecting to obtain a cyclohepta[2, 3]pyrrolo[5, 4-*d*]pyrimidine derivative such as (A). The condensation reaction was carried out in excess formamide by means of a modification of the method of Robins *et al.*[3,4]; this gave an almost colorless substance (II) in a



(I)



(A)

35—40% yield. II is hard to purify because of its insolubility in most organic solvents, and it can not be analyzed well. However, by a consideration of the results of the analysis of the its monoacetate (III)and monomethyl derivative (IV), the molecular formula of II is found to be not the expected $C_{11}H_7ON_3$, but $C_{11}H_{13}ON_3$. Neither the results of elemental analysis nor the ultraviolet spectra of II and IV show any absorption band longer than 320 mμ, as is shown in Fig. 1, even though the spectra of azaazulenes and their 2-hydroxy derivatives show strong absorption bands in the visible region.[5] The shape of the spectrum of II is analogous to those of 7-azaindole,[6] pyrrolo-[2, 3-*d*]pyrimidine,[7] and purines.[8] The IR spectrum of II (Fig. 2) shows strong bands at 2838

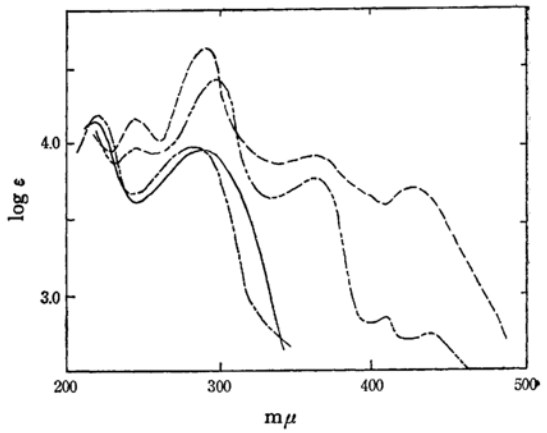


Fig. 1

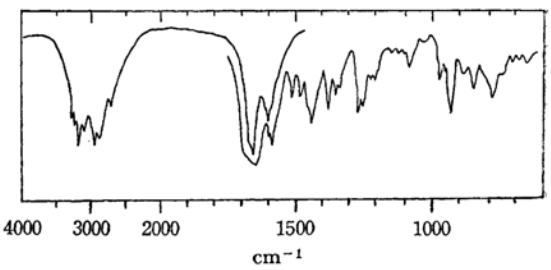


Fig. 2. KBr pellet.

1) Part of the D. Sc. thesis of Takashi Toda, March, 1958, Tohoku University.
2) Present address: the Chemical Research Institute of Non-aqueous Solutions, Tohoku University.
3) R. K. Robins, K. J. Dille, C. H. Willits and B. E. Christensen, *J. Am. Chem. Soc.*, **75**, 263 (1953).
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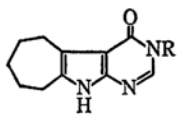
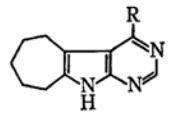
5) T. Nozoe, S. Seto, S. Matsumura and T. Terasawa, *Chem. & Ind.*, **1954**, 1357, 1358.
6) M. M. Robison, F. P. Butler and B. L. Robison, *J. Am. Chem. Soc.*, **79**, 2573 (1957).
7) J. Davoll, *J. Chem. Soc.*, **1960**, 131.
8) J. F. Cavalierie, A. Bendich, J. F. Tinker and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3875 (1948).

and 2920 cm^{-1} due to methylene CH stretching,[9] and at 1650 cm^{-1} a broad, strong bands correspond to the carbonyl band of pyrimidin-4-ones,[10] while the three bands at 1478, 1511 and 1588 cm^{-1} are assigned to the skeltal vibration of such heterocyclic compounds as pyrimidines.[11] It is known that 1-azaazulenes are sensitive to reducing reagents and that the reduction of the seven-membered ring of those compounds takes place easily to give perhydro-compounds.[12] The consideration of the above facts and of the properties of formamide as a reducing reagent leads to the conclusion that the seven-membered ring of I is reduced by formamide during the reaction; therefore, the structure of II is 5, 6-pentamethylene-7*H*-pyrrolo[2, 3-*d*]pyrimidin-4(3*H*)-one.



II: R=H
IV: R=Me



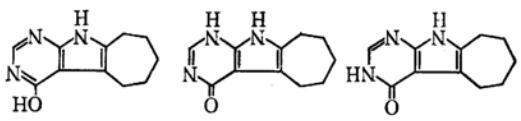
V: R=Cl
VI: R=OMe
VII: R=$NHNH_2$

Under milder conditions, however, the condensation reaction does not take place and I is recovered. The reason for the low yield of II is the formation of some intractable powder which is not soluble in most organic solvents. Although the molecular weight of the powder could not be measured because of its insolubility, this powder is presumably a mixture of the dimers or polymers formed by self-condensation during the reaction.

The treatment of II with phosphorous oxychloride afforded 4-chloro-5, 6-pentamethylene-7*H*-pyrrolo[2, 3-*d*]pyrimidine (V). 4-Methoxy (VI) and 4-hydrazino derivatives (VII) were derived when V was treated with sodium methoxide in methanol and with hydrazine respectively. VI was also obtained when V was treated with hydrazine in methanol, but VII was not obtained.

In order to obtain 5, 6-pentamethylene-7*H*-pyrrolo[2, 3-*d*]pyrimidine, a modified Stevenes-McFadyen decomposition reaction[13] was applied to VII, but the attempt was unsuccessful. The dehydrogenation of II by means of chloranil afforded a dark yellow, gummy substance (VIII) in a poor yield. Although it was hard to obtain in an analytically pure state, the ultraviolet and visible spectra of VIII are analogous to those of I, as is shown in Fig. 1; VIII is thus probably the expected cyclohepta[2, 3]pyrrolo[5, 4-*d*]pyrimidine derivative. However, VIII could not be investigated further because of the low yield of VIII and the lack of the starting material.

It is possible that II exists in such tautomeric forms as IIA, IIB and IIC. However, the ultraviolet spectra of II and IV differ from those of V and VI as Figs. 1 and 3 show, and the following investigation of their IR spectra leads to the conclusion that II is favorable to the IIA form.



IIA IIB IIC

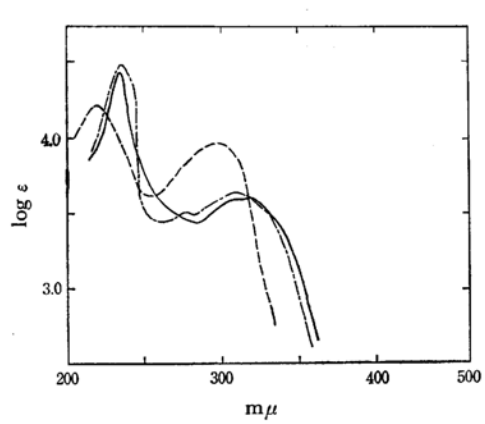


Fig. 3
V ——— VI —·—· VII ———

The strong band at 1650 cm^{-1} and several bands between 3100 and 3300 cm^{-1} of II in its IR spectrum can be reasonably explained on the basis of the IIA form which possess carbonyl and NH groups. α- or γ-Pyridone makes several different kinds of inter- and intramolecular hydrogen bonds between carbonyl and NH groups in the solid state; this is the reason why II shows a strong broad carbonyl band and several different kinds of NH stretching bands. IV shows a strong carbonyl band at 1655 cm^{-1} in its IR spectrum and so differs from VI, which does not show a carbonyl band. The problem of the α- or γ-pyrimidone form can be solved from the analogy with 4-hydroxypyrimidines; a consideration of their ultraviolet spectra and chemical properties shows the tautomeric form of those compounds to favor α-pyrimidones.[14] Thus the structures of II and IV are 5, 6-pentamethylene-7*H*-pyrrolo[2, 3-*d*]pyrimidin-4(3*H*)-one and 3*N*-methyl-5, 6-pentamethylene-7*H*-pyrrolo-[2, 3-*d*]pyrimidin-4(3*H*)-one respectively.

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10) L. N. Short and H. W. Thompson, *J. Chem. Soc.*, **1952**, 168.
11) H. Tsubomura, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **78**, 1528 (1957).
12) Unpublished observation made in the authors' laboratory.
13) S. Seto, *Sci. Repts. Tohoku Univ., Ser. I*, **37**, 286, 295 (1953).
14) D. J. Brown and L. N. Short *J. Chem. Soc.*, **1953**, 331.

The ultraviolet spectrum of VII is rather analogous to that of II, but not to those of V and VI. VII presumably exists in its tautomeric (hydrazone) form. The IR spectrum of VII is not very helpful in determining its tautomeric form. Other evidence to support the tautomeric form of VII is as follows: the ultraviolet spectrum of VII is analogous to that of 4-pyrimidones, but not to that of 4-chloropyrimidines.[4] This relation is parallel with the relation of II, V, and VII, described above.

Experimental[15]

2-Amino-3-ethoxycarbonyl-1-azaazulene (I). In an autoclave, a solution of 5.0 g of 2-chloro-3-ethoxycarbonyl-1-azaazulene[5] in 50 m*l* of alcohol, which had been saturated with ammonia, was heated for 5 hr at 120°C. After cooling, the alcohol was removed and the residue was washed with water, dried, and chromatographed on alumina. From the benzene eluate, 4.5 g of yellow needles were obtained, while recrystallization from cyclohexane afforded yellow scales of I, mp 150—151°C.

Found: C, 66.89; H, 5.31; N, 13.27%. Calcd for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96%.

5, 6-Pentamethylene-7*H*-pyrrolo[2, 3-*d*]pyrimidin-4(3*H*)-one (II). A solution of 3.20 g of I and 10.0 m*l* of formamide was heated for one and a half hours at 200°C. After the reaction, the solution was poured into 100 m*l* of cold water, and the precipitate thus formd was separated by filtration, washed with water and a small amount of ethyl acetate, and dried *in vacuo*. A pale brown powder, 2.40 g, was thus obtained. This powder decomposed near 280°C when heated. The powder is hardly soluble at all in benzene, ether, chloroform, ethyl acetate, acetone, and ethanol, but soluble in acetic acid and dioxane. It does not dissolve in aqueous sodium bicarbonate, but it does dissolve in dilute alkali. However, if the pH of the solution goes below 9, the precipitate forms immediately.

Finally, the reaction product (3.20 g) was dissolved in a large amount of methanol and chromatographed on alumina. The first eluate was recrystallized from methanol to give 1.20 g of micro prisms of II, mp 326—328°C (colored about 260°C, Koffler block).

Found: C, 62.92; 63.24; H, 6.14; 6.05; N, 20.16; 20.20%. Calcd for $C_{11}H_{13}ON_3$: C, 65.00: H, 6.45; N, 20.68%.

The methanol-water eluate of the chromatograph could not be obtained in a pure state and did not show any clear melting point but it gradually blackened between 250—300°C.

Acetylation of II (III). A solution of 0.10 g of II in 1.0 m*l* of acetic anhydrided was heated to reflux for 4 hr, and then the excess acetic anhydride was removed under reduced pressure to give pale yellow micro needles of III, mp 234—236°C. The recrystallization of this crude product from ethyl acetate and decolorizing charcoal afforded 0.08 g of pale yellow micro needles of III, mp 237—239°C.

Found: C, 63.24; H, 5.81; N, 17.26%. Calcd for $C_{13}H_{15}O_2N_3$: C, 63.66; H, 6.16; N, 17.13%.

15) All melting points are uncorrected.

λ_{max}^{MeOH} mμ (log ε); 237 (4.10), 265 (3.86) and 308 (3.82).

Methylation of II with Dimethyl Sulfate (IV). To a solution of 0.10 g of II and 0.04 g of sodium hydroxide in 1.0 m*l* of water, 0.07 g of dimethyl sulfate was added, and then the solution was shaken continuously for 5 hr. The pH of the solution was adjusted to about 6 with N hydrochloric acid to form resinous precipitate. This precipitate was separated by filtration, washed with water, extracted with ethyl acetate, and dried over sodium sulfate. After the sodium sulfate had been filtered off, the ethyl acetate was removed under reduced pressure to give a crystalline substance. The crude IV thus obtained was recrystallized from ethyl acetate with active charcoal to give 0.05 g of colorless scales of IV, mp 318—320°C (colored about 280°C, Koffler block).

Found: N, 18.91%. Calcd for $C_{12}H_{15}ON_3$: N, 19.34%.

λ_{max}^{MeOH} mμ (log ε); 220 (4.19) and 285 (4.00).

4-Chloro-5, 6-pentamethylene-7*H*-pyrrolo[2,3-*d*]pyrimidine (V). A solution of 0.30 g of II in 2.0 m*l* of phosphorous oxychloride in a sealed tube was heated for 3 hr at 100°C, and the excess phosphorous oxychloride was removed under reduced pressure. The pH of the residue was adjusted to about 8.5 with diluted aqueous ammonia, extracted with ethyl acetate, and dried over sodium sulfate. The sodium sulfate was then separated by filtration, and the residue was sublimed under reduced pressure (0.5 mmHg at 150°C). The sublimate was recrystallized from benzene to give 0.14 g of pale yellow prisms of V, mp 228°C.

Found: C, 59.63; H, 5.00; N, 19.00%. Calcd for $C_{11}H_{12}N_3Cl$: C, 59.59; H, 5.46; N, 18.96%.

λ_{max}^{MeOH} mμ (log ε); 234 (4.40) and 316 (3.60).

4-Methoxy-5, 6-pentamethylene-7*H*-pyrrolo[2, 3-*d*]pyrimidine (VI). A suspension of 0.20 g of V and 1.20 g of hydrazine hydrate (80%) in 5.0 m*l* of methanol was refluxed for 4 hr, after which the excess methanol was removed under reduced pressure. The residue was sublimed under reduced pressure (0.1 mmHg at 150°C), and the sublimate was recerystallized from acetone to give colorless scales of VI, mp 246—247°C; yield, 0.14 g.

Found: N, 19.16%. Calcd for $C_{12}H_{15}ON_3$: N, 19.34%.

λ_{max}^{MeOH} mμ (log ε); 234 (4.14), 275 (3.40) and 310 (3.53).

A mixed-melting-point determination of VI with IV clearly showed a depression. When sodium methoxide was used instead of hydrazine, VI was obtained in a quantitative yield.

4-Hydrazino-5, 6-pentamethylene-7*H*-pyrrolo-[2, 3-*d*]pyrimidine (VII). A mixture of 0.1 g of V and 1.0 m*l* of hydrazine hydrate (80%) was refluxed for 5 hr, thus the precipitate was formed. The formed precipitate was then recrystallized from methanol to give 0.07 g of colorless scales of VII, mp 233—235°C (decomp.).

Found: C, 60.86; H, 6.43; N, 31.81%. Calcd for $C_{11}H_{15}N_5$: C, 60.80; H, 6.96; N, 32.24%.

λ_{max}^{MeOH} mμ (log ε); 216 (4.22) and 294 (3.98).

The Decomposition of VII. A solution of 0.05 g of VII in 1 m*l* of acetic acid was poured into a boiling solution of 0.50 g of cupric sulfate in 1 m*l* of water.

The solution turned black with the evolution of gas; after it had cooled, 10 m*l* of water were added. The pH of the solution was then adjusted to about 8 by means of aqueous bicarbonate and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, separated by filtration, and concentrated to give an intractable, gummy substance.

Dehydrogenation of II. To a solution of 0.50 g of II in 10 m*l* of refluxing isoamyl alcohol, 1.50 g of chloranil were added in five portions over a period of 2 hr; refluxing was then continued for 4 hr. The amyl alcohol was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The ethyl acetate solution was then chromatographed on silica gel; a small amount of amorphous powder was thus obtained.

λ_{max}^{MeOH} mμ; 245, 300, 368 and 399.

The powder dissolved in benzene, ethyl acetate, and acetone, but it formed a gelly substance when concentrated. Further purification by means of recrystallization and other methods failed to produce a pure substance.

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