Benzoylation of 1,3-Diazaazulene[1]

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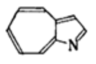
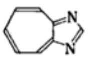
In 1949, Nozoe[2] predicted the possibility that the so-called 2-aminotropoimine and azaazulenes, which may be considered as the nitrogen homolog of tropolone and azulene respectively, are stable enough to exist. Later studies have confirmed their presence by the syntheses of azaazulenes such as 1-azaazulene (I)[3] and 1,3-diazaazulene (II)[4].


(I)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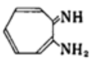
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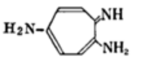
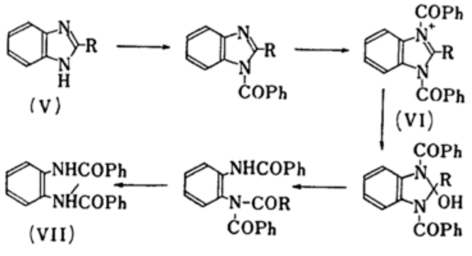

(IV)

However, the only derivative of 2-aminotropoimine (III) known to date is 2,5-diaminotropoimine (IV)[5] obtained by the reduction of 5-nitrosotropolone dioxime (*p*-tropoquinone trioxime)[6].

In a sense, 1,3-diazaazulene (II) may be considered as a seven-membered ring homolog of benzimidazole (V). From such a view point, the cleavage reaction of an imidazole ring by the Schotten-Baumann method, known as the Bamberger reaction[7,8] in imidazole compounds, was applied to II.



Scheme 1.

The Bamberger reaction is considered to poceed as indicated in Scheme 1, starting with benzoylation, followed by the formation of a quaternary base (VI) by the presence of excess benzoyl chloride and the cleavage of the base by the action of alkali hydroxide, forming *o*-phenylenediamine dibenzoate (VII)[8].

II differs from the imidazole ring in not possessing an N-H group that could be benzoylated. However, since II easily forms a methiodide[4], the possibility of its ring fission may be considered and examination of this reaction was made.

A solution of II dissolved in 4 molar equivalents of sodium hydroxide solution, and chilled in ice, was added with 4 molar equivalents of benzoyl chloride, the mixture was shaken thoroughly, and allowed to stand overnight. This was extracted with chloroform and the brown oil obtained from the extract was separated and purified by alumina chromatography, from which yellow scales (VIII), m. p. 157~158°C, and pale yellow needles (IX), m. p. 94~95°C, were obtained besides recovery of the starting II.

By exactly the same procedure, the reaction of 6 molar equivalents of sodium hydroxide and 4 molar equivalents of benzoyl chloride gave a small amount of pale yellow prisms (X), m. p. 158°C, besides VIII and recovery of II.

When this reaction was carried out at 70~72°C, the kind and amount of the products obtained were different, as indicated in Table I.

The reaction of II and benzoyl chloride

TABLE I. REACTION OF 1,3-DIAZAAZULENE AND BENZOYL CHLORIDE

Molar ratio			Temp.	Product (%)			
II	NaOH	C_6H_5COCl	(°C)	VIII	IX	X	II
1	4	4	0	25	30	—	37
1	6	4	0	30	—	5	40
1	4	4	70~72	—	60	—	15
1	6	4	70~72	—	—	62	14

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[1] Presented at the Local Meeting of Tohoku District of the Chemical Society of Japan, held at Yonezawa, June 25, 1956.

[2] T. Nozoe, *Science of Drugs* (*Yakugaku*), **3**, 191 (1949); T. Nozoe, *Science Repts. Tohoku Univ.*, **I**, **34**, 225 (1950).

[3] T. Nozoe, S. Seto, S. Matsumura and T. Terasawa, *Chem. and Ind.*, **1954**, 1357.

[4] T. Nozoe, T. Mukai and I. Murata, *J. Am. Chem. Soc.*, **76**, 3352 (1954).

[5] T. Nozoe, M. Sato, S. Ito, K. Matsui and T. Matsuda, *Proc. Japan Acad.*, **29**, 565 (1953); T. Nozoe and S. Ito, unpublished data.

[6] T. Nozoe and S. Seto, *Proc. Japan Acad.*, **27**, 188 (1951).

[7] E. Bamberger, *Ann.*, **273**, 267 (1893); E. Bamberger, B. Berle, ibid., **273**, 342 (1893).

[8] A. Weissberger, "The Chemistry of Heterocyclic Compounds, Imidazole and its Derivatives", Part I, Interscience Publishers, New York (1953), p. 48, 273.

afforded, according to conditions of the reaction, VIII and IX or X. Examinations were made on the structure of these three products.

VIII and X show the same melting point but a distinct depression of the melting point occurs on their admixture and they show different degrees of solubility, color, and crystal form. The ultraviolet absorption spectra[9] of the two compounds, shown in Fig. 1, are also entirely different. Elementary analytical values of X correspond to the molecular formula of $C_{14}H_{10}N_2$, not containing any oxygen. It easily forms a picrate of m. p. 210°C, a styphnate of m. p. 231°C (decomp.), and a hydrochloride of m. p. 210°C (decomp.), whose analytical values also agree with those calculated for a salt of the foregoing composition.

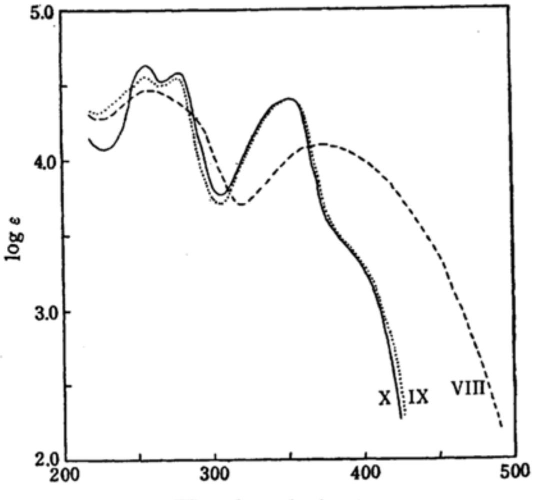

Fig. 1. U. V. absorption spectra of VIII, IX and X in methanol.

The infrared absorption spectrum[10] of X (Fig. 2) exhibits an absorption band at 1604 cm^{-1}, corresponding to the C=N stretching vibration or ring vibration (1602 cm^{-1}) in 1, 3-diazaazulene, and absorption bands at 717 and 686 cm^{-1} due to the C–H out-of-plane vibration of mono-substituted benzene. These facts suggest that X is a phenyl derivative of II.

Oxidation of X with potassium dichromate in diluted sulfuric acid affords 2-phenylimidazole-4,5-dicarboxylic acid(XI)[11] of m.p. 264°C (decomp.), and its decarboxylation gives 2-phenylimidazole (XII)[11] of m. p. 143°C, which showed no depression on admixture with XII synthesized from tartaric acid. The ultraviolet absorption spectra of these two compounds were also identical. It follows, therefore, that the structure of X is 2-phenyl-1,3-diazaazulene.

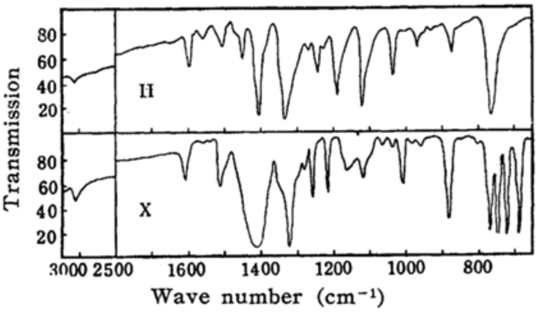

Fig. 2. I. R. absorption spectra of II and X in KBr.

IX is converted into X merely by mild treatment with dilute alkali and liberates one molar equivalent of benzoic acid during this course. The ultraviolet spectrum (Fig. 1) of IX is almost identical with that of X except for the absorption at around 230 mμ[12]. Since the heating of X with an equivalent amount of benzoic acid in ethanol results in quantitative formation of IX and from the analytical

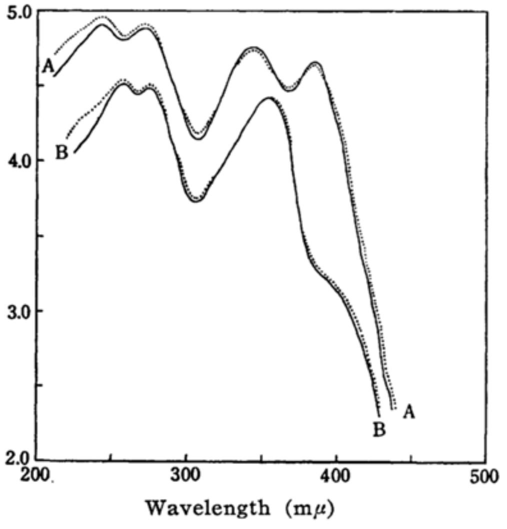

Fig. 3. U. V. Absorption spectra
—— X …… VIII
A, in 0.1N HCl ($Y=\log \varepsilon+0.5$)
B, in 0.1N NaOH ($Y=\log \varepsilon+0$)

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[9] Measured by the Beckman Model DU Spectrophotometer.

[10] I. R. spectra are measured using Perkin-Elmer Model 21 double beam spectrophotometer by Mr. Y. Ikegami of this Institute, to whom the author is deeply indebted.

[11] R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, **115**, 217 (1919).

[12] This is considered to have appeared by the overlapping of the K-band of benzoic acid. Cf. A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Orgaic Chemistry", Edward Arnold Publishers, London (1954), p. 126.

values of IX, it is assumed that IX is a benzoic acid salt of X.

Analytical values of VIII agree with $C_{21}H_{16}O_2N_2$. Its mild treatment with dilute acid or alkali affords X from the basic portion and one molar equivalent of benzoic acid from the acid portion. The ultraviolet spectrum of VIII (Fig. 1) shows an entirely different curve from those of IX and X, but its spectrum in acid and alkaline solvents (Fig. 3) shows a curve extremely similar to the absorption of X in acid and alkaline media with the exception of the absorption at around 230 mμ[12].

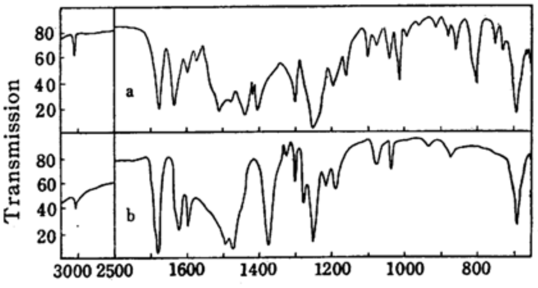
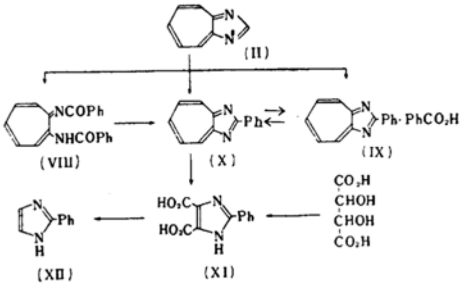


Fig. 4. I. R. absorption spectra of VIII.
a, in KBr-pellet; b, in CCl_4 soln.

In the infrared absorption spectrum of VIII (Fig. 4), there are absorptions considered to be the C=O stretching vibration of secondary amide[13] at the wave number[15] of 1683 (1676), the N-H deformation vibration at 1492 (1515), the N-H strectching vibration at (3290), and the C=O stretching vibration of tertiary amide at 1622 (1630).



Scheme 2.

The foregoing results suggest that VIII is 2-aminotropoimine dibenzoate formed by the ring-cleavage of II. These changes are presented in Scheme 2.

Attempts were made to remove the benzoyl group from VIII by hydrolysis and to obtain the parent structure, 2-aminotropoimine (III), but the attempts failed because of the extreme facility with which VIII underwent cyclization[16] and its facile conversion to X under the conditions for hydrolysis.

Experimental[17]

Reaction of 1,3-Diazaazulene (III) and Benzoyl Chloride.—a) To a solution of 300 mg. (2.3 mmol.) of II dissolved in a solution of 370 mg. (9.2 mmol.) of sodium hydroxide in 8 cc. of water, 1.29 g. (9.2 mmol.) of benzoyl chloride was added in one lot, under ice cooling, and the mixture was stirred thoroughly. This treatment is accompanied by a considerable generation of heat and the mixture must be chilled efficiently. When yellowish brown clay-like substance began to separate out on the wall of the vessel, the mixture was allowed to stand overnight and extracted with chloroform, from which 1.02 g. of brown oily substance was obtained. This oil was dissolved in 2 cc. of mixture of benzene and petroleum ether (1 : 1), and the solution was passed through a column (10×150 mm.) of alumina. The column was eluted with petroleum ether and 80 mg. of yellow crystals, m. p. 146~151°C, was obtained. Four recrystallizations from ethanol afforded 2-aminotropoimine dibenzoate (VIII) as yellow scaly crystals, m. p. 157~158°C.

Further elution of the alumina column with mixture of benzene and petroleum ether (1 : 1) afforded 90 mg. of pale yellow oil which was crystallized from cyclohexane to crystals of m. p. 91~92°C. Recrystallization from benzene-cyclohexane mixture afforded 2-phenyl-1,3-diazaazulene benzoic acid salt (IX) as pale yellow needles, m. p. 94~95°C.

Further elution of the column with benzene, followed by elution with ethanol, gave dark brown oil from both. These products were derived to respective picrates and decomposed by dilute hydrochloric acid, from which 110 mg. of unchanged II was recovered.

b) To a solution of 500 mg. (3.8 mmol.) of II dissolved in a solution of 915 mg. (22.8 mmol.) of sodium hydroxide in 16 cc. of water, 2.13 g. (15.2 mmol.) of benzoyl chloride was added and reacted as in a). Purification through a column (10×180 mm.) of alumina was carried out similarly and 140 mg. of VIII from the fraction eluted with petroleum ether and 25 mg. of yellow crystals,

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[13] Absorption of 2-benzoylaminotropone[14] as the secondary amide with unsaturated seven-membered ring was as follows: 1685 (1678), 1502 (1513), 3270 (3275); these values were read by the author.

[14] T. Nozoe, S. Seto, H. Takeda, S. Morosawa and K. Matsumoto, *Science Repts. Tohoku Univ.*, I, **36**, 126 (1952).

[15] Measurements were made by the KBr-pellet method. Values in parentheses are of those measured as CCl_4 solution.

[16] It has been also known that *o*-phenylenediamine dibenzoate also undergoes facile dehydration and cyclization to 2-phenylbenzimidazole. Cf. O. Gerngross, *Ber.*, **46**, 1913 (1913).

[17] All melting points are uncorrected. Petroleum ether used in this work was of b. p. 40~60°C. The microanalyses were carried out by Mr. S. Ohyama and Miss A. Iwanaga, to whom the author's deep gratitude is hereby expressed.

m. p. 142~153°C, from a fraction eluted with benzene-petroleum ether were obtained. Recrystallization of the latter from benzene-petroleum ether mixture afforded 2-phenyl-1, 3-diazaazulene (X) as yellow prisms, m. p. 158~159°C.

c) A solution of 830 mg. (6.34 mmol.) of II dissolved in a solution of 1.02 g. (25.5 mmol.) of sodium hydroxide in 26 cc. of water was heated to 70~72°C on a water bath and 3.57 g. (25.5 mmol.) of benzoyl chloride was added in one lot with stirring. The mixture was maintained at this temperature for 1 hr., cooled, and extracted with chloroform. The oily substance obtained from this extract was purified by chromatography and 510 mg. of IX was obtained besides recovery of 155 mg. of II.

d) A solution of 850 mg. (6.5 mmol.) of II dissolved in a solution of 1.56 g. (39 mmol.) of sodium hydroxide in 27 cc. of water was reacted with 3.64 g. (26 mmol.) of benzoyl chloride as in c) and 520 mg. of X and 120 mg. of II were obtained.

2-Aminotropoimine Dibenzoate (VIII).—*Anal.* Found: C, 76.89; H, 4.80; N, 8.76. Calcd. for $C_{21}H_{16}O_2N_2$: C, 76.81; H, 4.91; N, 8.53%.

2-Phenyl-1, 3-diazaazulene Benzoic Acid Salt (IX).—*Anal.* Found: C, 76.28; H, 4.71; N, 8.56. Calcd. for $C_{14}H_{10}N_2 \cdot C_7H_6O_2$: C, 76.81; H, 4.91; N, 8.53%.

2-Phenyl-1, 3-diazaazulene (X).—*Anal.* Found: C, 78.05; H, 5.06; N, 13.37. Calcd. for $C_{14}H_{10}N_2 \cdot \frac{1}{2}H_2O$: C, 78.12; H, 5.15; N, 13.02%.

Found (in a sample dried over P_2O_5 at 50°C/10 mmHg): C, 81.28; H, 4.95; N, 13.82. Calcd. for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58%.

a) Hydrochloride of X: Pale yellow prisms, m. p. 210°C (blacken) as recrystallized from ethanol.

Anal. Found: N, 11.47. Calcd. for $C_{14}H_{10}N_2 \cdot HCl$: N, 11.53%.

b) Picrate of X: Pale yellow, silky needles, m. p. 209~210°C, as recrystallized from water.

Anal. Found: C, 55.12; H, 3.43; N, 16.17. Calcd. for $C_{14}H_{10}N_2 \cdot C_6H_3O_7N_3$: C, 55.18; H, 3.01; N, 16.09%.

c) Styphnate of X: yellow silky needles, m. p. 231°C (decomp.), as recrystallized from 50% ethanol.

Anal. Found: C, 52.87; H, 3.24; N, 15.31. Calcd. for $C_{14}H_{10}N_2 \cdot C_6H_3O_8N_3$: C, 53.22; H, 2.90; N, 15.52%.

d) Benzoic acid salt (IX) of X: A solution of 50 mg. of X and 20 mg. of benzoic acid dissolved in 1 cc. of ethanol was heated for a few minutes, ethanol was evaporated, and the residue was recrystallized from benzene-petroleum ether mixture to pale yellow needles, m. p. 93~94°C, which showed no depression on admixture with IX.

Oxidation of X with Potassium Dichromate.—A solution of 150 mg. of X and 490 mg. of potassium dichromate dissolved in 12 cc. of 6 N sulfuric acid was heated on a water bath for 45 min. and the mixture was allowed to stand for 3 days at room temperature. The crystals that separated out were collected by filtration and 55 mg. of XI, m. p. 263~264°C (decomp.), was obtained. This XI was sublimed under diminished pressure to effect decarboxylation and 30 mg. of colorless crystals, m. p. 138~140°C, was obtained which showed no depression in the melting point on admixture with 2-phenylimidazole (XII), synthesized from tartaric acid[18].

Hydrolysis of VIII.—a) A mixture of 200mg. of VIII in 1.5 cc. of 2 N sulfuric acid was heated on a water bath for a few minutes, by which time the crystals dissolved to form an orange solution. This solution was extracted with chloroform and 50 mg. of crystals; m. p. 111~120°C, was obtained. Recrystallization from petroleum ether raised the melting point to 119~120°C, undepressed by admixture with benzoic acid. The aqueous layer separated after chloroform extraction was made weakly alkaline with sodium hydrogen carbonate and extracted with chloroform, from which 125 mg. of crystals melting at 156~157°C, identified with X, was obtained.

b) A mixture of 50 mg. of VIII dissolved in 1 cc. of ethanol and 0.5 cc. of 2 N sodium hydroxide solution was refluxed on a water bath for 5 min., ethanol was evaporated, and the residual solution was diluted with water. This was extracted with chloroform and 20 mg. of X was obtained from the extract. Extraction of the aqueous layer after acidification afforded 10 mg. of benzoic acid.

The author takes this opportunity to express his deep gratitude to Professor Tetsuo Nozoe for his unfailing guidance and to Assistant Professor Toshio Mukai for much helpful advice.

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[18] Ultraviolet absorption spectra of the sample and synthesized product were in good agreement, both showing λ_{max}^{MeOH} 269 mμ (log ε 4.20) and λ_{min}^{MeOH} 230 mμ (log ε 3.37).