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Synthesis and Properties of 3-Formyl-1-azaazulan-2-one[1]

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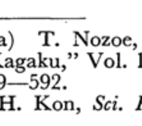
3-Formyl-1-azaazulan-2-one was synthesized in a good yield from 1-azaazulan-2-one by means of a Vilsmeire reaction and its chemical properties were investigated. The synthesis of the tryptophan analogue from the formyl compound was also attempted.

1-Azaazulan-2-ones[2] and 1-azaazulenes[3] are non-benzenoid analogues of indoles and isomers of quinolins, therefore, it is interesting not only to investigate their chemical properties, but also to study their physiological properties. For this purpose, the Mannich reaction of 1-azaazulan-2-one (I) was investigated and compounds analogous to gramine and tryptophan were synthesized.[4,5] As a part of these studies, the synthesis of 3-formyl-1-azaazulan-2-one, a key compound in the above synthesis, was attempted. The formylation of indole by the Vilsmeier-Haack reaction has been reported to give 3-formyl indole in a good yield.[6] As with indole, the electron density of I is high at the 3-position due to a resonance contribution from the lone pair electrons on the nitrogen atom; furthermore, the π-electrons of the seven-membered ring in I (and azulene or azaazulene systems) have a strong tendency to go to the 1, 3-positions of the five membered ring.[7] In fact, I is very active in the cationoid substitution reaction.[2,3] Therefore, it may be expected that the formylation of I by the Vilsmeier-Haack reaction would give good results.



I: R=H
II: CHO
III: CH=NNH$_2$
IV: CH=NOH
V: CH$_3$
XI: CH$_2$OH

When the Vilsmeier-Haack reaction was applied to I, 3-formyl-1-azaazulen-2-one (II) was obtained in an almost quantitative yield. The ultraviolet spectrum of II is typical of the 1-azaazulan-2-one type,[2,7a] but it has shifted to a longer wavelength,

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1) Taken from the D. Sc. thesis of T. Toda, Tohoku University, March, 1958.

2) T. Nozoe, S. Seto, S. Matsumura and T. Terasawa, *Chem.* & *Ind.*, **1954**, 1356.

3) T. Nozoe, S. Seto, S. Matsumura and T. Terasawa, *ibid.*, **1954**, 1357.

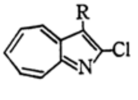
4) Shigeo Nozoe, M. Sc. essay, Tohoku University, March, 1957.

5) Akira Sato, *ibid.*, March, 1959.

6) M. Onda, M. Kawanishi and M. Sasamoto, *Yakugaku Zasshi,* **76**, 472 (1956).

7) a) T. Nozoe, T. Asao and K. Kikuchi, "Dai Yuki Kagaku," Vol. 13, Asakura Shoten, Tokyo (1960), pp. 449—592.
b) H. Kon, *Sci. Repts. Tohoku Univ., Ser. I*, **38**, 67 (1954).

indicating the presence of a formyl group in the azaazulanone nucleus; its infrared spectrum shows an aldehyde CH stretching peak at 2730 cm^{-1} and a conjugated carbonyl band at 1681 cm^{-1}.[8] II readily forms a hydrazone (III) and an oxime (IV); however, 3-carboxy-1-azaazulen-2-one could not be isolated when II was treated with Tollen's reagent or potassium permanganate, although some acidic material was formed which probably contained the 3-carboxy-1-azaazulan-2-one. The Wolff-Kischner reduction[9] of III afforded 3-methyl-1-azaazulan-2-one (V) in a good yield, indicating that the azaazulanone skeleton is sufficiently stable to withstand drastic reaction conditions such as those of the Wolff-Kischner reduction: this stability may be of use in further synthetic studies. The phosphoryl chloride treatment of V gave 2-chloro-3-methyl-1-azaazulene (VI). When IV was treated with phosphoryl chloride under mild conditions, the oxime (VII) of 2-chloro-3-formyl-1-azaazulene was obtained, but the 3-formamide derivative could not be detected.

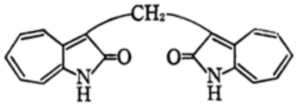


VI: R=CH_3
VII: CH=NOH
VIII: CN
IX: CHO
XV: CH=$CHNO_2$

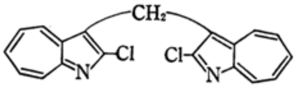
The structure of VII was proved by its analysis and by its infrared spectrum, which shows normal oxime OH stretching at 3150 cm^{-1}, but no formyl carbonyl nor CH stretching.[8] The treatment of IV with phosphoryl chloride under more drastic conditions afforded the known 2-chloro-3-cyano-1-azaazulene (VIII).[10] Therefore, the formyl group must be at position 3 in the 1-azaazulan-2-one skeleton.

2 - Chloro - 3 - formyl - 1-azaazulene (IX) was obtained in a good yield by the direct treatment of II with phosphoryl chloride. The infrared spectrum of IX shows a conjugated carbonyl at 1674 cm^{-1} and aldehyde CH stretching at 2720 cm^{-1}. Its ultraviolet spectrum is very similar to those of other 1-azaazulenes,[3] but the absorption maxima are shifted to longer wavelengths than in the case of 2-chloro-1-azaazulene.[3] In expectation of obtaining a condensed oxazole ring on the 1-azaazulene nucleus, IX was treated with hydroxylamine, but only the VII, oxime, was obtained. By treatment with hydrazine, the starting material was recovered; not even the hydrazone of IX was obtained under the reaction conditions. By the action of phenyl hydrazine on IX, the phenylhydrazone (X) was obtained, together with a small amount of 3-formyl-2-[2-phenylhydrazino]-1-azaazulene: small amounts of an unidentified by-product were also isolated.

The sodium borohydride reduction of II afforded 3-hydroxymethyl-1-azaazulan-2-one (XI), which is very unstable and which did not give good analysis. However, the ultraviolet spectrum of XI is typical of an azaazulanone, and its infrared spectrum clearly shows a strong absorption at 3420 cm^{-1}, while the aldehyde carbonyl at 1681 cm^{-1} has disappeared. Heating an alcoholic solution of XI resulted in the formation of 3, 3′-bis(1-azaazulanonyl) methane (XII) from two molecules of XI. The same type of condensation reaction was observed when an alcoholic solution of 3-hydroxymethyl indole was heated.[11] The treatment of XI with iodine and red phosphorous did not give V, but XII was obtained; the acid treatment of XI also gave XII. XII is hard to purify, and it does not give a good analysis: however, both treatments seem to produce a product containing a molecule of water of crystallization, as is indicated by its infrared spectrum (a broad band at 3400 cm^{-1}).



XII



XIII

The application of the Lederer-Mannasse reaction[12] and chloromethylation[13] on I also afforded XII in a good yield. Once again, XII did not give a good analysis and appeared to contain water of crystallization. However, the phosphoryl chloride treatment of the XII obtained by any of the above methods afforded 3, 3′-bis[(2, 2′-dichloro)-1-azaazulanyl]methane in a good yield. The mechanism of the formation of XII from I is possibly similar to that of the formation of phenol resin from formalin and phenol.[14] The intermediate of the reaction can be considered to be rather stable as a result of the resonance contribution of its canonical formulas, A, B and others, for the same reason as has been pointed out before. Similar reactions, in which two azulene molecules are

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8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., Methuen, London (1958).

9) Haung-Minlon's method was applied: Haung-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

10) T. Nozoe, S. Seto and S. Nozoe, *Proc. Japan Acad.*, **32**, 472 (1956).

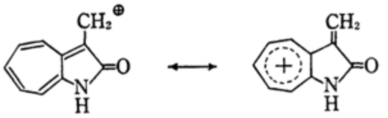
11) L. Marion and E. Leete, *Can. J. Chem.*, **31**, 775 (1953).

12) a) L. Lederer, *J. Prakt. Chem.*, **2**, **50**, 223 (1894).
b) O. Mannasse, *Ber.*, **27**, 2409 (1894).

13) R. Oda, "Synthetic Organic Chemistry," Kyoritsu Shuppansha, Tokyo (1949), p. 283.

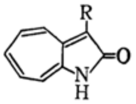
14) M. Imoto, "Reaction Mechanism in Organic Chemistry," Vol. II, Kyoritsu Shuppansha, Tokyo (1952), pp. 285—290.

joined together by a methylene bridge, have been reported in the Mannich reaction, chloromethylation, and hydroxymethylation of azulenes.[15]



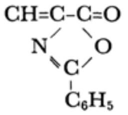
A B *etc.*

In order to synthesize gramine and tryptophan analogues of 1-azaazulenes, the condensation reactions of II with nitromethane and hippuric acid were investigated, products such as (XIV) and XVI were obtained. These condensation products are barely soluble in most organic solvents. The product, XIV, did not give a good analysis. XIV gave 2-chloro-3(β-nitrovinyl)-1-azaazulene (XV) upon phosphoryl chloride treatment; however, the preparation of a gramine-like substance by the hydrogenation of XIV was not successful.

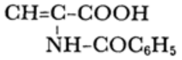


XIV: R = $CH{=}CHNO_2$

XVI:

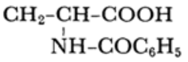


XVII:



$\underset{\displaystyle NH\text{-}COC_6H_5}{CH{=}C\text{-}COOH}$

XVIII:



$\underset{\displaystyle NH\text{-}COC_6H_5}{CH_2\text{-}CH\text{-}COOH}$

The alkaline hydrolysis of the azulactone XVI afforded unsaturated acid (XVII). The further reduction of XVII did not, however, give α-benzoylamino-β[1-azaazulanon-2-yl-3]propionic acid (XVIII) in the pure state.

Experimental[16]

3-Formyl-1-azaazulan-2-one (II). To a solution of 0.50 g of I in 3 m*l* of dimethylformamide cooled in an ice bath, a mixture of 4.0 m*l* of dimethylformamide and 1.0 g of phosphoryl chloride was added drop by drop. After the mixture had then been allowed to stand at room temperature for one day, it was heated at 50°C for an hour after the addition of 0.50 g of sodium acetate, and then poured into 50 m*l* of cold water. The pH of the solution was adjusted to about 5 with aqueous sodium bicarbonate, and the precipitate which formed was filtered off, washed with water, and dried in a desiccator. Orange scales of II, 0.50 g, mp 273—275°C, were obtained; recrystallization from methanol did not raise its melting point.

Found: C, 69.88; H, 4.51; N, 8.39%. Calcd for $C_{10}H_7O_2N$: C, 69.36; H, 4.07; N, 8.09%. λ_{max}^{MeOH} mμ (log ε); 228 (4.32), 257 (4.47), 292 (4.54), 438 (4.45). 0.05 g of II, mp 265—268°C, was obtained from the aqueous layer by ethyl acetate extraction.

Hydrazone of II (III). From 50 mg of II and 20 mg of hydrazine hydrate in alcohol, 50 mg of reddish purple microprisms of III were obtained; mp>300°C, after recrystallization from alcohol.

Found: N, 22.12%. Calcd for $C_9H_9ON_3$: N, 22.45%.

Oxime of II (IV). Red purple scales, mp 247°C (d), from alcohol.

Found: N, 14.32%. Calcd for $C_{10}H_8O_2N_2$: N, 14.89%. λ_{max}^{MeOH} mμ (log ε); 232 (4.45), 275 (4.20), 295 (4.29), 438 (4.07).

3-Methyl-1-azaazulan-2-one (V). A solution of 0.22 g of III and 0.60 g of potassium hydroxide in 50 m*l* of ethylene glycol was heated at 200°C for four hours, and then the solvent was removed under reduced pressure. Water was added to the residue, and the pH of the solution was adjusted to about 5 with N hydrochloric acid. The solution was extracted with ethyl acetate, and the combined ethyl acetate layers were washed with water, dried over sodium sulfate, and concentrated. The solid residue was recrystallized from ethyl acetate to afford 0.18 g of orange needles which failed to show any depression in melting point upon admixture with authentic 3-methyl-1-azaazulan-2-one.[4] The UV spectra of these compounds are superimposable.

2-Chloro-3-methyl-1-azaazulene (VI). In a sealed tube, 50 mg of V and 1.0 m*l* of phosphoryl chloride were heated on a water bath for an hour; then the excess phosphoryl chloride was removed under reduced pressure. The residue was treated with aqueous sodium bicarbonate to adjust its pH to about 9, and then extracted several times with benzene. The combined benzene washings were washed with water, dried over sodium sulfate, and chromatographed on alumina. The benzene elutes afforded 50 mg of carmine needles of VI, mp 97°C, after recrystallization from cyclohexane.

Found: C, 67.97; H, 4.16; N, 7.75%. Calcd for $C_{10}H_8NCl$: C, 67.61; H, 4.54; N, 7.83%. λ_{max}^{MeOH} mμ (log ε); 228 (4.24), 276 (4.67), 325 (3.57), 356 (3.18), 480 (3.13).

Reaction of IV with Phosphoryl Chloride. a) A mixture of 50 mg of IV and 1.0 g of phosphoryl chloride in a sealed tube was heated on a water bath for two hours and then treated in the same way as VI. The chromatography of the resulting residue and elution with benzene afforded 30 mg of yellow needles of VII, mp 226—228°C.

Found: N, 13.48%. Calcd for $C_{10}H_7ON_2Cl$: N, 13.61%.

The melting point of VII was depressed on admixture with VIII, mp 230°C,[10] but it did not show any such depression with the oxime of IX, mp 227°C.

b) When the reaction was carried out at 140°C for five hours, 50 mg of IV afforded 20 mg of VIII, which failed to show any depression in melting point upon admixture with an authentic sample.[10] IR, 2210 cm^{-1}.

2-Chloro-3-formyl-1-azaazulene (IX). A solution of 0.12 g of II in 1.0 m*l* of phosphoryl chloride was heated on a water bath for four hours and then treated in the way which has been described for VI. A chromatograph of the product gave yellow needles which, after recrystallization from cyclohexane, afforded 0.10 g of yellow needles of IX, mp 178—179.5°C.

Found: C, 62.53; H, 3.17; N, 7.61%. Calcd for

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15) a) H. Arnold and K. Pahles, *Chem. Ber.*, **89**, 121 (1956). b) K. Hafner and W. Senf, *Ann.*, **656**, 34 (1962).

16) All melting points are uncorrected.

$C_{10}H_6ONCl$: C, 62.68; H, 3.16; N, 7.31%. λ_{max}^{MeOH} mμ (log ε); 218 (4.24), 243 (4.09), 294 (4.60), 325 (3.93), 352 (3.70), 435 (3.08).

Oxime of IX. A solution of 20 mg of IX and 10 mg of hydroxylamine hydrochloride in 1.0 m*l* of tetrahydrofurane (THF) was heated on a water bath for two hours; after the completion of the reaction, the THF was removed by distillation. The residue was dissolved in benzene, and the solution was chromatographed on alumina. Benzene eluted 10 mg of yellow needles of oxime, mp 226—227°C.

The Reaction of IX with Phenylhydrazine. A solution of 30 mg of IX and 18 mg of phenylhydrazine in 1.0 m*l* of anhydrous THF was allowed to stand overnight at room temperature. After the THF had been removed, the residue was dissolved in a benzene petroleum ether mixture (1 : 1) and chromatographed on alumina. Benzene and petroleum ether eluted black yellowish needles of 2-(2′-phenyl)hydrazino-3-formyl-1-azaazulene which, after recrystallization from the same mixed solvent, afforded 5 mg of silky, yellowish black needles, mp 190—191°C.

Found: N, 16.14%. Calcd for $C_{16}H_{13}ON_3$: N, 15.96%.

From the benzene elutes, 25 mg of dark brown prisms of phenylhydrazone of IX, mp 186°C (d), were obtained on recrystallization from benzene.

Found: C, 68.85; H, 4.50; N, 14.82%. Calcd for $C_{16}H_{12}N_3Cl$: C, 68.20; H, 4.29; N, 14.91%.

In addition, a few milligrams of silky black needles, mp 249.5°C (d) were obtained. Presumably, this was the phenylhydrazone of 2-(2′-phenyl)hydrazino-3-formyl-1-azaazulene.

3-Hydroxymethyl-1-azaazulan-2-one (XI). To a suspension of 0.25 g of powdered II in 50 m*l* of methanol, 0.12 g of sodium borohydride was added in small portions over a one hour period; the mixture was then allowed to stand at room temperature for a further four hours. Methanol was removed under reduced pressure at room temperature, and acetic acid was added to the ice cold residue in order to adjust the pH of the solution to about 5. The precipitate which formed was filtered off, washed several times with cold water, and dried in a desiccator; 0.24 g of a brown solid, mp 252—255°C (d), was thus obtained. The compound was fairly unstable and gradually dimerized to XII when heated.

Found: C, 69.75; H, 4.48; N, 8.39%. Calcd for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00%. λ_{max}^{MeOH} mμ (log ε); 225 (4.07), 265 (4.47), 415 (4.02).

3, 3′-Bis[1-azaazulan-2-onyl]methane (XII). a) A mixture of 30 mg of XI, 20 mg of iodine, and 20 mg of red phosphorus in 1.0 m*l* of acetic acid and 0.3 m*l* of water was heated on a water bath for one and a half hours. The solvent was then removed under reduced pressure, and the excess iodine was removed with sodium thiosulfate. The residue was separated by filtration, washed with water, and dried in a desiccator. Recrystallization from ethyl acetate yielded 20 mg of a brown powder which did not melt below 300°C.

Found: C, 72.20; H, 5.36; N, 8.87%. C, 69.75; H, 4.48; N, 8.59: C, 70.68; H, 4.28; N, 8.72%. Calcd for $C_{19}H_{14}O_2N_2$: C, 75.48; H, 4.67; N, 9.27%. $C_{19}H_{14}O_2N_2 \cdot H_2O$: C, 71.24; H, 5.03; N, 8.75%. $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00%. λ_{max}^{MeOH} mμ (log ε); 265 (4.52), 416 (4.08).

b) A solution of 0.10 g of I, 0.5 m*l* of 40% formalin, and 2 N sodium hydroxide in 5.0 m*l* of methanol was heated at 50°C for thirty minutes. The brown precipitate, which formed slowly, was filtered off, washed with water, and dried in a desiccator. Recrystallization from alcohol afforded a gel which, when dried, gave 90 mg of an amorphous brown powder. The powder did not have a sharp melting point.

Found: N, 8.57%. λ_{max}^{MeOH} mμ (log ε); 265 (4.52), 416 (4.10).

When paraformaldehyde was used instead of 40% formalin, the same results were obtained.

c) A mixture of 0.10 g of I, 0.5 m*l* of 40% formaldehyde, and 1.0 m*l* of concentrated hydrochloric acid, when treated as above, yielded 0.10 g of a brown powder.

Found: N, 8.68%. λ_{max}^{MeOH} mμ (log ε); 264 (4.50), 415 (4.08).

All the substances obtained above show a broad, strong absorption in the IR region between 3300 and 3500 cm^{-1}, indicating the presence of water of cyrstallization.

3, 3′-[(2, 2′-Dichloro)-1-azaazulenyl]methane (XIII). A mixture of 0.10 g of XII and 1.0 m*l* of phosphoryl chloride in a sealed tube was heated on a water bath for one hour; after reaction, the mixture was then treated just as in the case of VI. The crude product in benzene-chloroform (10 : 1) was chromatographed on alumina to give 0.10 g of carmine-red needles of XIII, which did not have a sharp melting point and which turned black above 210°C.

Found: C, 67.60; H, 3.32; N, 8.26%. Calcd for $C_{19}H_{12}N_2Cl_2$: C, 67.27; H, 3.57; N, 8.26%. λ_{max}^{MeOH} mμ (log ε); 228 (4.54), 227 (4.83), 325 (3.95), 355 (3.68), 474 (3.39).

XII obtained by different methods gave XIII in a good yield when treated with phosphoryl chloride.

3-(β-Nitrovinyl)-1-azaazulan-2-one (XIV). After having been allowed to stand for one week at room temperature, a solution of 0.10 g of II, 0.05 g of monomethyl amine hydrochloride, 0.02 g of sodium carbonate, and 0.05 g of nitromethane in 50 m*l* of absolute alcohol afforded a precipitate. After the alcohol had been removed under reduced pressure, the precipitate was washed with water, dried in a desiccator, and recrystallized several times from a large amount of dioxane to yield 0.11 g of purple brown needles of XIV, mp 294—296°C (d).

Found: C, 58.87; H, 4.33; N, 11.81%. Calcd for $C_{11}H_8O_3N_2 \cdot 1/2H_2O$: C, 58.66; H, 4.03; N, 12.44%. λ_{max}^{MeOH} mμ (log ε); 228 (4.24), 255 (4.12), 290 (4.42), 360 (3.68), 439 (4.29).

2-Chloro-3-(β-nitrovinyl)-1-azaazulene (XV). A mixture of 0.05 g of XIV and 1.0 m*l* of phosphoryl chloride, when heated on a water bath for one hour afforded 0.04 g of orange brown needles of XV, which did not show a sharp melting point, after recrystallization from benzene.

Found: C, 56.87; H, 3.36; N, 12.60%. Calcd for $C_{11}H_7O_2N_2Cl$: C, 56.30; H, 3.01; N, 11.94%.

Azlactone (XVI). A mixture of 0.50 g of II, 0.65 g of hippuric acid, and 0.30 g of sodium acetate in 2 m*l* of acetic anhydride was heated in a sealed tube in a water bath. The semi-solid mass gradually dissolved to form a purple brown solution, and then it solidified again. Heating was continued for one hour; the resulting semi-solid mass was separated by filtration, washed with water and hot alcohol, and dried in a desiccator. The resulting solid, 0.56 g was hardly soluble in most organic solvents, and its melting point was over 300°C. A small amount, 0.10 g, when recrystallized from 200 m*l* of dioxane gave silky micro needles of XVI, mp$>$300°C.

Found: C, 72.31; H, 4.13; N, 8.79%. Calcd for $C_{19}H_{12}O_3N_3$: C, 72.14; H, 3.82; N, 8.86%. λ_{max}^{MeOH} mμ (log ε); 238 (4.27), 273 (4.39), 315 (4.11), 464 (4.09), 510 (4.05).

Hydrolysis of Azlactone. Azlactone, 0.20 g, when treated with 20 m*l* of 1% sodium hydroxide on a water bath for thirty minutes, afforded a clean red solution. The acidification of the solution with N hydrochloric acid to about pH 4 afforded a precipitate which, after being filtered off, washed with water, and dried, gave 0.22 g of a reddish brown solid. Recrystallization from alcohol afforded purple brown micro prisms of the free acid, mp 250—250.5°C(d).

Found: C, 67.56; H, 4.31; N, 8.19%. Calcd for $C_{19}H_{14}O_4N_2$: C, 68.25; H, 4.22; N, 8.38%.

The author is very much indebted to Professors Tetsuo Nozoe and Shuichi Seto for their continuous encouragement and kind guidance during the course of the present work, and to Dr. Melvin Woods for his friendship.